CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125561Orig1s000

<u>MEDICAL REVIEW(S)</u>

CLINICAL REVIEW

Application Type	BLA- New Molecular Entity
Application Number(s)	BLA 125561
Priority or Standard	Priority
Submit Date(s)	Rolling Review
Received Date(s)	January 8, 2015
PDUFA Goal Date	September 8, 2015
Division / Office	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer Name(s)	Lauren Weintraub, MD, Medical Officer Jessica J. Lee, MD, Clinical Team Leader
Review Completion Date	September 8, 2015
Established Name	Sebelipase alfa (SBC-102)
(Proposed) Trade Name	Kanuma
Therapeutic Class	Enzyme replacement therapy
Applicant	Alexion Pharmaceuticals Inc. (formerly Synageva BioPharma Corp.)
Formulation(s)	20 mg/10 mL (2 mg/mL) injection, for intravenous use
Dosing Regimen	For patients with infantile-onset disease: Starting dosage 1 mg/kg IV once weekly with increase to 3 mg/kg once weekly
Indication(s)	Lysosomal acid lipase deficiency
Intended Population(s)	Patients with lysosomal acid lipase deficiency

Template Version: March 6, 2009

Clinical Review
Lauren Weintraub, MD
BLA 125561
Kanuma (sebelipase alfa)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical review evaluates the original biologics license application for Kanuma (sebelipase alfa, BLA 125561). Kanuma is a recombinant form of human lysosomal acid lipase (rhLAL), proposed for use as an enzyme replacement therapy for lysosomal acid lipase (LAL) deficiency. Patients with LAL deficiency can be divided into two general phenotypes—early onset (<6 months of age), rapidly progressive disease (i.e., Wolman disease) and a milder phenotype with later, more variable onset, affecting pediatric and adult patients [i.e., cholesteryl ester storage deficiency (CESD)]. The Applicant seeks approval for a single treatment indication of LAL deficiency. Although the proposed enzyme replacement therapy is specifically targeted to correct the underlying defect that results in the disease manifestations in both phenotypes, the data submitted to support Kanuma treatment in these 2 phenotypes were obtained in separate clinical trials, using different endpoints to assess efficacy. In addition, different drug dosages were evaluated in the 2 subpopulations of patients.

This review focuses on the data submitted for patients with the early-onset, rapidly progressive phenotype of LAL deficiency who were enrolled in Study LAL-CL03 (N=9). Historically, this phenotype of LAL deficiency is universally fatal within the first year of life. By comparison, the cholesteryl ester storage disease (CESD) has a more variable presentation and clinical course, with most patients surviving into adulthood (See Section 2, Introduction). Patients ≥ 4 years of age with the CESD phenotype were enrolled in a double-blind, randomized, placebo-controlled trial to evaluate the safety and efficacy of sebelipase alfa in patients with CESD (Study LAL-CL02). The Applicant's proposed treatment of patients with the CESD phenotype based primarily on the data from LAL-CL02 is reviewed separately by Dr. Juli Tomaino (see Clinical Review dated June 8, 2015).

In Study LAL-CL03, the primary efficacy endpoint was survival at 12 months of age. The infants in LAL-CL03 were treated with 2 initial small doses of sebelipase alfa (0.35 mg/kg), followed by planned maintenance treatment with weekly infusions of 1 mg/kg once tolerability was demonstrated. In patients who met pre-specified criteria for suboptimal treatment response, the protocol permitted a dose escalation to 3 mg/kg once weekly. Six of the 9 patients (67%) survived to 12 months of age, compared to 0% of patients in a historical cohort with similar baseline characteristics, thus demonstrating a clear survival benefit in the sebelipase-alfa treated patients. In addition, patients demonstrated improvements in several of the clinical disease-related abnormalities in these patients. However, due to the very small patient population, frequency of missing clinical assessments, and differences in baseline disease parameters, these assessments were reviewed on a case-by-case basis and compiled to reach a general conclusion regarding the global treatment benefit of sebelipase alfa.

All patients surviving beyond the first month of treatment required a dose increase to 3 mg/kg for suboptimal treatment response. When secondary and exploratory clinical parameters, including, but not limited to, weight gain, serum lipid levels, serum transaminases, organ (spleen and liver)

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volumes, and serum hemoglobin/packed red blood cell transfusion requirements, are simultaneously assessed in the context of sebelipase alfa dose and anti-drug antibody status, treatment with sebelipase alfa dose at a dose of 3 mg/kg was associated with more consistent and greater magnitude of improvements across these efficacy endpoints.

Safety concerns associated with sebelipase alfa treatment in this population were limited to expected hypersensitivity reactions and the development of anti-drug antibodies. Compared to comparable infantile populations with the most severe manifestations of other lysosomal storage disorders, these reactions were milder in severity and more generally more transient. It is unclear whether this very small patient population will be representative of this population over time. However, data in LAL$^{-/-}$ mice suggest that this finding may be explained by abnormal T-cell development due to lack of LAL activity, which has been identified as playing a regulatory role in the development and maturation of T cells.

Therefore, this reviewer recommends approval of BLA 125561 for the treatment of patients with lysosomal acid lipase deficiency. For adequate efficacy in patients with early-onset, rapidly progressive disease, this reviewer recommends an initial dose of 1 mg/kg with a dose escalation to 3 mg/kg once weekly.

This reviewer also agrees with the recommendation for post-marketing registry study to demonstrate the long-term clinical benefit of sebelipase alfa treatment on the progression of liver disease and cardiovascular events. For this population of patients with early-onset, rapidly-progressive disease, this study will also be useful to obtain additional dose-response information and to assess whether the immunogenic risk of this drug in a larger population of patients. This population of patients with early-onset, rapidly progressive LAL deficiency appears to have a higher dose requirement than patients with the milder CESD phenotype. The reason for this discrepancy is unclear, and inadequate PK data were available to compare drug exposures between the two patient subpopulations. Aside from differences in dose-exposure, lower residual enzyme activity and loss of enzyme via gastrointestinal protein losses have also been explored as potential reasons for differences in dose requirements. In addition, limited data are available to determine whether some patients may tolerate a dosage decrease (i.e., decreased infusion frequency). The only attempt to decrease the frequency of sebelipase infusions in LAL-CL03 was unsuccessful; however, a review of this patient's graphical profile (Figure 17) raises questions as to whether this patient had received sufficient treatment at optimal doses prior to this dosage adjustment.

Because the long-term sequelae of surviving patients with the infantile-onset phenotype of LAL deficiency are unknown, longitudinal data are needed to assess long-term outcomes and adequacy of treatment in these patients.

1.2   Risk Benefit Assessment

The early-onset, rapidly-progressive phenotype of LAL deficiency is associated with an extremely poor prognosis and limited survival, and there are currently no available treatments for patients with LAL deficiency. Sebelipase alfa represents the first viable therapeutic option for

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these patients, for whom there has been a critically unmet need for treatment. The clinical trial data in the 9 patients with early-onset, rapidly progressive LAL deficiency demonstrates a clear survival benefit associated with sebelipase-alfa treatment, and the overall tolerability of sebelipase alfa was acceptable.

The greatest risks associated with the class of enzyme replacement therapies are hypersensitivity reactions, and these reactions have been manageable with infusion rate adjustments and treatment with antipyretics, antihistamines, and/or corticosteroids. In addition, only 1 patient experienced loss of efficacy attributable to neutralizing anti-drug antibodies. In this patient, the decreased effectiveness of sebelipase alfa was not associated with any life-threatening sequelae, and appeared to show signs of improvement following a dose escalation to 5 mg/kg.

The risks and mitigating strategies of anaphylaxis and hypersensitivity reactions will be described in the labeling, and the long-term outcomes of patients with LAL deficiency, including ADA development and adequacy of dosing will be assessed in a post-marketing required registry study.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A REMS is not recommended for BLA 125561.

1.4 Recommendations for Postmarket Requirements and Commitments

This reviewer concurs with the postmarketing commitment study to further evaluate the long-term clinical benefit of Kanuma on liver and cardiovascular diseases in patients with both phenotypes of LAL deficiency. Of note, the applicant currently maintains a registry for patients with LAL deficiency and submitted the protocol upon request for our review. The study to be performed under a post-marketing commitment will evaluate the long-term, prospective clinical outcome of 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, weight z-scores). At a minimum, liver assessments will include liver biopsies, imaging, deterioration of liver synthetic function, clinical progression to end stage liver disease (e.g., assessed by MELD score), receipt of liver transplantation, and death. Cardiovascular assessments will include incidence rates of stroke, myocardial infarction, and death. Additional evaluations will include dosing regimens and reasons for any dose modifications. This trial will also collect safety data including 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 follow for a minimum of 10 years from the time of enrollment or until death, whichever comes first. This trial may be conducted as a separate trial or as a sub-trial within the Lysosomal Acid Lipase registry.

Unlike other severely-affected patients with infantile-onset of lysosomal storage disorders, the immunogenicity assessments of the patients in LAL-CL03 did not reveal any life-threatening sequelae attributable to ADA development. Therefore, investigations of pre-emptive

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immunotolerance regimens do not appear to be indicated in this population at this time. Given that immunosuppression in this patient population may be poorly tolerated, or even contraindicated prior to ERT initiation due to severe baseline immune dysregulation, additional data are needed to determine whether the safety data in the 9 LAL-CL03 clinical trial patients adequately represent this patient subpopulation.

2 Introduction and Regulatory Background

Lysosomal acid lipase (LAL) is the sole enzyme responsible for intralysosomal acidic hydrolysis of triglycerides (TG) and cholesteryl esters (CE) and plays a key role in lipid metabolism and homeostasis.[1,2] LAL is ubiquitously expressed, and deficiency of LAL activity leads to accumulation of lipid substrates in various tissues and cell types. [3,4]

LAL deficiency is inborn error of metabolism encompassing two general clinical phenotypes— the severe early-onset subtype, known as Wolman disease (WD), and the milder late-onset subtype, known as and cholesteryl ester storage disease (CESD). Despite striking differences in clinical presentations, extent of organ involvement, and rate of disease progression, both phenotypes are allelic disorders caused by mutations in the *LIPA* gene and are inherited in an autosomal recessive pattern. [5-7] Furthermore, in both cases, disease manifestations are attributable to disruption in LAL's biochemical pathways and regulatory effects, which includes cellular accumulation of lipid substrate and organ infiltration of lipid-laden macrophages.[4]

WD is a rare, infantile-onset, rapidly lethal condition (incidence ~1:500,000 live births), characterized by massive accumulation of TG and CE in tissues, most notably in cells of the reticuloendothelial system, including Kupffer cells in the liver, histiocytes in the spleen, and macrophages in the lamina propria of the small intestine.[8] Patients with WD 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 ~1.3 months, with severe malnutrition and liver failure as key contributors to mortality. [5]

In contrast to WD, CESD is a less severe variant of LAL deficiency, in which liver involvement and dyslipidemia are the predominant features. Unlike WD, the lipid substrate that accumulates in CESD is predominantly CE. [5,7] Hepatomegaly, often mild, may be the only clinical symptom, and diagnosis frequently occurs after discovery of biochemical abnormalities, such as elevated serum transaminases and abnormal lipid parameters.[9,10] 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. [10,13] Because diagnosis typically requires a high index of suspicion, and for this reason, CESD is believed to be an underrecognized condition.[10]

Correlations between residual enzyme activity and LAL disease severity have indicated that mutations causing WD mutations result in the complete loss of enzyme function, while mutations causing with CESD are associated with low levels of LAL activity. [5-7] In addition, in vitro

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studies have demonstrated greater substrate affinity of LAL for TG than CESD, consistent with the preferential storage of cholesteryl esters observed in CESD, but not WD. However, conflicting data from genotype-phenotype analyses have challenged the hypothesis that phenotype is determined solely by residual enzyme activity. [14-17] More recently, site-directed mutagenesis analyses have demonstrated that *LIPA* mutations result in variable changes in LAL catalytic activity, some of which result in isolated or greater effects on catalytic activity of CE. These studies have begun to elucidate phenotypic differences in substrate accumulation and organ involvement. [14,18]

Although many clinical features of WD and CESD are dissimilar, abnormal lipoprotein levels are present in the majority of patients with LAL deficiency, regardless of phenotype. The presence of severely abnormal lipoprotein levels often aids in diagnosis, although the full characteristic type IIb pattern of hyperlipidemia [i.e., hypercholesterolemia, hypertriglyceridemia, and low high-density lipoprotein (HDL)] is more common among patients with CESD than WD, in whom malnutrition and liver failure are often confounding factors.[5,10,11,19]

Nevertheless, abnormal lipoprotein levels result from the disruption of multiple homeostasis mechanisms for which LAL activity plays a vital role in preventing cellular lipid overload in multiple tissues, particularly the liver, spleen, and macrophages. Among these regulatory processes are suppression of endogenous cholesterol production via downregulation of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase activity, transcriptional regulation of the low density lipoprotein (LDL) receptor, and stimulation of reverse cholesterol transport via effects on cholesterol efflux and HDL particle formation. [1,20-24] [See Figure 23 in the Section 9.5 (Appendix)]

Liver involvement is also a feature common to both phenotypes. Typical findings on liver histopathology include microvesicular steatosis, enlarged and vacuolated sinusoidal and portal Kupffer cells, and vary degrees of bridging fibrosis and micronodular cirrhosis. Because standard histologic staining methods are not sensitive for distinguishing lysosomal vs. cytoplasmic lipid droplets, liver pathology of LAL deficiency often resembles nonalcoholic steatohepatitis.[4,8]

In WD, a subset of patients present with a fulminant form liver disease associated with significant elevations in serum ferritin and lactic dehydrogenase, resembling the life-threatening condition of hemophagocytic lymphohistiocytosis (HLH).[26] HLH represents a severe hyperinflammatory condition due to macrophage activation. While HLH is most commonly triggered by infectious agents or associated with an underlying rheumatologic disease, HLH has been reported in patients with inborn errors of metabolism, including another lysosomal storage disorder, Gaucher disease. [25]. Although several of the features of HLH overlap with LAL deficiency (i.e., hypertriglyceridemia, cytopenias, and splenomegaly, and abnormal liver chemistries), several cases of LAL deficiency have been reported which fulfill the diagnostic criteria of HLH, including findings of hemophagocytosis in bone marrow. [26]

Macrophages play a central role in the pathophysiology of LAL deficiency, particularly in WD. Even under normal circumstances, macrophages are particularly susceptible to lipid overload due to unregulated pathways of LDL influx (i.e., scavenger receptor-mediated uptake, pinocytosis,

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and phagocytosis) and depend on LAL-mediated cellular efflux mechanisms to prevent lipid accumulation. [27-30] Without LAL, reduced lipid efflux and loss of feedback inhibition LDL receptor-mediated uptake macrophages results in high levels of lipid accumulation, which leads to chronic inflammation associated with aberrant cytokine/chemokine secretion. [27-30] Furthermore, recent studies of LAL knockout mice have begun to identify additional regulatory roles of LAL in myelopoiesis and hematopoietic homeostasis and may provide additional insights into the pathophysiology of LAL deficiency. [31-34]

2.1 Product Information

Sebelipase alfa (molecular name SBC-102) is a purified recombinant form of human lysosomal acid lipase (rhLAL), a glycoprotein with (b)(4) N-linked glycosylation sites. Sebelipase alfa has an amino acid sequence that is identical to human LAL (hLAL) and has a molecular weight of approximately 55 kD. Sebelipase alfa is produced by recombinant DNA technology in egg white using a transgenic Gallus expression system and contains predominantly GlcNAc and mannose terminated N-linked glycan structures, some of which contain mannose-6-phosphate (M6P), which are recognized and internalized by macrophages via the cell surface macrophage mannose receptor (MMR), as well as by cells expressing the M6P receptor.

2.2 Currently Available Treatments for Proposed Indications

There is no approved specific treatment for LAL deficiency. For early-onset LAL deficiency, standard of care consists mainly of supportive measures. Bone marrow transplantation has the potential to correct the enzyme deficiency in the leukocytes, but engraftment has a high failure rate, possibly due to pre-existing pathology. In addition this therapeutic option is associated with significant morbidity and is often precluded by the severity of patients' clinical condition. [35,36]

Lipid-lowering agents, particularly HMG CoA-reductase inhibitors are often used for treatment of patients with CESD. Administration of HMG-CoA inhibitors has been shown to improve serum lipoprotein levels, particularly LDL, and decrease hepatic steatosis. However, the role of long-term administration of these agents in prevention of premature atherosclerosis or the progression of liver fibrosis is unclear. [13]

2.3 Availability of Proposed Active Ingredient in the United States

2.4 Important Safety Issues With Consideration to Related Drugs

An increased risk of hypersensitivity reactions, including anaphylaxis, is associated with the use of enzyme replacement therapies (ERT), and the prescribing information for all ERT for GD carry warnings and precautions regarding these risks. These products are also associated with the potential for anti-drug antibody development. Patients who develop anti-drug antibodies are at increased risk for hypersensitivity reactions, including anaphylaxis. In addition, the presence of neutralizing antibodies may be associated with decreased effectiveness of the drug.

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2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1: Regulatory Activity for Sebelipase Alfa, BLA125561

Date of Activity	Type of Regulatory Activity	Comments/Details
March 30, 2010	Investigational New Animal Drug (INAD) application submitted to the Center for Veterinary Medicine (CVM)	
July 2010	Orphan drug designation granted (ODD #10-3094)	
July 29, 2010	Type B (pre-IND) meeting	Included discussion of nonclinical study data to support clinical trials, acquisition of first-in-human trail data to support subsequent clinical trials, and conduct of natural studies; The division also encouraged the applicant to schedule a separate meeting with CVM to discuss requirements for a New Animal Drug Application (NADA)
December 22, 2010	Receipt of initial IND application	Intended for the treatment of LAL deficiency
February 7, 2011	Advice Letter	Included comments regarding pharmacokinetic methods, neutralization assessment of anti-drug antibodies, and communication from CVM stating that the lack of information regarding plans for preparing and filing an NADA prevented them from being able to provide requested information
June 14, 2011	Fast track granted	
April 24, 2012	Type C (CMC) meeting	
June 12, 2012:	Type B (End of Phase 1) meeting	Included comments regarding identification of an appropriate population for a confirmatory clinical trial and selection of clinically meaningful endpoints**

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November 6, 2012	Type C End of phase 1 meeting (follow-up)	Included comments regarding safety procedures for responding to anaphylaxis and detailed discussion of clinical trial endpoints, including lipid parameters, serum transaminases, **
May 13, 2013	Breakthrough designation granted*	Granted for Wolman disease, (b) (4)
February 12, 2014	Type B (CMC) meeting	Discussion of FDA requirement for approval of first regulated article prior to BLA approval and CVM ANDA requirements
December 10, 2013	Type C (Clinical WRO) meeting	Comments regarding plans for histopathological assessments, including need for objective biopsy scoring and pre-specification of criteria for histological improvement based on concrete, objective parameters, as well as concerns regarding the use of steatosis as a biomarker to predict disease progression and morbidity; included communication regarding the use of ALT as the primary clinical trial endpoint**
February 25, 2014	Type B (Breakthrough) meeting	Discussion regarding need for data to bridge the 2 clinical phenotypes of LAL deficiency in order to use infant data to demonstrate treatment benefit in the broader disease population, with a recommendation to prioritize drug development for infantile-onset LAL deficiency, followed by an efficacy supplement to broaden the indication after obtaining data to demonstrate clinical benefit of treatment in late-onset disease
April 1, 2014	Type C (Clinical) meeting	Discussed revised plans for assessment of liver biopsies
April 23, 2014	Pre-submission (CVM) meeting	

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June 25, 2014	Type C (clinical WRO) meeting	Addressed the Applicant's questions regarding the planned components for a biologics licensing application (BLA)
August 15, 2014	Pre-BLA meeting (preliminary comments)	Addressed questions regarding plans for BLA submission; included recommendation to focus efficacy assessments on data from infantile-onset patients with supportive data from late-onset patients due to concerns regarding the inability of proposed clinical trial endpoints to measure clinical benefit of treatment in late-onset patients**; meeting cancelled after preliminary comments sent
		The Division informed the Applicant that submission of a complete NADA is required prior to BLA filing.
August 1, 2014	Proprietary name granted	
October 21, 2014	Rolling submission initiated	Application submission completed January 8, 2015

* Breakthrough Therapy designation for LAL deficiency presenting in infants based on compelling survival data, which was considered strong evidence of a clinically meaningful treatment benefit in infantile-onset patients with LAL deficiency.

** Communication included comments stating that the Division does not consider serum ALT to be an established biomarker which represents a clinically meaningful outcome in patients with LAL deficiency, nor a surrogate endpoint reasonably likely to predict clinical benefit under the Accelerated Approval Pathway.

2.6 Other Relevant Background Information

Sebelipase alfa received marketing approval by the Europe Commission on September 1, 2015. A New Drug Application has also been submitted to Japan's Ministry of Health, Labour and Welfare. Sebelipase alfa received Orphan Drug designation in the EU in October 2012 and Japan in August 2012.

A pediatric rare disease voucher request was submitted by the Applicant along with the BLA submission.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This application was submitted electronically. Datasets were complete, and the application was well-organized and easily navigable using the hyperlinks provided by the Applicant.

3.2 Compliance with Good Clinical Practices

The Applicant stated that the clinical trials were conducted in accordance with the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC), and in accordance with United States and international standards of Good Clinical Practice (GCP) as defined by the Food and Drug Administration [FDA] Title 21 part 312 and International Conference on Harmonization [ICH] guidelines.

Clinical sites chosen for inspection included clinical sites and contract research organizations (CROs). The clinical sites were chosen on the basis of high enrollment and participation in more than one study. The CROs were chosen because of their roles in central reading of important efficacy parameters for Protocol LAL-CL02, a blinded, randomized clinical trial population (vs. the open-label treatment of patients in LAL-CL03. The Sponsor was inspected because this product is a new molecular entity (NME).

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Table 2: Results of Clinical Site Inspections

Type of Inspected Entity, Name, and Address	Protocol #, Site #, and # of Subjects	Inspection Date	Classification*
CI: Edward Neilan Boston Children's Hospital 3 Blackfan Circle, Room CLS-14070 Boston, MA 02115	LAL-CL02 Site 2109 3 Subjects	February 3 to 11, 2015	NAI
CI: Simon Jones, M.D. Central Manchester University Hospitals NHS Foundation Trust St. Mary's Hospital, Oxford Road Manchester M13 9 WL, UK	LAL-CL03 Site 01 3 Subjects	March 30 to April 2, 2015	NAI
CI: Vassili Valayannopoulos, M.D. Centre de Reference Maladies Metaboliques de l'enfant et de l'adulte Hopital Necker 149 Rue de Sevres 75015 Paris, France	LAL-CL03/Site 02 3 Subjects LAL-CL02 Site 701/4 Subjects	April 13 to 17, 2015	NAI
CI : Alejandra Consuelo, M.D. Hospital Infantil de México No. 162 Col. Doctores, Delegación Cuauhtémoc Mexico, 06720	LAL-CL02 Site 1302 4 Subjects	April 6 to 10, 2015	Pending NAI
CRO: (b) (4)	LAL-CL02 Central reading of MRI/sample processing for MRI fat quantitation and liver biopsy	(b) (4)	NAI
CRO: (b) (4)	LAL-CL02 Liver fat content reduction on MRI	(b) (4)	NAI
CRO: (b) (4)	LAL-CL02 Liver histopathology readings	(b) (4)	NAI
Sponsor: Synageva BioPharma Corp 33 Hayden Avenue, Lexington, Massachusetts 02421	LAL-CL03 and LAL-CL02	May 28 to June 3, 2015	Pending VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary
communication with the field; EIR has not been received from the field, and complete
review of EIR is pending.

(Source: Clinical Site Inspection Summary by Susan Leibenhaut, M.D, Medical Officer, Division of Clinical
Compliance Evaluation, Office of Scientific Investigations)

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Inspections of LAL-CL03, Sites 1 and 2, at which a total of 6 subjects were screened and enrolled (3 subjects/site). At site 1 for Protocol LAL-CL03, three subjects were screened and enrolled. One subject died and two subjects completed the study. At site 2 Protocol LAL-CL03, three subjects were screened, enrolled, and completed the study. In addition, four subjects for Protocol LAL-CL02 were screened, enrolled, and completed the study at this site. At both sites, a review of source documents, informed consent documents, ethics committee correspondence and approvals, sponsor correspondence, investigator agreements, financial disclosure, and eCRFs revealed no evidence of under-reporting of adverse events and the efficacy data was verifiable. Both sites appear to have been conducting the studies adequately, and the data generated may be used in support of the respective indication. Overall, results of the inspection indicated that, in general, records were well organized and available for review. Monitoring of investigators was adequate and the sponsor maintained adequate oversight of the trials. Data receipt and handling and test article accountability were considered to be adequate. A Form FDA 483 was issued for a single observation, failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND.

Specifically, for Protocol LAL-CL03 the sponsor did not ensure that all serious adverse events were reported by one clinical site to the sponsor or designee within 24 hours, as required by the protocol. These adverse events, specifically infusion related reaction (urticaria), abdominal adenomegalies, worsening of growth failure, and systemic infection, were reported to FDA in a timely manner once the sponsor was made aware by the clinical site. On June 11, 2015, the sponsor responded adequately to the Form FDA 483. Therefore, site inspections indictate that studies have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

A total of 380 protocol deviations were reported for the 9 patients in LAL-CL03. Twenty-nine protocol deviations were safety-related, of which all but 6 were due to missing vital sign assessments. The other 6 represented violations of adverse event reporting. (2 of these were considered major protocol deviations. Most of the non-safety related protocol deviations include missing assessments or assessments performed outside of the protocol-specified time window. Three subjects missed ≥1 scheduled study infusion:

- Subject (b) (6) missed 3 infusions due to illness (Weeks 6, 10, 37), and one other infusion during transfer to a local site (Week 29)
- Subject (b) (6) missed a single infusion at Week 73 to accommodate the subject's schedule during the holidays
- Subject (b) (6) did not have a reported infusion at Week 13 due to an adjustment in the nominal time points of infusions to accommodate the differing scheduling windows in ATU and LAL-CL03 when merging the data from ATU into the clinical database; this subject also missed an infusion at Week 160 for unknown reasons.

There were no deviations to inclusion/exclusion criteria for any treated subject. Three major protocol deviations occurred, including one dosing error, in which a patient was initially administered with undiluted sebelipase alfa. Upon noting this, site personnel interrupted the infusion, administered chlorpheniramine, diluted the remaining 10 mL of drug in 20 mL, and completed the infusion. None of these protocol deviations were determined to affect the validity

or interpretation of study data, and no subject data were excluded from any trial analyses due to a protocol deviation.

3.3 Financial Disclosures

Financial disclosures were reviewed and deemed adequate. No questions were raised about the integrity of the data included in this application. Refer to Section 9.4 (appendix) for additional details.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review team (Drs. Christopher Downey, Simon Williams, and Arulvathani Arudchandran) recommends approval recommend approval of this application, following resolution of the 483 items from the facility inspections. The CMC reviewers have concluded that the data submitted in this BLA demonstrate that the manufacture of sebelipase alfa is adequately controlled and yields a product that is pure and potent, using conditions which have been sufficiently validated and results in a consistent product.

At a storage temperature of 2 – 8°C, the CMC reviewers recommend a (b) (4) month expiration-dating period for sebelipase alfa drug substance and a 24-month expiration-dating period for sebelipase alfa drug product.

4.2 Clinical Microbiology

Sebelipase alfa drug product is a sterile, preservative-free 2 mg/ml solution for infusion. The drug product is manufactured by aseptically filling formulated sebelipase alfa drug substance into single-use vials. The Clinical Microbiology Reviewer has identified outstanding issues to be addressed by the Applicant. However, none of these issues would preclude approval and can be resolved through labeling revisions and postmarketing requirements/commitments. The reader is referred to the microbiology review by Dr. Colleen Thomas for details.

4.3 Preclinical Pharmacology/Toxicology

The nonclinical reviewer did not identify issues that would preclude approval and recommended approval for its proposed use as indicated in the labeling. Refer to nonclinical review by Dr. Tamal Chakraborti for details.

4.4 Clinical Pharmacology

The clinical pharmacology review team concluded that the information submitted in this BLA is acceptable to support a recommendation for the approval of Kanuma. In patients with early

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onset, rapidly progressive LAL deficiency, insufficient data were obtained to characterize the pharmacokinetics (PK) of sebelipase alfa or evaluate the exposure-response (E-R) relationship. In patients with the CESD phenotype of LAL deficiency, higher sebelipase alfa exposures appeared to be associated with a greater change in LDL from baseline. However, because the biological activity of sebelipase alfa is primarily driven by the exposure in the lysosomes of target tissues, and the relationship between systemic exposure and the concentration of sebelipase alfa in the lysosomes is unknown, results of E-R analyses were considered to be supportive evidence of effectiveness. Therefore, in both patient populations, dosing recommendations were based primarily on efficacy and safety data of doses evaluated during the patients' respective clinical trials.

The proposed dosage for treatment of pediatric and adult patients with the CESD phenotype of LAL deficiency, and the dose evaluated in clinical trials, is 1 mg/kg as an intravenous infusion once every other week. The clinical pharmacology reviewer agreed with the clinical reviewer's conclusion that sufficient data are available to support approval of this dose in this population.

In patients with early-onset rapidly progressive LAL deficiency, the Applicant's proposed is 1 mg/kg as an intravenous infusion once weekly, with a dose escalation to 3 mg/kg once weekly in patients who demonstrate a suboptimal response to treatment on the 1 mg/kg dose. The

Refer to clinical pharmacology review by Dr. Jing Fang for additional details.

4.4.1 Mechanism of Action

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) purified from the egg whites of rhLAL transgenic gallus (hens). The enzyme has a terminal n-actelyglucosamine and mannose structures (e.g. mannose-6-phosphate) that allow binding of the protein to cell surface receptors and targeting of the enzyme to cell lysosomes. Sebelipase alfa allows cleavage of cholesteryl esters and triglycerides, thereby reducing the accumulated substrate and correcting the associated abnormalities of lipid homeostasis.

4.4.2 Pharmacodynamics

4.4.3 Pharmacokinetics

Minimal pharmacokinetic data were obtained from patients in LAL-CL03. These data were deemed insufficient by the clinical pharmacology review team to characterize the pharmacokinetics of sebelipase alfa in this clinical trial population. The reader is referred to the review by Dr. Jing Fang for a review of sebelipase alfa clinical pharmacology data in older children and adults.

5 Sources of Clinical Data

This primary source of data for this clinical review is Study LAL-CL03, a multi-center, open-label clinical trial to evaluate the safety and efficacy of sebelipase alfa in infants presenting

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within the first 6 months of life with rapidly progressive LAL deficiency. A demographically-similar historical comparator group with similar baseline disease severity was derived from the population included in the Applicant's retrospective, observational natural history study of patients diagnosed with LAL deficiency at ≤2 years of age (Study LAL-1-NH01). This application also included safety and efficacy data from Study LAL-CL02, a multi-center, randomized, double-blind, placebo-controlled clinical trial in pediatric and adult patients with the CESD phenotype of LAL deficiency. These data were reviewed by Dr. Juli Tomaino (BLA 125561, Clinical Review dated June 8, 2015).

At the time of this review, the Applicant has 5 ongoing clinical trials (Table 3) in Section 5.1 below). Patients from the LAL-CL02 and LAL-CL03 clinical trials are continuing to receive treatment with sebelipase alfa in their respective trials. (For LAL-CL02, both sebelipase-treated and placebo patients are receiving open-label treatment in an extension phase of the trial.) As of April 8, 2015 (Day 120 Safety Report late-breaking cutoff date), 106 patients between 0 and 59 years old with LAL deficiency (33 adults, 57 children, and 14 infants) have been treated with sebelipase alfa in clinical trials. An additional 2 patients have received treatment under expanded access ("compassionate use") programs. The Applicant is also conducting 2 additional open-label clinical trials (LAL-CL06 for patients >8 months old and LAL-CL08 for patients <8 months old) to broaden the overall sebelipase alfa clinical trial to include patients not eligible for other clinical trials, including subjects with severe liver disease, subjects with a previous liver or hematopoietic stem cell transplant, and subjects with an atypical presentation of LAL Deficiency.

5.1   Table of Studies/Clinical Trials

Completed and ongoing sebelipase alfa clinical trials are summarized in Table 3. One additional clinical trial, LAL-CL05, was initiated to serve as the extension study for patients who completed LAL-CL03, which at that time, was a 4-month safety trial in infants with LAL deficiency. This clinical trial was merged with LAL-CL03 after the implementation of Protocol Amendment 6, which amended the LAL-CL03 study objectives and changed the primary efficacy endpoint to survival at 12 months of age.

Table 3: Overview of Sebelipase Clinical Trials (as of April 8, 2015)

Descriptor	Study Number					
	LAL-CL01	LAL-CL02	LAL-CL03	LAL-CL04	LAL-CL06	LAL-CL08
Study Design	Phase 1/2, single-arm, open-label, dose escalation; safety, PK, PD	Phase 3, randomized, double-blind, placebo-controlled; safety & efficacy, PK, with open-label extension	Phase 2/3, single-arm, open-label; safety & efficacy, PK	Phase 2, single-arm, open-label extension for subjects who completed LAL-CL01 safety & efficacy	Phase 2, single-arm, open-label, safety & efficacy	Phase 2, single-arm open-label, safety & efficacy
Number of Countries with Centres Enrolling Subjects	4	15	5	5	9	1
Study Status	Completed	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
Number of Subjects Treated	9	66	9	8	17	5
Number of Subjects Completed or Ongoing Treatment in Study	9 (completed)	66 (ongoing)	5 (ongoing)	8 (ongoing)	15 (ongoing)	4 (ongoing)
Age at First Dose	19 to 45 years	4 to 59 years	0.08 to 0.42 years	19 to 45 years	3 to 54 years	0.17- 0.33 years
Age at LAL Deficiency Symptom Onset (n)	0.83 to 30 years (n=9)	Birth to 42 years (n=66)	Birth to 0.33 years (n=9)	0.83 to 30 years (n=8)	Birth to 30 years (n=7)	Birth to 0.33 years (n=4)
LAL Deficiency Population	Adults (≥18 years)	Children and adults (≥4 years)	Infants (≤2 years)	Adults (≥18 years)	Adults, children, and infants (> 8 months)	Infants < 8 months
Dosing Regimen	Cohort 1: 0.35 mg/kg, qw, IV dose Cohort 2: weekly 1 mg/kg, qw, IV dose Cohort 3: weekly 3 mg/kg, qw, IV dose	1 mg/kg qow IV; increase up to 3 mg/kg qow for clinical progression or reducing to 0.35 mg/kg for tolerability	Dose escalation from 0.35 mg/kg to 1 mg/kg qw IV; increase up to 3 mg/kg qw for clinical progression or reduction to 0.35 mg/kg qw for tolerability; Provision for increasing to 5 mg/kg qw for clinical progression	0.35, 1, or 3 mg/kg, qw IV for 4 weeks; 1 or 3 mg/kg qow IV	1 mg/kg qow IV; increase up to 3 mg/kg qw for clinical progression or reducing to 0.35 mg/kg for tolerability	1 mg/kg qw, IV doses, with potential for dose escalation to 3 to 5 mg/kg qw, IV doses, followed by potential for dose reduction to 1 or 3 mg/kg qow, IV doses at 96 weeks
Treatment Duration	4 weeks	20-week double-blind period & open-label extension up to 130 weeks	Up to 260 weeks	Up to 260 weeks	Up to 96 weeks	Up to 156 weeks
Analysis Cut-off Date for ISS	06 Jan 2012 (final)	30 May 2014	10 Jun 2014	27 Jul 2014	NA	NA
Analysis Cut-off Date for Pooled Safety Analyses (Day 120 Update)	06 Jan 2012 (final)	26 Jan 2015	26 Jan 2015	26 Jan 2015	26 Jan 2015	26 Jan 2015
Analysis Cut-off Date for Late Breaking Safety Information	06 Jan 2012 (final)	08 Apr 2015	08 Apr 2015	08 Apr 2015	08 Apr 2015	08 Apr 2015

(Source: Applicant's Table 1 entitled "Completed and Ongoing Clinical Studies with Sebelipase Alfa Included in the Updated Pooled Safety Set", Day 120 Safety Update Report, page 9/105, BLA 125561, Module 5.3.5.3)

5.2   Review Strategy

The efficacy and safety of sebelipase alfa for treatment of patients with rapidly progressive LAL deficiency presenting within the first 6 months of life was evaluated using data from 9 patients enrolled in an open label, multicenter, dose escalation study (LAL-CL03). This is an ongoing study, with enrollment from May 2011 to December 2013. This application included all available data for these patients from the initiation of sebelipase alfa treatment until data cutoff on June 10, 2014.

The primary efficacy analysis was based on the proportion of patients surviving at 12 months of age. Several secondary and exploratory efficacy analyses were specified to perform a comprehensive evaluation of the effect of sebelipase alfa on the scope of clinical manifestations associated with LAL deficiency. Of these, assessments of patient growth were most informative since growth failure was an inclusion criterion for LAL-CL03 (with the exception of 1 patient

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enrolled under an exception which permitted enrollment of patients with other evidence of rapidly progressive disease requiring emergent intervention). For other clinical variables, the extremely small patient population and variability in baseline disease-related abnormalities limited population analyses. However, these data were used to generate individual graphical patient profiles for the 6 surviving patients in LAL-CL03 (Figures 15 to 20), which were used for global assessments of treatment response.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 LAL-CL03

Title

An Open Label, Multicenter, Dose Escalation Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of SBC-102 in Children with Growth Failure Due to Lysosomal Acid Lipase Deficiency

Study Objectives

➢ Primary objective: to evaluate the effect of sebelipase alfa therapy on survival at 12 months of age in children with growth failure or other evidence of rapidly progressive lysosomal acid lipase (LAL) Deficiency presenting in the first 6 months of life

➢ Secondary/exploratory objectives:

- To evaluate the safety and tolerability of sebelipase alfa
- To evaluate the effect of sebelipase alfa therapy on survival beyond 12 months
- To evaluate the effects of sebelipase alfa on hepatomegaly, splenomegaly, and liver function
- To evaluate the effects of sebelipase alfa on hematological parameters
- To characterize the pharmacokinetics (PK) of sebelipase alfa delivered by intravenous (IV) infusion.
- To determine the effects of sebelipase alfa on lipid parameters
- To assess developmental milestone achievement in sebelipase alfa-treated infants
- To assess the tolerability of an unrestricted diet in sebelipase alfa-treated infants
- To evaluate potential disease-related biomarkers

Note: these study objectives reflect the most recently approved protocol amendment (Protocol Amendment 10, dated January 24, 2014). Study LAL-CL03 was originally conducted as a safety trial with a 4-month treatment period. After nonclinical chronic toxicology data and extended clinical experience in adults became available, LAL-CL05 was initiated as an extension study to evaluate the long-term efficacy and safety (including a survival analysis) of sebelipase alfa in infants who had initiated treatment in LAL-CL03 or under an expanded access protocol. Subsequently, Study LAL-CL03 was merged with its extension study, LAL-CL05, under a single protocol (Protocol Amendment 6 dated April 5, 2012). At this time, survival at 12 months of age was established as the primary objective and the secondary and exploratory study objectives were modified.

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Study Design

LAL-CL03 is an open-label, repeat-dose, intra-subject dose escalation study was designed to evaluate the efficacy and safety of ERT with sebelipase alfa in subjects who presented with LAL Deficiency as infants and were considered to have rapidly progressive disease based primarily on the presence of growth failure within the first 6 months of life.

Study Population

- ➢ Inclusion Criteria
  - LAL deficiency documented by decreased LAL activity relative to the normal range of the lab performing the assay or molecular genetic testing with 2 mutations confirming a diagnosis of LAL Deficiency
  - Growth failure with onset before 6 months of age, as defined by at least 1 of the following:
    - Weight decreasing across at least 2 of the 11 major centiles on a standard WHO weight-for-age (WFA) chart
    - Body weight in kg below the 10th centile on a standard WHO WFA chart AND no weight gain for the 2 weeks prior to screening
    - Loss of > 5% of birth weight in a child who is older than 2 weeks of age

  An exception to the above criteria (added as part of Protocol Amendment 8) permitted enrollment of patients who do not meet the growth failure criteria as defined if patients have evidence of a rapidly progressive course of LAL deficiency that, in the judgment of the investigator, requires urgent medical intervention and receives approved from the Sponsor.

Table 4: Amendments to Growth Failure Criteria in Study LAL-CL03

	Original Protocol	Amendment 2	Amendment 3	Amendment 6	Amendment 8	Amendment 9
Type	Global	France only	Global	Global	Global	Global
Approval Date	10 Jan 2011	19 Apr 2011	20 May 2011	05 Apr 2012	05 Feb 2013	19 Mar 2013
Growth Failure Criteria [a]	crossing below 2nd percentile lines on standard weight for age curves over time	crossing 2 percentile lines on standard weight for age curves over time	crossing 2 major centile lines on standard weight for age curves over time	weight decreasing across at least 2 of the 11 major centiles on a standard WHO WFA chart (1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th, 99th)	No change	No change
	less than 10th percentile weight for age and falling from the curve	No change	No change	body weight in kg below the 10th centile on a standard WHO WFA chart AND no weight gain for the 2 weeks prior to screening	No change	No change
	loss of ≥ 5% of birth weight	No change	No change	loss of > 5% of birth weight in a child who is older than 2 weeks of age	No change	No change
Additional Criterion Allowing Enrolment without Confirmed Growth Failure	No	No	No	No	Evidence of rapid disease progression requiring urgent medical intervention AND a sibling with documented early growth failure [b]	Evidence of rapid disease progression requiring urgent medical intervention [c]

(Source: Applicant's Table 3, entitled "Amendments to Growth Failure Criteria in Study LAL-CL03", LAL-CL-03 Clinical Study Report, page 80/233, BLA 125561, Module 5.3.5.2)

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➢ Exclusion criteria:

- Clinically important concurrent disease or co-morbidities which, in the opinion of the Investigator and Sponsor, would interfere with study participation, including, but not restricted to, congestive heart failure, ongoing circulatory collapse requiring inotropic support, acute or chronic renal failure, additional severe congenital abnormality, or sebelipase alfa other extenuating circumstances such as life-threatening under nutrition or rapidly progressive liver disease
- Age > 24 months of age (Subjects > 8 months of age on the date of first infusion were not eligible for the primary efficacy analysis)
- Treatment with another investigational treatment within 14 days prior to the first dose of sebelipase alfa in this study
- Myeloablative preparation, or other systemic pre-transplant conditioning, for hematopoietic stem cell or liver transplantation
- Previous hematopoietic stem cell or liver transplant
- Known hypersensitivity to eggs

Study Treatments

The LAL-CL03 clinical trial protocol, as of Protocol Amendment 10, specifies a treatment period of up to 4 years.

Sebelipase Alfa Dosing Procedures (LAL-CL03):

➢ Initiation of treatment with a dose of 0.35 mg/kg once weekly (minimum 2 doses)

➢ Planned dose escalation to 1 mg/kg once weekly if acceptable safety and tolerability were demonstrated with at least 2 infusions at the dose of 0.35 mg/kg.

One patient (Subject (b) (6) *) initiated treatment with sebelipase alfa under an expanded access protocol (Autorisation Temporaire d'Utilisation; ATU) prior to enrolling in LAL-CL03. Under the ATU, this patient's sebelipase dose was gradually escalated over a period of 4 weeks—0.2 mg/kg at Week 0, 0.3 mg/kg at Week 1, 0.5 mg/kg at Week 2, 0.75 mg/kg at Week 3, and 1 mg/kg at Week 4 and thereafter. This patient was later transitioned into extension study LAL-CL05 and then into study LAL-CL03 on a dose of 1 mg/kg once weekly.*

➢ Further dose increase to 3 mg/kg once weekly after at least 4 infusions at a dose of 1 mg/kg in patients exhibiting a suboptimal treatment response based on protocol-defined criteria (described below under the subheading "Dose Escalation for Suboptimal Treatment Response")

➢ Dose reduction permitted in the event of poor tolerability

➢ After at least 96 weeks of treatment and at least 24 weeks of a stable dose, change to an every-other-week dosing schedule at the same total dose (mg/kg) per infusion permitted

During the conduct of the study, the protocol was amended to include an option for dose escalation to 5 mg/kg weekly in subjects who had evidence for a continued suboptimal response/loss of efficacy in association with the presence of neutralizing antibodies.

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Subjects initially received infusions at a primary study center. Subjects who were medically stable, as determined by the Investigator, could transfer to a local medical center for long-term treatment, contingent upon the local medical center being appropriately qualified and securing the required regulatory approvals.

Dose Escalation for Suboptimal Treatment Response

The LAL-CL03 study protocol pre-specified 2 sets of criteria for suboptimal treatment response—early, i.e., within the first 3 months of treatment, and late, i.e., after at least 3 months of treatment.

> ➤ Early- the presence of at least 2 of the following:
>   - Failure to gain an average of 5 g /kg body weight per day, and 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: 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.

Study Procedures/Safety Considerations & Monitoring

Study LAL-CL03 consists of a screening period of up to 3 weeks, an open-label treatment period of up to 4 years, and a follow-up visit at least 30 days after the last dose of sebelipase alfa administered in the trial.

The scheduled of planned LAL-CL03 study procedures are shown in Table 5 (from screening to Study Week 16) and Table 6 (from Study Week 17 until study completion).

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Table 5: Schedule of Assessments for Study LAL-CL03 (Screening to Week 16)

Assessments	Screening Day -21 to Day -1	W 0	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16
											± 2 days at each visit							
Informed Consent	X																	
Inclusion/ Exclusion	X	X																
Medical/ Family History	X																	
Physical Exam [b]	X				X					X							X	
Anthropometrics [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	If clinically indicated																
Denver II	X																	
Abdominal Ultrasound		X												X				
Abdominal MRI [e]	X															X		
Clinical Lab Tests [f, g]	X	X^{Pre}	X^{Pre}	X^{Pre}	X^{Pre}	X^{Pre}		X^{Pre}		X^{Pre}		X^{Pre}		X^{Pre}				X^{Pre}
Exploratory Biomarkers [g]	X			X						X				X				X
DNA Sample (subject) [g, h]	X																	
DNA Sample (parents)	X																	
PK Sample [g, i]		X																
PBMC LAL Activity [g]	X																	
DBS LAL Activity [g]	X																	
Sebelipase alfa Infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-drug Antibody [g]	X			X						X				X				X
Adverse Events	CONTINUOUS																	
Concomitant Therapies	CONTINUOUS																	

(Source: Applicant's Table 1 entitled "Schedule of Assessments for Study LAL-CL03 (Screening to Week 16)", LAL-CL03 Clinical Study Report, page 52-53/223, BLA 125561, Module 5.3.5.2)

Table 6: Schedule of Assessments for Study LAL-CL03 (Week 17 to Study Completion)

Assessments	Treatment Phase [a]								Repeating Assessments Relative to Week 24						Follow-up / Early With- drawal [f]
	W 17	W 18	W 19	W 20	W 21	W 22	W 23	W 24	Every Week	Every Month	Every 2 Months (8 weeks)	Every 3 Months (12 weeks)	Every 6 Months (24 weeks)	Annually (48 weeks)	
	± 2 days at each visit								± 2 days	± 2 days	± 5 days	± 5 days	±15 days	±15 days	
Physical Exam [a]				X				X				X			X
Anthropometrics				X				X		X [g]		X [g]			X
Vital Signs [b]	X	X	X	X	X	X	X	X	X						
12-lead ECG	If clinically indicated								If clinically indicated						
Denver II								X						X	X
Abdominal Ultrasound								X						X	
Abdominal MRI								X [h]						X [h]	
Liver Biopsy (optional)														X [l]	
Clinical Laboratory Assessments [c, d]				X [Pre]				X [Pre]			X [Pre, i]	X [Pre, i]			X
Exploratory Biomarkers [c]								X					X		X
PK Sample [c, e]						X								X [j]	
Sebelipase alfa Infusion [k]	X	X	X	X	X	X	X	X	X						
Anti-drug Antibody [c]				X				X					X		X
Adverse Events	CONTINUOUS														
Concomitant Medications/ Therapies	CONTINUOUS														

(Source: Applicant's Table 2 entitled "Schedule of Assessments for Study LAL-CL03 (Week 17 to Study Completion or Early Withdrawal)", LAL-CL03 Clinical Study Report, page 54-55/223, BLA 125561, Module 5.3.5.2)

Study Endpoints

➢ Primary endpoint: proportion of subjects surviving to 12 months
➢ Secondary endpoints:

- Proportion of subjects surviving to 18, 24, 30, and 36 months of age
- Anthropometrics:
- Z-scores and percentiles, calculated based on age-gender normative data from the WHO (<2 years old) or CDC (≥2 years old) [38]
- Weight-for-age (WFA)
- Length-for-age (LFA)
- Weight-for-length (WFL)
- Mid-upper arm circumference-for-age (MUACFA)
- Head circumference-for-age (HCFA)
- Body mass index-for-age (BMIFA)
- Percentages of subjects meeting criteria for the following dichotomous indicators of under nutrition [39]
- Underweight (defined as < -2 SD from the median for WFA)
- Wasting (defined as < -2 SD from the median for WFL)
- Stunting (defined as < -2 SD from the median for LFA)

- Liver Parameters: aspartate aminotransferase (AST), ALT, alkaline phosphatase, GGT, bilirubin (total, direct, indirect)
- Proportion of subjects achieving transfusion-free hemoglobin normalization (TFHN)
- Short term: ≥ 4 weeks at any time during the study
- Sustained early: for ≥ 13 weeks beginning at Week 6
- Exploratory endpoints:
  - Lipids: total cholesterol, triglycerides HDL, low density lipoprotein (LDL),
  - Change in other laboratory parameters: albumin, platelet counts, serum ferritin,
  - Liver and spleen volumes by abdominal imaging
  - Developmental analysis using Denver II

Planned Methods of Analysis

The Applicant specified the following analysis datasets:

- Primary efficacy set (PES)
- Per protocol set (PPS)
- Pharmacokinetic (PK) Set
- Full analysis set (FAS), previously called the 'Safety Set'

Due to the very small sample size, this reviewer did not use these defined datasets to analyze or discuss LAL-CL03 clinical trial data. Instead, descriptions of the patient subgroup (e.g., entire study population, surviving patients) are specified for individual analyses.

Primary Endpoint Analyses

The proportion of subjects surviving to 12 months of age exact 95% CI was calculated (Clopper-Pearson), and Kaplan-Meier survival curves were generated. These analyses were also performed for the historical control group from the natural history study, LAL-1-NH01.

Protocol Amendments

Ten protocol amendments were issued for Study LAL-CL03. Amendments to growth failure criteria are summarized in Table 4. The following is a summary of the major changes implemented in each protocol amendment.

- Amendment 1 (February 9, 2011, global amendment)- changed the system for AE severity grading to NCI CTCAE based on a regulatory request) and added individual patient discontinuation and study stopping criteria
- Amendment 2 (April 19, 2011, France only)
  - Clarified the first criterion in the definition of growth failure (Table 4)
  - Excluded patients >24 months of age from clinical trial participation
- Amendment 3 (May 20, 2011, global)-
  - Incorporated changes from the previous country-specific amendment (2) with further clarification of the first criterion in the definition of growth failure (Table 4)

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- Allowed a screening period of <7 days
- Allowed the dose (mg) of sebelipase alfa to be determined based on a subject's last available weight measurement if weight could not be obtained on the day of the infusion due to the subject's condition
- Amended the definition of extreme prematurity from < 32 weeks gestational age at birth to < 36 weeks gestational age at birth.

➢ Amendment 4 (June 2, 2011, France only)- modified exclusion criteria, upon regulatory request (French Agency for the Safety of Health Products [AFSSAPs]), to exclude subjects with severe under-nutrition.

➢ Amendment 5 (September 20, 2011, global)- clarified safety reporting guidelines to comply with local regulations, updated nonclinical and clinical information for sebelipase alfa

➢ Amendment 6 (April 5, 2012, global)-

- Merged Study LAL-CL03 with its extension study, LAL-CL05, under a single protocol
- Incorporated country-specific changes from Amendment 4
- Extended the treatment period from 16 weeks to a maximum of 3 years
- Allowed patients to be transferred to a local medical center for long-term treatment if pre-specified criteria were met
- Increased planned enrollment to approximately 10 subjects
- Specified enrollment of a minimum of 8 subjects who were ≤ 8 months of age on the date of their first infusion of sebelipase alfa
- Clarified that subjects qualifying for the PES who received fewer than 4 infusions could be replaced
- Increased the number of planned study centers
- Modified study eligibility criteria:
- Removed exclusion criteria pertaining to prematurity and life expectancy <2 weeks
- Expanded exclusion criteria to prohibit specific clinical conditions that might be present which could potentially interfere with the conduct or interpretation of the study
- Allowed enrollment of patients with prior exposure to sebelipase alfa
- Clarified definition of growth failure (Table 4)
- Modified sebelipase alfa dosing to implement one dosing scheme for all patients, allowed dose reductions in the event of poor tolerability and in patients who were clinically stable after at least 18 months of treatment at a dose of 3 mg/kg once weekly
- Added a definition of suboptimal treatment response to support dose escalation decisions from 1 mg/kg weekly to 3 mg/kg weekly
- Modified study objectives and endpoints
- Added survival to 12 months of age as a primary objective, and the proportion of subjects surviving to 12 months of age as a primary endpoint
- Moved safety and tolerability to a secondary objective/endpoint
- Modified safety endpoints to include an evaluation of vital signs relative to pre-infusion values
- Added evaluation for ADA and exploratory analysis of the impact of ADAs on efficacy, safety, and PK endpoints

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- Added secondary endpoints for anthropometric, laboratory, radiologic, dietary, development, and limited PK assessments
- Updated statistical methods based on changes to study objectives/endpoints; added 3 analysis data sets (PES, PPS, and PK sets)
- Updated planned anthropometric analyses to specify use of WHO growth charts and add analysis of dichotomous indications of under-nutrition
- Updated study assessments to specify procedures related to the changes in study endpoints

➤ Amendment 7 (October 23, 2012, global)-

- Added the option for an every-other-week dosing schedule for patients who have received least 96 weeks of treatment and have been on a stable dose for at least 24 weeks
- Modified the definition of suboptimal response to distinguish between early (within the first 3 months of treatment) and late (after 3 months of treatment) suboptimal response and added criteria for late suboptimal response
- Added ADA and serum tryptase testing in patients who experience a moderate or severe infusion-associated reaction
- Clarified that continuation of hospitalization in patients already hospitalized at the start of the study due to severity of disease would not be considered a serious adverse event (SAE)

➤ Amendment 8 (February 5, 2013, global)- added exception to eligibility criteria to allow enrollment of a patient who had not yet met the criteria for growth failure if (a) the investigator has substantial clinical concerns based on evidence of the rapid disease progression requiring urgent medical intervention and (b) the subject had an older (biological) sibling who had a documented rapidly progressive course of LAL deficiency with growth failure before 6 months of age (added as a footnote to the growth failure inclusion criterion); Investigators required to obtain approval for enrollment of such patients

➤ Amendment 9 (March 19, 2013, global)- modified the language in Amendment 8 to remove the requirement that the patient have an older (biological) sibling who had a documented rapidly progressive course of LAL deficiency with growth failure before 6 months of age

➤ Amendment 10 (January 24, 2014, global)-

- Extended the treatment period for each patient up to maximum of 4 years
- Refined the definition of suboptimal treatment response
- Added optional dose increase up to 5 mg/kg weekly in patients with continued suboptimal treatment response after at least 4 infusions at a dose of 3 mg/kg in association with the presence of neutralizing ADA
- Modified study procedures to add annual MRIs, monthly weights after Week 24, and an optional liver biopsy

5.3.2 LAL-1-NH01

Title

A retrospective natural history study of patients with lysosomal acid lipase deficiency/ Wolman phenotype

Study Objectives

➢ To characterize patient survival and key aspects of the clinical course of LAL Deficiency/Wolman phenotype

➢ To serve as a historical reference for efficacy studies of enzyme replacement therapy (ERT) in patients with LAL Deficiency/Wolman phenotype

Study Design

This was a multinational, multicenter, retrospective natural history study of patients diagnosed with LAL Deficiency presenting in infancy. All data were extracted from patients' medical records. No clinic visits or prospective assessments were performed as part of this study.

Study Population

Patients with a confirmed diagnosis of LAL deficiency prior to 2 years of age with available data meeting the minimum requirement (see below) were eligible for inclusion in this retrospective natural history study patients. A feasibility questionnaire was sent to approximately 500 physicians globally in 44 countries located in North America, Latin America, Europe, Asia, and Australia. The final sites selected for this study were those in which the Investigator was a physician involved in the care and treatment of infants with LAL deficiency and were willing to participate in the study.

The minimum data required for inclusion were:
- Date of birth
- Sex
- Date of death (approximate date acceptable)
- Birth weight
- At least one additional weight measurement obtained at least 4 weeks after birth and prior to any hematopoietic stem cell therapy (HSCT)/pre-conditioning or ERT for LAL deficiency
- Test results, date (approximate date acceptable), and name of testing center for LAL enzyme and/or *LIPA* gene mutation analysis confirming the diagnosis of LAL deficiency(only 1 required)
- Date of initiation of HSCT or pre-conditioning for HSCT, if applicable
- Date at initiation of ERT, if applicable

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A subgroup of patients with "early growth failure" was identified using criteria similar to those applied to patients in Study LAL-CL03. To be designated as having "early growth failure", a patient met at least of the following criteria within the first 6 months of life:

➢ Body weight decreased across at least 2 of the 11 major centiles (1, 3, 5, 10, 25, 50, 75, 90, 95, 97 and 99) on a standard WHO weight-for-age (WFA) chart;

➢ Body weight in kilograms was below the 10th centile on a standard WHO WFA chart, with no weight gain in the prior 2 weeks;

➢ Loss of at least 5% of birth weight in a patient older than 2 weeks of age

This definition of early growth failure is consistent with the criteria used in LAL-CL03.

Study Procedures

A retrospective chart review was performed to extract the following information:

(The Applicant notes in the Clinical Study Report that extensive investigation was often not performed in these infants due to the nature of the clinical presentation and lack of available therapies.)

- Demographics
- Clinical history, including symptoms of LAL deficiency, birth weight, gestation age at birth, nutritional data
- Family history, including history of siblings with LAL deficiency, oligohydramnios, still births
- Anthropometric data
- Physical examination findings
- Diagnostic testing
- Clinical chemistry and hematology results
- Histopathology results
- Radiology results
- Virology test results
- Supportive interventions
- Treatments with curative intent (i.e., HSCT, liver transplantation, ERT)
- Autopsy results

The following information was also recorded:
- Duration of chart record
- Date of onset of symptoms
- Date of diagnosis
- Date of treatments with curative intent
- Date of death

For the complete list of assessments for Study LAL-1-NH01 (i.e., data elements for extraction from medical records), see Table 24 in Appendix 9.5.

Planned Methods for Analysis

The planned methods for analysis for LAL-1-NH01 were similar to those for the clinical trial LAL-CL01.

➢ Survival analyses included time to death (in days) [calculated as (date of death) – (date of birth) + 1], time in months (computed by dividing time to death in days by 30.4), and Kaplan-Meier survival curves. Estimates of the median (with exact 95% CI) and lower and upper quartiles of time to death were derived and plotted.

➢ Continuous parameters were summarized as the number of patients with non-missing values (n), mean, standard deviation (SD), minimum, first quartile (Q1), median, third quartile (Q3), and/or maximum observed values.

➢ Categorical parameters were summarized as frequencies (i.e., number and percentage of patients in each category) and/or using shift tables.

- For aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), total bilirubin, TC, LDL, TG, ferritin, prothrombin time (PT), and partial thromboplastin time (PTT), shift tables used categories of (1) > 3x upper limit of normal (ULN), (2) > 2 to 3xULN, (3) > ULN to 2xULN, (4) within the normal limits (WNL), and (4) below the lower limit of normal (LLN).

- For hemoglobin, hematocrit, albumin, platelets, HDL, and total protein, categories of (1) > ULN, WNL, (2) < LLN to 75% LLN, (3) < 75% to 50% LLN, and (4) < 50% LLN were used

  Laboratory values were categorized relative to the normal range provided by the testing laboratory. In cases where a normal range was not available, published normal ranges were used for AST and ALT [37]; for other laboratory parameters, a category was not defined.

➢ For anthropometric data:

- WFA, LFA/HFA, HCFA, WFL/WFH, and BMIFA were standardized to Z-scores according to age-gender normative data gathered by the World Health Organization (WHO) [38] and summarized as continuous data

- Percentiles were also computed from the z-scores

- Anthropometric data were also represented according to the number and percentage of patients meeting criteria for the dichotomous indicators of under-nutrition (underweight, wasting, and stunting) [39]

Protocol Amendments

➢ <u>Amendment 1</u> (November 9, 2010)- expanded enrollment to include patients who had undergone HSCT/preparation for HSCT

➢ <u>Amendment 2</u> (September 7, 2011)- expanded enrollment to including both living and deceased patients and established an upper age limit of 2 years at diagnosis (to avoid enrolling patients with the CESD phenotype)

➢ <u>Amendment 3</u> (March 23, 2011)- extended the study duration to increase enrollment

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5.3.3 LAL-CL02

To support the safety and efficacy of sebelipase alfa for treatment of patients with LAL deficiency, the Applicant also submitted data from a clinical trial conducted in patients with the CESD phenotype, Study LAL-CL02, entitled "a multicenter, randomized, placebo-controlled study of sebelipase alfa (SBC-102) in patients with lysosomal acid lipase deficiency." The results of this clinical trial have been reviewed in detail by Dr. Juli Tomaino (Clinical Review for BLA 125561, dated June 8, 2015). The following is a brief summary of Study LAL-CL02.

Study LAL-CL02 is a multi-center center clinical trial with a 20-week randomized, placebo-controlled, double-bind treatment period, followed by an open-label extension period of up to 130 weeks. Eligible patients (age ≥4 years old with LAL deficiency confirmed by DBS testing at screening, with ALT level ≥1.5 times the ULN and without severe hepatic dysfunction or history of HSCT or liver transplant) were randomized in a 1:1 ratio to receive sebelipase alfa 1 mg/kg or placebo intravenous (IV) infusion every other week during the 20-week double-blind period. After completing the double-blind period, all patients (sebelipase-treated and placebo controls) could begin the open-label treatment with sebelipase alfa at a dose of 1 mg/kg IV infusion every other week during the extension period. As compared to placebo, sebelipase-alfa treated patients demonstrated significant improvement in LDL cholesterol, as well as other lipid parameters and liver-related pharmacodynamic measures. For details, the reader is referred to the Clinical Review by Dr. Juli Tomaino, dated June 8, 2015.

6 Review of Efficacy

Efficacy Summary

The treatment benefit of sebelipase alfa in patients with early onset (<6 months of age), rapidly progressive LAL deficiency was demonstrated by significant improvement in patient survival at 12 months of age [6 of the 9 (66%) sebelipase alfa-treated patients in LAL-CL03; 95% CI: 29.93%, 92.51%], compared to a historical control group of patients with similar baseline characteristics with 0% survival at 12 months of age (95% CI: 0%, 16.11%). The 3 deaths in clinical trial patients prior to data cut-off all occurred within the first month of treatment in patients with a fulminant disease presentation and baseline multi-system organ dysfunction. At the time of data cut-off, the 6 surviving patients were between 12 and 42.2 months of age and had been treated with sebelipase alfa 6.2 to 38.0 months (median 14.67 months).

Growth failure is a predominant symptom and predictor of mortality in patients with early-onset rapidly progressive LAL deficiency. At baseline, evidence of growth failure was present in 8 of the 9 LAL-CL03 clinical trial patients (5 of the 6 of the surviving patients). During treatment with sebelipase alfa, weight-for-age (WFA) Z-scores [i.e., age- and sex-based standard deviation scores using World Health Organization (WHO) normative data] improved in all 5 patients with growth failure at baseline. Although improvements in other anthropometric parameters were observed and may be clinically meaningful, weight measurements were most consistently and reliably collected and therefore, used as the primary indicator of patient growth in this review.

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The Applicant provided data for numerous other disease-related clinical, laboratory, and radiologic assessments. However, several factors limited the ability to make generalizations regarding treatment-related effects on these outcome measures in this 9-patient clinical trial population, including heterogeneity in baseline disease-related abnormalities, high frequency of missing study assessments, variability in timing and procedures of assessments, and missing/inconsistent results reported from local facilities. Nevertheless, despite the lack of useful group data, many improvements in secondary and exploratory outcome variables can be attributed to the effects of sebelipase alfa treatment, based on the natural history of the disease and the magnitude of observed treatment effect. Examples of these improvements include improvement in anemia without need for packed red blood cell transfusions; marked reduction in organ size; improvement and/or normalization of serum albumin levels; improvement and maintenance of LDL and HDL levels, which may be necessary to achieve favorable long-term cardiovascular outcomes; and normalization in serum ferritin and LDH levels, along with improved serum triglyceride levels, which indicate resolution of HLH.

6.1   Indication

The Applicant proposes a treatment indication of "   (b) (4)
for patients with Lysosomal Acid Lipase (LAL) Deficiency" for sebelipase alfa. The intended patient population includes patients with both the CESD and Wolman disease (infantile-onset) phenotypes of LAL deficiency.

6.1.1   Methods

The efficacy of sebelipase alfa treatment in patients with early-onset (<6 months of age), rapidly progressive LAL deficiency was evaluated using data from Study LAL-CL03 (N=9). A historical control group with comparable baseline characteristics to the LAL-CL03 patient population was identified from patients in the natural history study, LAL-1-NH-01. Survival data for this cohort was used as a comparator for primary efficacy analyses (the primary efficacy endpoint). Due to the small clinical trial patient population (N=9) and early mortality in the historical cohort, only descriptive analyses could be performed for secondary and exploratory endpoints and were used primary for assessing overall treatment response to inform dosing of this patient population. For this reason, graphical patient profiles were generated to facilitate concurrent assessment of clinical variables, along with dose changes and immunogenicity data.

6.1.2   Demographics

LAL-CL03

The LAL-CL03 clinical trial population consisted of 9 patients with median age of 3.0 months (range 2.2 to 5.8 months) at the time of first sebelipase alfa infusion. Median age of symptoms onset was 1.5 months (range 0 to 5 months). Medical history for all patients included vomiting, diarrhea, abdominal distention hepatosplenomegaly, and adrenal calcification.

Eight of the 9 patients had evidence of growth failure within the first 6 months of life, which met the pre-specified criteria for enrollment in LAL-CL03 (Table 7). In 7 patients (78%), weight decreased across at least 2 of the major centiles on the WHO growth chart, and one patient had confirmed growth failure based on a body weight below the 10th centile with no weight gain for 2 weeks prior to screening. The one patient who did not meet criteria for early growth failure (b) (6)) was enrolled based on evidence of rapidly progressive disease requiring urgent medical intervention, under the enrollment exception implemented following Protocol Amendment 8 (Table 4). The Applicant cites the presence of abdominal distension, hepatosplenomegaly (liver and spleen 10 cm and 5 cm below costal margin, respectively), ascites, vomiting, diarrhea, and anemia among the signs and symptoms which qualified this patient for study participation. Demographics and baseline clinical data are summarized, along with data for the historical cohort, in Table 9. For the LAL-CL03 clinical trial patients, individual baseline data are shown in Table 10.

Table 7: Growth Failure Criteria for LAL-CL03 Study Eligibility

	All Subjects (N=9)
Growth Failure Criteria Met, n (%):	
Weight decreasing across at least 2 of the 11 major centiles	7 (78)
Body weight (kg) below the 10th centile and no weight gain for 2 weeks prior to screening	1 (11)
Loss of > 5% of birth weight in a subject > 2 weeks of age	0
Subject has rapidly progressive course of LAL Deficiency but does not meet growth failure criteria	1 (11)

(Source: Extracted from Applicant's Table 5 entitled "Baseline Anthropometric Characteristics and Growth Failure Status of Subjects Treated in Study LAL-CL03", LAL-CL03 Clinical Study Report page 98/233)

All patients had confirmed LAL Deficiency based on LAL enzyme activity measured in peripheral blood mononuclear cells (PBMC, n=6) and/or in a reconstituted dried blood spot (DBS) assayed at the central lab (n=5) or a local lab n=1. The 6 surviving patients also had *LIPA* mutation analyses. Distinct mutations were identified in each of the 6 subjects, and consistent with published data, none of the 6 tested patients had a copy of the previously described c.849G>A common exon 8 splice junction mutation, which is commonly associated with the CESD phenotype. [17] LAL enzyme activity LIPA mutation analysis test results are shown in Table 8.

Table 8: Confirmatory Diagnostic Test Results (LAL Enzyme Activity and *LIPA* Genotype) for LAL-CL03 Patients (N=9)

Subject ID (b)(6)	LAL Enzyme Activity		*LIPA* Genotype		
	PBMC* (µmol/g/hr)	DBS** (nmol/punch)	Allelic Mutations	Effect of Mutation	Variant Severity
69	*ND*	*ND*	*ND*	*NA*	*NA*
32	ND	c.398delC, HOM	Documented Causative	Pathogenic
41	0.004	c.884A>G, HET	Undocumented	VUS
5.1	ND	c.539-5C>T, HET; c.482delA, HET; c.538G>A, HET	Intronic; Documented Causative; Undocumented	Common variant; Pathogenic; VUS
ND	0.007	c.419G>C, HOM	Undocumented	VUS
57	0.007	c.676-2A>G, HOM	Documented Causative	Pathogenic
65	0.018	c.350_351insCC, HET; c.797G>T, HET	Undocumented; Undocumented	VUS; VUS
ND	*0.014*	*ND*	*NA*	*NA*
ND	*< 0.02*	*ND*	*NA*	*NA*

(Source: Applicant's Table 4, entitled "LAL Enzyme Activity and LIPA Genotype", LAL-CL03 Clinical Study Report page 95/233)

Abbreviations: DBS, reconstituted dried blood spot; HET, heterozygous (compound); HOM, homozygous; NA, not applicable; ND, not done; PBMC, peripheral blood mononuclear cells; VUS, variant of unknown significance

Italicized font indicates a patient who died prior to the data cut-off

* Normal range 350 to 2000 µmol/g/hr

** Affected range is 0 to 0.016 nmol/punch for all results (central laboratory) except the sample from Subject (b)(6) , which was a historical result from a local laboratory (affected range <0.02 nmol/punch)

LAL-1-NH-01

A retrospective, chart review was performed for 35 patients at 18 sites in the US, UK, Canada, Egypt, France, and Italy. Twenty-six (74%) patients were "untreated" (i.e., had not received therapy with curative intent), and 10 (24%) were "treated patients"—9 underwent hematopoietic stem cell transplantation (HSCT) and 1 was treated with both HSCT and liver transplantation. Diagnosis was confirmed by LAL enzyme activity (n=34) and/or by LIPA gene mutations (n=12). With the exception of 2 patients who were siblings, all study patients had unique mutations, and as discussed above, none of the patients for whom data were available had the 'common mutation' often observed in LAL Deficiency presenting in children and adults.

Twenty-one of the 26 untreated patients (81%) and 5 of the 10 treated patients (50%) met criteria for growth failure within the first 6 months of life. This subgroup of patients with early growth failure and were untreated (n=21) most closely resembled the LAL-CL03 patient population. (Table 9)

Table 9: Baseline Demographic and Disease Characteristics for Patients in LAL-CL03 (N=9), Compared to the Historical Control Group of Untreated Patients with Early Growth Failure in Study LAL-1-NH01 (N=21)

Parameter		LAL-CL-03 (N=9)	LAL-1-NH01* (N=21)
Sex (n,(%))	Male	5 (56)	10 (48)
	Female	4 (44)	11 (52)
Race (n,(%))	Asian	1 (11)	8 (38)

	White	4 (44)	6 (29)
	Black	1 (11)	0 (0)
	Other	0 (0)	4 (19)
	Unknown*	3 (33)	3 (14)
Ethnicity (n,(%))	Hispanic/Latino	0 (0)	1 (5)
	Non-Hispanic/Latino	6 (67)	16 (76)
	Unknown*	3 (33)	4 (19)
Age-symptom onset (months)	n	9	21
	Mean ± SD	1.5 ± 1.6	1.4 ± 1.1
	Median	1.6	1.1
	Range	(0.0, 5.0)	(0.0. 3.0)
Age-diagnosis (months)	n	9	21
	Mean ± SD	2.9 ± 2.0	2.8 ± 1.0
	Median	2.8	2.6
	Range	(0.0, 5.8)	(1.3, 5.0)
Age-1st Infusion (months)	n	9	
	Mean ± SD	3.4 ± 1.67	N/A
	Median	3.0	
	Range	(1.1, 5.8)	
Birth weight† (Z-score)	n	9	21
	Mean ± SD	0.27 ± 1.15	-0.12 ± 0.93
	Median	0.89	-0.10
	Range	(-2.28, 1.10)	(-3.00, 1.30)
Baseline weight‡ Z-score	n	8	20
	Mean ± SD	-1.63 ± 1.73	-2.1 ± 1.7
	Mean	-1.76	-2.6
	Range	(-4.79, 0.74)	(-4.2, 1.9)
Dichotomous growth indicators at baseline‡ (n,(%))	Underweight	2 (22)	13 (62)
	Wasting	2 (22)	0 (0)
	Stunting	4 (44)	2 (10)
	Missing weight	*1*	*1*
	Missing length	*1*	*16*
ALT (n,(%))	Normal	2 (22)	7 (33)
	1-2 times normal	2 (22)	3 (14)
	2-3 times normal	0 (0)	5 (24)
	>3 times normal	5 (56)	2 (10)
	Missing	*0 (0)*	*3 (33)*
AST (n,(%))	Normal	0 (0)	2 (10)
	1-2 times normal	4 (44)	2 (10)
	2-3 times normal	1 (11)	1 (4)
	>3 times normal	4 (44)	10 (48)
	Missing	*0 (0)*	*6 (29)*
Triglycerides (mg/dL)	n	5	9
	mean ± SD	143.2 ± 77.8	217.0 ± 127.2
	median	163.9	175.4
	range	(31.0, 218.2)	(115.4, 504.8)
Total cholesterol (mg/dL)	n	5	9
	mean ± SD	136.6 ± 63.7	109.7 ± 29.6

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	median	139.2	103.2
	range	(67.1, 225.3)	(59.6, 156.2)
LDL (mg/dL)	n	5	2
	mean ± SD	97.2 ± 10.5	N/A
	median	109.4	N/A
	range	(18.8, 194.3)	(10.8, 42.9)
HDL (mg/dL)	n	5	5
	mean ± SD	6.7 ± 4.4	19.3 ± 12.0
	median	8.9	13.9
	range	(0.0, 10.1)	(1.16, 29.0)

(Source: Reviewer's table created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein; N/A, not applicable
* For the 3 patients enrolled at sites in France, Race and ethnicity were not reported by the site, in compliance with local regulations.)

Table 10: Individual Patient Demographic and Baseline Disease Characteristics (N=9)

(b) (6)

Sex									
Race									
Family History=	*Yes*	No	No	No	Yes	Yes	No	*No*	*No*
Age (months)									
Symptom onset	*1.9*	0.5	5.0	1.0	0	0	0.5	*1.5*	*3.0*
Diagnosis	*2.6*	2.8	5.8	3.4	0	0.3	5.5	*2.4*	*3.3*
1st infusion	*2.63*	2.99	5.78	4.24	1.08	1.64	5.82	*2.73*	*3.45*
Body weight (Z-score)									
Birth Weight	0.10	-2.28	1.04	1.02	-0.84	0.35	1.10	*0.89*	*1.08*
Baseline WFA	ND	-4.79	0.74	-1.98	-1.74	-1.78	-2.70	*0.38*	*-1.20*
Baseline Laboratory Studies									
Triglycerides (mg/dL)	*ND*	203.7(H)	ND	163.9(H)	ND	99.2	218.0(H)	*31.0*	*481.0(H)*
Cholesterol (mg/dL)	*ND*	85.1	ND	166.3	ND	139.2	225.3(H)	*67.1(L)*	*163.2*
LDL (mg/dL)	*ND*	38.7	ND	124.5	ND	109.4	194.3(H)	*18.8(L)*	*ND*
HDL (mg/dL)	*ND*	4.6(L)	ND	10.1(L)	ND	8.9(L)	0(L)	*10.0(L)*	*ND*
ALT (units/L)	*145 (H)*	16	35	68(H)	50(H)*	149(H)	297(H)	*185(H)*	*226(H)*
AST (units/L)	*360 (H)*	75(H)	94(H)	125(H)	71(H)	94(H)	547(H)	*562(H)*	*716(H)*
AST:ALT*	**2.5**	**4.7**	**2.7**	**1.8**	**1.4**	**0.6**	**1.8**	**3.0**	**3.2**
Ferritin (µg/L)	*2107(H)*	586(H)	316(H‡)	253	ND	302(H‡)	11812(H)	*ND*	*48740(H)*
LDH	*670(H)*	835(H)	564(H)	ND	461(H)	435(H)	1889(H)	*346(H)*	*ND*

(units/L)									
Albumin (g/dL)	2.9	1.9(L)	2.3(L)	3.2	3.4	3.4	1.8(L)	1.9(L)	4.0
Alk. Phos (units/L)	121	186	94	204	183	350(H)	977(H)	96	272
GGT (units/L)	40	18	14	129(H)	47(H)	150(H)	1000(H)	46	ND
Bilirubin,Total (mg/dL)	27.1(H)	0.3	0.2	0.6	0.4	ND	2.9(H)	3.8(H)	25.9(H)
Hemoglobin (g/dL)	9.3(L)[#]	7.7(L)	7.2(L)	9.4(L)	9.3[‡]	9.5[‡]	7.4(L)	1.4(L) [#,†]	10.3[#]
Platelets (10^3/mm^3)	39(L)	173	444	227	257	563(H)	54(L)	3(L) [#,†]	81(L)
PTT (sec)	65.2(H)	36.9(H)	25	10.2	10.3	22	25.4	45.5(H)	57.5(H)
PT (sec)	31.7(H)	17.3(H)	12.1	11.1	10.2	10.2	11.7(H)	19.6(H)	20.1(H)

(Source: Reviewer's own table created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

Abbreviations: ALT, alanine aminotransferase; Alk Phos, alkaline phosphatase; AST, aspartate aminotransferase; F, female; GGT, gamma glutamyltransferase; H, high; HDL, high density lipoprotein; L, low; LDH, lactate dehydrogenase; LDL, low density lipoprotein; M, male; ND, not done; Unk., unknown; WFA, weight-for-age

Italicized font indicates sebelipase alfa-treated patients (received ≥1 dose) who prior to data cut-off

* The disproportionate elevation in AST levels compared to ALT levels suggests other etiologies other than liver injury, such as hematologic and/or bone marrow disease.

[#] indicate patient receiving frequent or continuous transfusions with blood product which invalidate these data

[‡] Normal values are defined by the reference ranges provided by individual local laboratories. Therefore, classification is inconsistent. For Subject (b) (6) (age (b) (6) months), hemoglobin level of 9.4 g/dL was reported as low, while hemoglobin levels of 9.3 and 9.5g/dL were reported as normal in Subjects (b) (6) and (b) (6), ages (b) (6) and (b) (6) months, respectively.

[†] Baseline complete blood count results for Subject (b) (6) were considered to be erroneous. Screening values for this patient were considered more reliable—hemoglobin was 8.6 g/dL and platelets were 63.4 x10^3 /mm^3 Regardless, this patient was receiving frequent blood product transfusions; therefore these values are not clinically meaningful

LAL deficiency: (1) Subject (b) (6) had a sibling (sex not specified) who was diagnosed with LAL deficiency and died at 3 months of age; (2) Subject (b) (6) had a brother diagnosed with LAL deficiency at 1.5 months of age d and died at 5.5 months of age; and (3) Subject (b) (6) who had a sister diagnosed with LAL deficiency at 2.5 months of age and died at 4 months of age.

Clinical Review
Lauren Weintraub, MD
BLA 125561
Kanuma (sebelipase alfa)

6.1.3   Subject Disposition

LAL-CL03

Patient disposition for the LAL-CL03 study population is shown in Figure 1.

Figure 1: Disposition for Patients in LAL-CL03
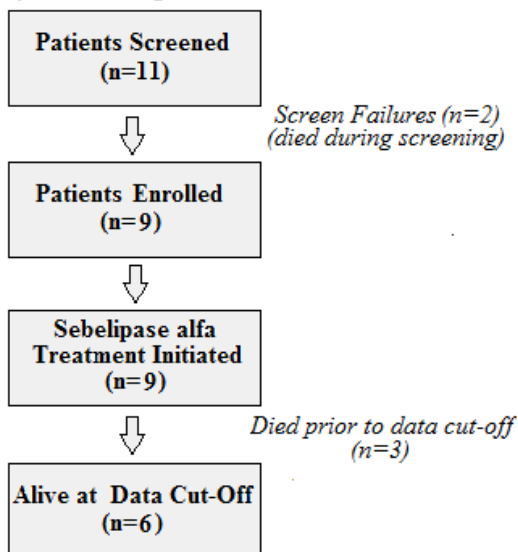
(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

The LAL-CL03 clinical trial population (n=9) were enrolled from May 2011 through December 2013. During this time, the Applicant filed 10 protocol amendments to the LAL-CL03 study protocol, of which 5 included adjustments to eligibility criteria. Protocol Amendments are summarized in Section 5.3.1.

Table 11: Enrollment in LAL-CL03 by Protocol Amendment

Amendment	Patient(s)	n (%)
1	(b) (6)	1 (11)
3		1 (11)
6		2 (22)
7		2 (22)
9		3 (33)

(Source: Reviewer's table created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

* Although enrollment of Subject (b) (6) in LAL-CL03 occurred after Amendment 6 went into effect, (b)(6) was the first patient treated with sebelipase alfa, initiating treatment under an expanded access protocol. Because the patient would have met study eligibility criteria, (b)(6) was later enrolled in LAL-CL03 after Amendment 6 permitted enrollment of patients with prior history of sebelipase alfa treatment.

Eight patients were enrolled directly into Study LAL-CL03, while one patient in France (Subject (b) (6)) initially received emergency treatment with sebelipase alfa under an expanded access protocol (Autorisation Temporaire d'Utilisation, ATU). At Week 40 of treatment, this patient

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enrolled in an extension trial intended to provide ongoing treatment with sebelipase alfa treatment to patients with early-onset, rapidly progressive LAL deficiency (LAL-CL05). At Week 85 of treatment, (b)(6) transitioned into Study LAL-CL03 following Amendment 6 which merged LAL-CL-05 and LAL-CL03 into a single trial and changed eligibility criteria to allow enrollment of patients in LAL-CL03 with prior history of sebelipase alfa treatment. The Applicant states that this patient would have met enrollment criteria for LAL-CL03; however, (b)(6) was started emergently on treatment prior to the initiation of clinical trials, and was, thus, the first ever patient treated with sebelipase alfa.

Three of the 9 patients died prior to data cut-off. Because the primary efficacy endpoint of this clinical trial is survival, these data are reviewed in detail in Section 6.1.4 (Analysis of Primary Endpoint). No patient discontinued study participation for reasons other than death.

LAL-1-NH01

The identification of patients eligible for the natural history study, LAL-1-NH01 and the subset of patients for use as a historical comparator group for LAL-CL03 are shown in Figure 2.

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Figure 2: LAL-1-NH-01 Recruitment, Enrollment, and Patient Disposition
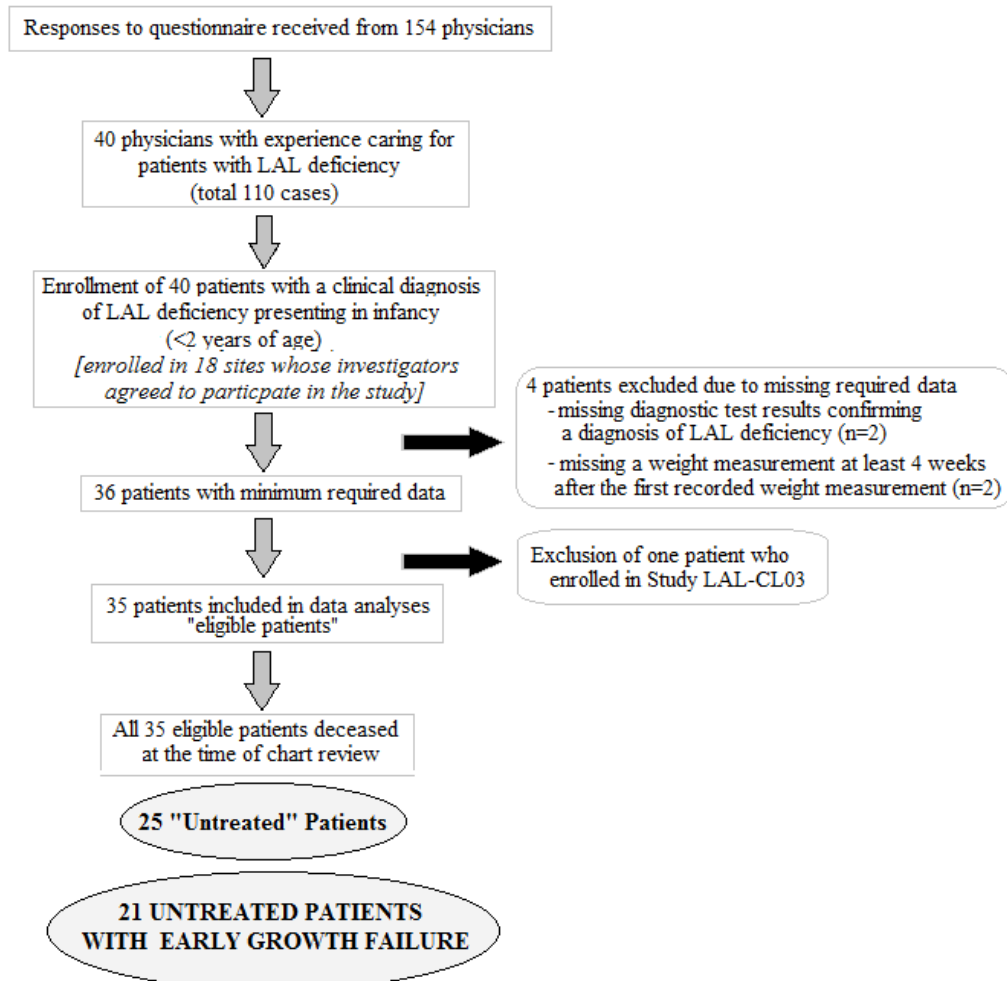
(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

Over 500 questionnaires were sent to physicians in Of the 154 physicians responding to the questionnaire, 40 physicians indicated that they had cared for patients with LAL Deficiency presenting in infancy (for a total of 110 cases) and were considered for participation in the study. Final sites were selected on the basis of each physician's willingness to participate in the study.

All patients in LAL-1-NH-01 (N=35) were diagnosed after January 1, 1985, and all patients included in LAL-1-NH01 were deceased at the time the study was conducted. Median age at the time of death for all eligible patients (n=35) was 3.7 months (range 1.4 to 46.3 months). One living patient met study eligibility criteria but was excluded because the patient enrolled in LAL-CL03. For the 21 patients in the subgroup identified as the historical comparator group for LAL-CL03 (patients who met criteria for a diagnosis of early growth failure and had not received treatment with curative intent), the median age of death was 3.0 months (range 1.4 to 7.1 months).

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6.1.4   Analysis of Primary Endpoint(s)

Survival at 12 Months of Age

The proportion (exact 95% CI) of patients in LAL-CL03 surviving to 12 months of age was 67% (29.93%, 92.51%) using Clopper-Pearson methodology; i.e., 6 of the 9 patients. At the time of data cutoff, the median age of the 6 surviving patients was 18.1 months (range 12 to 42.2 months).

A historical control group of untreated patients with LAL deficiency presenting with early growth failure was identified by a natural history retrospective chart review (Study LAL-1-NH01) conducted by the Applicant. Of the 21 patients in this historical cohort, the proportion (exact 95% CI) of patients surviving to 12 months of age was 0% (0%, 16.11%). All patients died before 8 months of age (median 3.5 months of age). Survival Plots (from birth to 12 months of age) for the sebelipase alfa-treated patients in LAL-CL03 (N=9) and the historical control group (N=21) are shown in Figure 3.

Figure 3: Kaplan-Meier Plot of Survival from Birth to 12 Months of Age for Sebelipase alfa-Treated Subjects (LAL-CL03, N=9) vs. a Historical Cohort of Untreated Patients with Early Growth Failure (LAL-1-NH01, N=21)
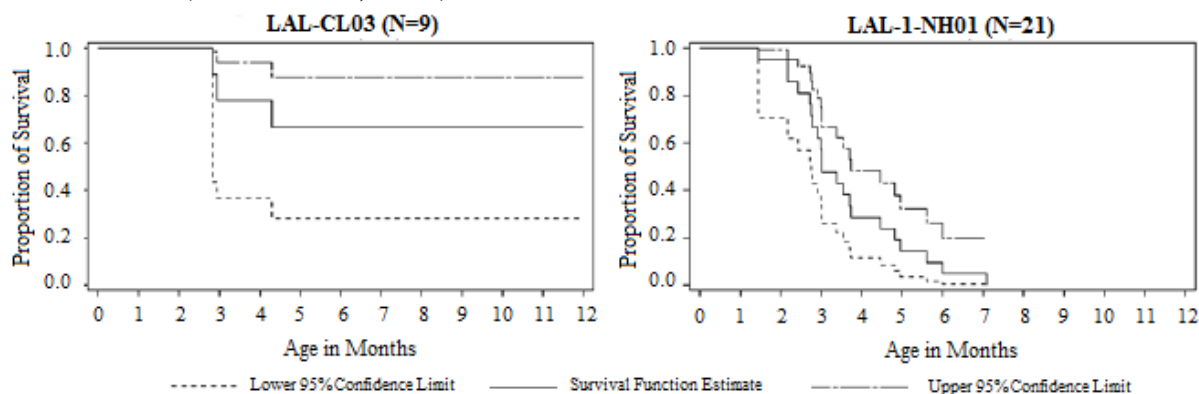
(Source: Applicant's Figure 3, entitled "Kaplan-Meier Plot of Survival from Birth to 12 Months of Age for Sebelipase alfa-Treated Subjects in LAL-CL03 (PES) vs. Untreated Patients in LAL-1-NH01 (Patients with Early Growth Failure Only)", LAL-CL03 Clinical Study Report, page 111/233, BLA 125561, Module 5.3.5.2)

Despite the small size of the LAL-CL03 patient population, the survival advantage among the sebelipase-alfa treated patients, compared to the control group, is statistically significant. In the Kaplan-Meier survival analysis, hazard ratio (95% CI) for the LAL-CL03 patient population was 0.141 (0.040, 0.496). (Figure 4) This statistical methodology is considered to be more appropriate for comparison of balanced concurrent cohorts. However, the non-overlapping confidence intervals of Clopper-Pearson analyses [67% (29.93%, 92.51%) vs. 0% (0%, 16.11%)] also demonstrate statistical significance of primary endpoint analyses.

Figure 4: Kaplan-Meier survival analysis from birth up to Month 12 [sebelipase alfa-treated patients in LAL-CL03 (N=9) vs. historical control patients in LAL-1-NH01 (N=21)]
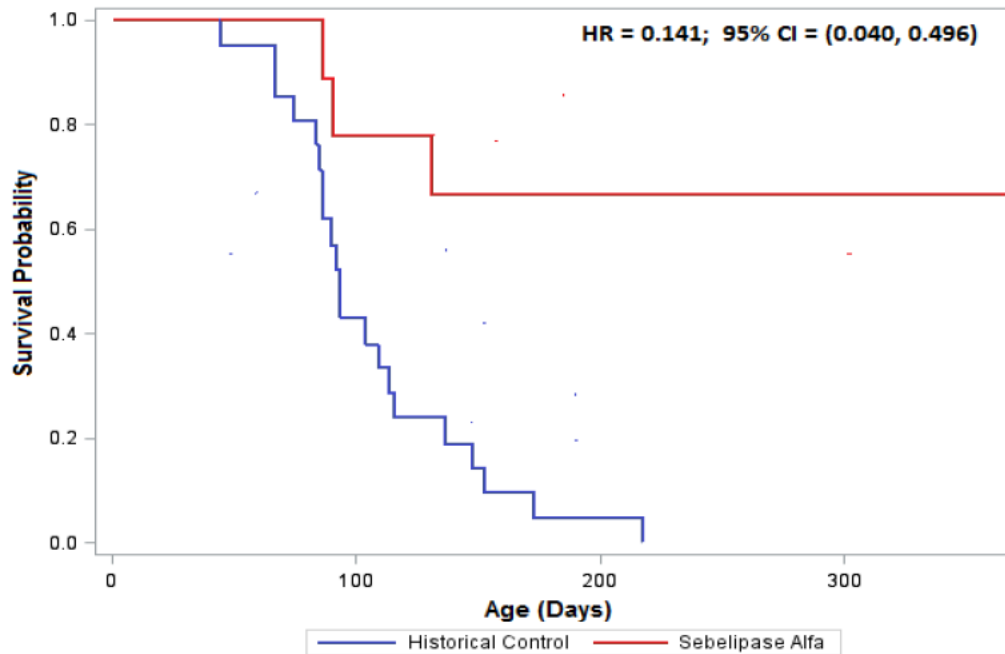
(Source: Kaplan-Meier Plot of Survival from provided by the Biometrics Reviewer, Dr. Benjamin Vali, generated from LAL-CL03 ADSL dataset and LAL-1-NH01 ADSL dataset)

At the time of data cut-off, the median age of the 6 surviving patients was 18.0 months (range 12.0 to 42.2 months), and patients had been receiving sebelipase alfa treatment for median 14.5 months (range 6.2 to 38.0 months).

Table 12: Age at Symptom Onset and Diagnosis of Patients in LAL-CL03 (N=9)

	Age (months) at Onset of LAL Deficiency Symptoms *	Age (months) at Diagnosis
(b) (6)	1.9 *	2.6
	0.5	2.8
	5.0	5.8
	1.5	3.4
	0 *	0
	0 *	0.3
	0.5	5.5
	1.5	2.4
	3.0	3.3

(Source: Applicant's Table 7 entitled "Age at Symptom Onset and Diagnosis of Subjects Treated in Study LAL-CL03", LAL-CL03 Clinical Study Report, page 103/233)
* Indicates patient with sibling previously diagnosed with LAL deficiency

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Table 13: Age at Death for Patients in the Natural History Study (LAL-1-NH01, N=35)

	Patients with Early Growth Failure		All Eligible Patients		
	Untreated N=21	All N=26	Untreated N=25	Treated N=10	All N=35
Mean (SD)	3.61 (1.413)	5.32 (6.799)	4.25 (3.435)	15.43 (15.615)	7.45 (9.957)
Median	3.02	3.46	3.02	8.57	3.71
Q1, Q3	2.76, 4.47	2.76, 5.15	2.76, 4.83	5.15, 26.92	2.79, 6.73
Min, Max	1.44, 7.09	1.44, 37.29	1.44, 19.34	2.56, 46.32	1.44, 46.32

(Source: Adapted from Applicant's Table (un-numbered, in Synopsis) entitled "Summary Statistics for Age at Death", LAL-1-NH01 Clinical Study Report page 10/126, BLA 125561, Module 5.3.5.4)

The 3 deaths in the primary endpoint analysis for LAL-CL03 all occurred within the first month of treatment. At the time of clinical trial enrollment, all 3 of these patients (Subjects (b) (6)) exhibited fulminant symptoms of LAL deficiency with a hemophagocytic lymphohistiocytosis-like syndrome.[25.26] In all patients who died within the first month of treatment, cause of death was due to complications secondary to the patient's underlying disease. Case narratives for each of the patient deaths can be found in Section 7.3.1. No autopsies were performed for these patients.

Table 14: Patient Deaths in LAL-CL03 Prior to Data Cutoff (n=3)

Subject	Study Days of Infusion(s)	Number of Infusions Prior to Death	Dosing Regimen at Time of Death	Study Day of Death	Age at Death (months)	Cause of Death, as Reported by the Investigator
(b) (6)	1	1	0.35 mg/kg	6	2.79	Liver failure secondary to Wolman disease
	1	1	0.35 mg/kg	5	2.92	Massive intraperitoneal bleeding
	1, 6, 14, 20	4	1 mg/kg	26	4.27	Cardiac arrest

(Source: Applicant's Table 18 entitled "Listing of Deaths in Study LAL-CL03", LAL-CL03 Clinical Study Report, page 180/233, BLA 125561, Module 5.3.5.2)

One additional patient (Subject (b) (6) died approximately 3 months following the data cutoff date. Subject (b) (6) received the first infusion of sebelipase alfa at age 5.8 months, and died at age 15 months due to sudden cardiac death, after the primary efficacy analyses and after the data cut-off date for this BLA submission. In addition to LAL deficiency, this patient also had a diagnosis of Hemoglobin E disease. At the time of death, the patient was receiving weekly sebelipase alfa infusions at a dose of 3 mg/kg. On (b) (6)), the patient was found in full cardiac arrest in (b) (6) crib. The patient's last sebelipase treatment was administered 6 days prior to death. On autopsy, the patient was found to have substantial findings of LAL deficiency, including infiltration of lipid laden macrophages in the gastrointestinal tract, liver, and lungs; diffuse, massive lymphadenopathy; pulmonary congestion with subpleural fibrosis; and hepatic fibrosis with areas of bridging portal fibrosis with otherwise preserved liver parenchyma. The

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patient was also found to have a right atrial mural thrombus, mild left ventricular hypertrophy, and diffuse pulmonary edema. There was no evidence of pulmonary thrombosis, cerebral thromboembolism, or seizure activity. A case narrative and comprehensive summary of autopsy findings can be found in Section 7.3.1.

As of the time of this review, 5 of the 9 LAL-CL03 patients are alive and receiving ongoing sebelipase alfa treatment in LAL-CL03.

6.1.5 Analysis of Secondary Endpoints(s)

Growth

Weight-for-Age (WFA) Z-scores

At the time of enrollment, 8 of the 9 patients in LAL-CL03 (5 of the 6 surviving patients) met at least one of the pre-specified criteria for growth failure. (see Table 7) For the 6 surviving patients, weight-for-age (WFA) and length-for-age Z-scores (i.e., age- and sex-specific standard deviation scores) are shown in Figure 5. Compared to WFA data, greater inconsistency was observed among LFA data, likely because these measurements are more error-prone. In general, patients' LFA and WFA tracked together, and during LAL-CL03, WFA was the main anthropometric parameter cited as the basis for clinical decisions by LAL-CL03 study Investigators. Therefore, a separate review of LFA was not performed.

Following initiation of sebelipase alfa treatment per protocol at the initial maintenance dose of 1 mg/kg, WFA Z-scores improved in 3 of the 5 surviving patients who had evidence of growth failure at baseline (Subjects   (b) (6)). In the 3 patients who died prior to data cutoff, minimal growth data are available for the 2 patients who died during Study Week 1, and no improvement in growth parameters were observed in Subject   (b) (6) who died on Study Day 26 after 4 doses of sebelipase alfa.

During LAL-CL03, sebelipase alfa doses in all surviving patients were escalated from 1 mg/kg to 3 mg/kg once weekly due to suboptimal treatment response. (Dose changes are indicated by arrows in Figure 6) During treatment with sebelipase alfa 3 mg/kg weekly, all 6 surviving patients demonstrated improvements in WFA Z-score by data cut-off, regardless of baseline growth failure status or previous WFA Z-score improvement. In 5 of the 6 patients (all 5 patients with baseline growth failure), WFA Z-scores had improved by 12 months of age (the analysis timepoint for the primary endpoint), and all 6 patients had Z-scores within the normal range (Figure 5). Median baseline Z-score for the 6 surviving patients was -1.89 (range -4.79 to +0.74) and increased to median -0.63 (range -1.42 to +0.52) at 12 months of age. All 12-month WFA Z-scores were within the normal range (-2 to +2 SD). Median change in Z-score was +1.28 (range -0.22 to 3.37). The one patient with decreased WFA Z-score at 12 months was Subject   (b) (6), who did not have evidence of growth failure at baseline.

Figure 5: Weight-for-Age Z-Scores at Baseline and Age 12 months for the Surviving Patients in LAL-CL03 (N=6)
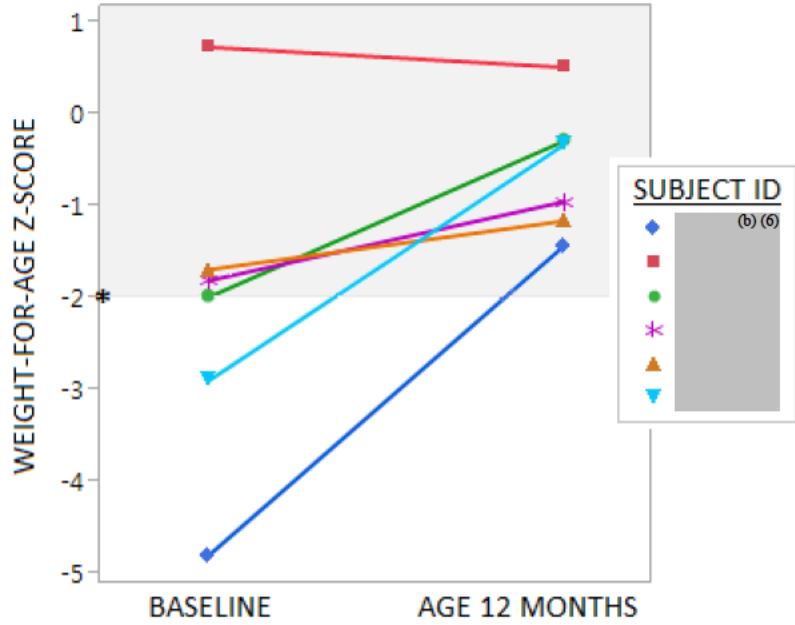
(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

* Z-scores (i.e., standard deviation scores between) -2 and +2 are considered to be within the normal range (shaded area)

Figure 6: Changes in Weight-for-Age (WFA) and Length-for-Age (LFA) Z-scores and Sebelipase Alfa Dose Changes in Surviving Patients with Early-Onset (<6 Months of Age), Rapidly Progressive LAL-Deficiency (Study LAL-CL03, N=6)

(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

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Dichotomous Anthropometric Indicators of Under-Nutrition

Growth status was also presented in terms of 3 dichotomous indicators of under-nutrition—underweight, wasting and stunting. For various study time points, the Applicant reported the prevalence of these anthropometric indicators mong LAL-CL03 patients, based on the following UNICEF 2009 definitions: [39]

➢ Underweight: >2 standard deviations below the median for weight-for-age (WFA)

➢ Wasting: >2 standard deviations below the median for weight-for-length (WFL)/ weight-for-height (WFH)

➢ Stunting: >2 standard deviations below the median for length-for-age (LFA)/ height-for-age (HFA)

The percentages of patients meeting the definition for each of the dichotomous indicators of under-nutrition at various time points are presented in Table 15.

Table 15: Summary of Anthropometric Indicators of Under-nutrition for LAL-CL03 Clinical Trial Population (N=9)

	Number (Percentage) of Subjects Meeting the Definition /* Number of Subjects with Data			
	Underweight	**Wasting**	**Stunting**	**No Indicator of Under-Nutrition**
Baseline	2 / 8 (25%)	2/ 8 (25%)	4 / 8 (50%)	3 / 8 (38%)
Week 2	3 / 7 (43%)	2 / 7 (29%)	3 / 7 (43%)	3 / 7 (43%)
Week 4 (Month 1)	2 / 6 (33%)	0 / 6 (0%)	3 / 6 (50%)	3 / 6 (50%)
Week 12 (Month 3)	3 / 6 (50%)	1 / 6 (17%)	1 / 6 (17%)	3 / 6 (50%)
Week 24 (Month 6)	3 / 5 (60%)	1 / 5 (20%)	2 / 5 (40%)	2 / 5 (40%)
Week 48 (Month 12)	0 / 4 (0%)	0 / 4 (0%)	1 / 4 (25%)	3 / 4 (75%)

(Source: Adapted from Applicant's Table 11 entitled "Summary of Anthropometric Indicators of Under-nutrition: Primary Efficacy Set", LAL-CL03 Clinical Study Report, page 126/233, BLA 125561, Module 5.3.5.2)
* Definitions based UNCICEF definitions in text prior to table [39]

Because of the variability in length of study participation and the timing of sebelipase alfa dosage adjustments, the change in individual patient's growth status is difficult to assess from Table 15. Therefore, this reviewer has listed each individual patient's status for the 3 indicators of under-nutrition at baseline and at the time of data cut-off. Each patient's length of sebelipase alfa treatment at the time of the data cut-off data is provided in the table footnote. At baseline, 4 of the 6 surviving patients met criteria for at least one anthropometric indicator of under-nutrition, with a total of 7 abnormal parameters among the 6 surviving patients. At the last visit with both LFA/HFA and weight data prior to data cutoff, only 1 parameter remained abnormal (Subject (b) (6) had persistent stunting). One additional patient (Subject (b) (6)) met criteria for underweight at a subsequent visit (Week 92) for which only weight was reported. This patient also exhibited concurrent worsening in other clinical parameters attributed to the presence of neutralizing antibodies.

Table 16: Patient's Growth Status based on Definitions for the Anthropometric Indicators of Under-Nutrition (Underweight, Wasting, Stunting) at Baseline and Last Assessment Prior to Data Cut-off

Patient	Underweight		Wasting		Stunting	
	Baseline	Data Cut-off	Baseline	Data Cut-off	Baseline	Data Cut-off
(b) (6)	Yes	No	Yes	No	Yes	No#
	No	No	No	No	No	No
	No	No	Yes	No	No	No
	No	No	No	No	No	No
	No	No	No	No	Yes	Yes
	Yes	No	No	No	Yes	No

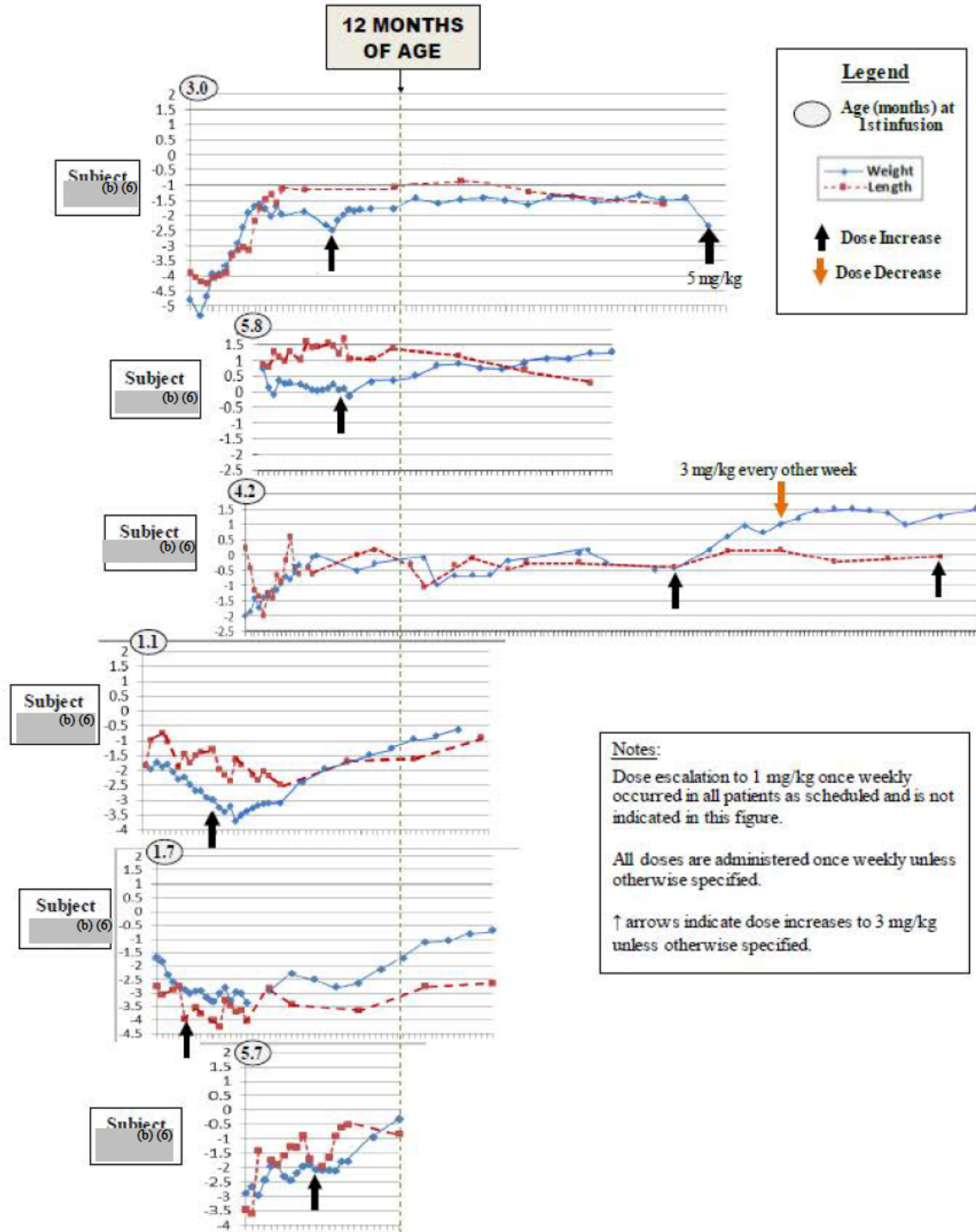*(Source: Reviewer's table created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)*

* Last Study Week prior to data cut-off with available WFA and LFA/HFA data for each patient (b) (6) : Week 84, (b)(6) Week 60, (b) (6) Week 156, (b) (6) : Week 60; (b) (6) : Week 60; (b) (6) Week 24

\# These data for Subject (b) (6) are from Week 84 (the last Study Visit with both height and weight measurements); at Week 92, only a weight was reported and this patient met criteria for underweight

Serum Lipids

Based on the clinical trial data in the CESD population, low density lipoprotein cholesterol (LDL) was determined by the clinical reviewer, Dr. Juli Tomaino, to be the most suitable endpoint to assess efficacy of sebelipase alfa in that patient population. Although LDL was not designated as the primary endpoint for the clinical trial in patients with CESD (LAL-CL02), LDL is a well-established risk factor for coronary heart disease [40,41], and it is on the causal pathway of LAL deficiency, which is associated with dyslipidemia and accelerated atherosclerosis [42]. Therefore, a reduction in LDL was considered likely to represent a clinical benefit in patients with CESD. In patients with early onset, rapidly progressive LAL deficiency, patient survival, even in recipients of hematopoietic stem cell transplant, was rare beyond 1 year of age; therefore, the risk of indolent complications of dyslipidemia in these patients is unknown

In LAL-CL03, serum lipid measurements were included among the scheduled laboratory assessments.

Triglycerides and Total Cholesterol

Serum triglyceride and total cholesterol levels over time for the 6 surviving patients are displayed in Figure 7.

The large variability (and values in the normal range) are consistent with the known presentation of this disease phenotype.[19] serum Median baseline triglyceride level was 183.8 mg/dL (range 31.0 to 481.0 mg/dL, n=6) and median total cholesterol level was 139.2 mg/dL (range 67.1 to 225.3 mg/dL, n=5). Because fluctuations in serum lipids, particularly triglyceride levels, are expected due to dietary factors, their usefulness to assess treatment response is limited. However, improvements in both parameters following treatment initiation are apparent in Figure 7, and even more evident are the increases in patient (b) (6) due to neutralizing antibodies and in

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(b) (6) following the change in dose frequency to every-other-week and the improvements in both patients following subsequent dosage increases (Figure 7, panels A and C).

Figure 7: Triglyceride and Total Cholesterol Levels (mg/dL) over Time for the Surviving Patients in LAL-CL-03 (N=6)
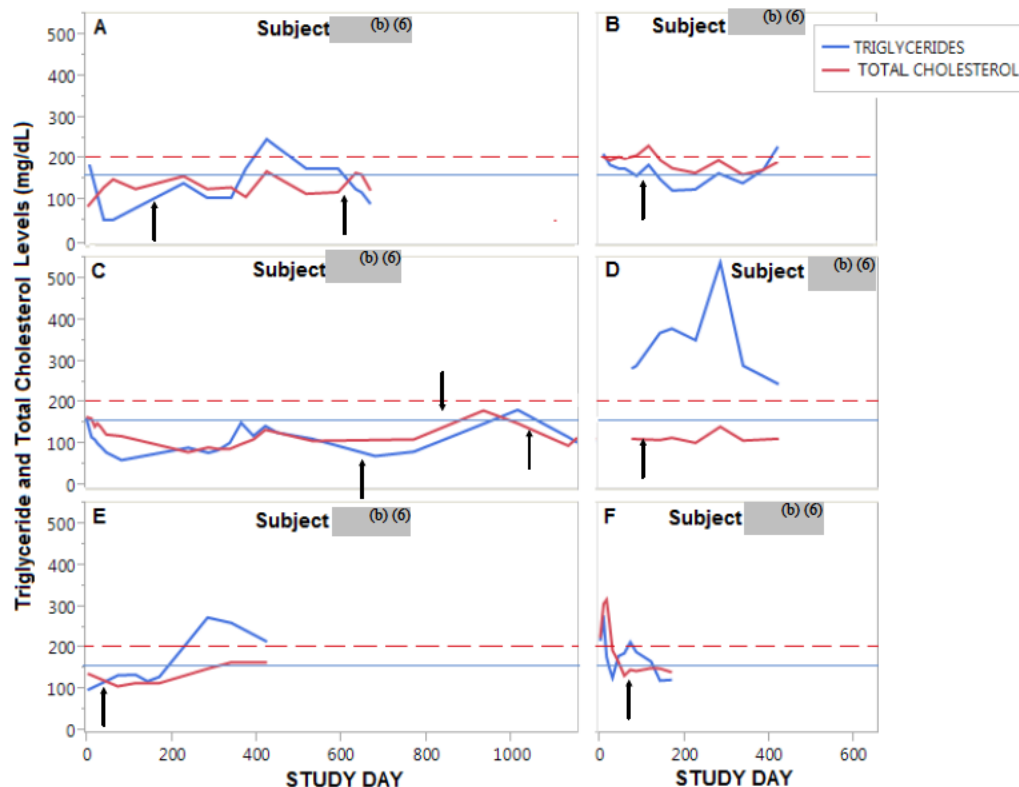
(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)
Arrows indicate timing and direction of changes in sebelipase alfa dosage

Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL)

Graphical serum LDL and HDL level data for the 6 surviving patients are shown in Figure 8. In general, increases in LDL occur in conjunction with decreases in HDL, particularly after treatment initiation.

Similar to total cholesterol levels, baseline LDL levels were inconsistent among the 5 patients with available data. Only Subject (b) (6) had a baseline LDL level which was categorized as abnormal (194.3 mg/dL). By comparison, baseline HDL levels were strikingly low for all patients with available data (median HDL level 8.9 mg/dL, range 0 to 10.0 mg/dL, n=5), thus representing the most consistent baseline laboratory abnormality observed in the LAL-CL03 clinical trial population.

In the 2 patients with clear exacerbations of their underlying disease (Subject ___(b)(6)___ with neutralizing antibodies and ___(b)(6)___ whose frequency of sebelipase alfa infusions was decreased from weekly to every other week), the concurrent increase in serum LDL and decrease in serum HDL with disease exacerbation and subsequent improvements following dosage increases (Figure 8, panels A and C) are more clearly identified for these lipid subtypes as compared to total cholesterol and triglycerides.

This reviewer proposes that these clinical parameters, particularly HDL, should be investigated as putative measures of treatment response adequacy. Compared to other markers, changes in HDL levels appear to track most closely with patient's growth and overall clinical status, but unlike growth parameters changes occur more rapidly, which would facilitate earlier detection of inadequate treatment response and more rapid assessment of dose changes. In addition, this parameter is likely to be less susceptible to confounding factors due to the pathophysiologic mechanisms which cause low HDL levels. (See Figure 23) However, the normal reference ranges of serum lipids in infants, particularly HDL levels, are not well-established and may differ from normal levels in older children and adults. For example, recent efforts to define normative values for patients in this age group suggest that normal HDL levels may be lower than adults (~30 mg/dL).[42-44] Therefore, is information will be important for interpretation of lipids levels in patients with early onset of LAL deficiency.

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Figure 8: Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL) levels (mg/dL) over Time for the Surviving Patients in LAL-CL-03 (N=6)
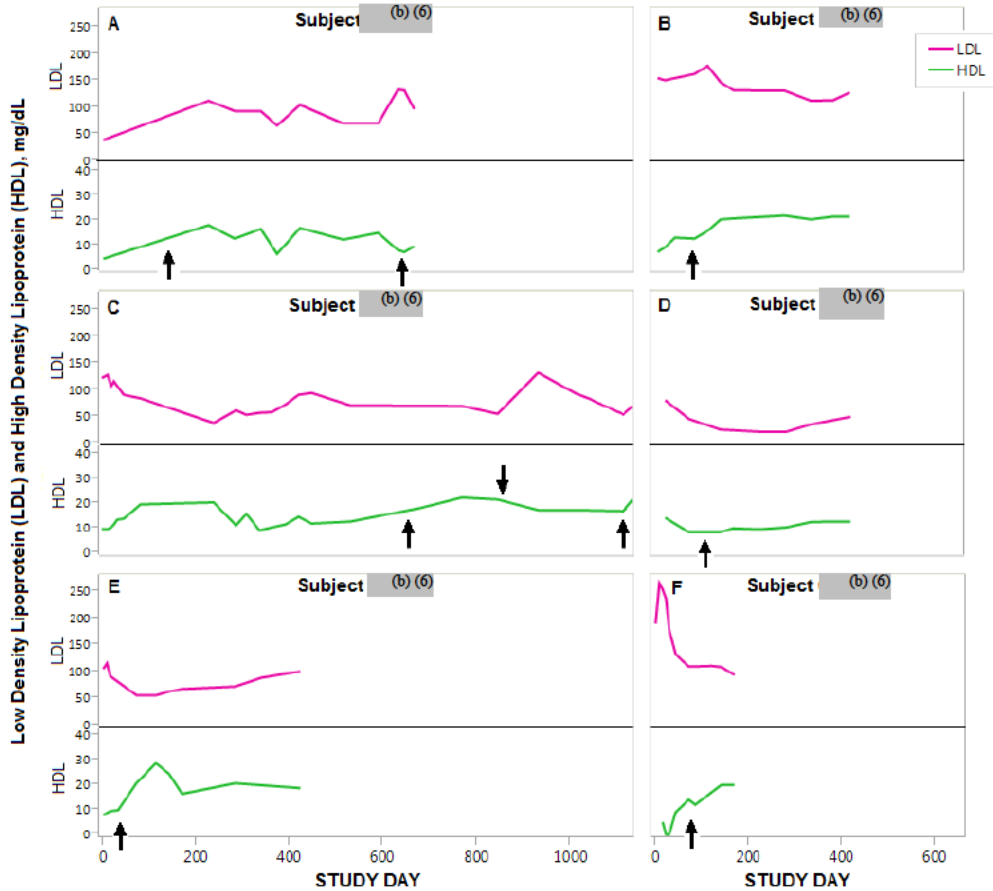
(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)
Arrows indicate timing and direction of changes in sebelipase alfa dosage

Serum Transaminases, Ferritin, and Lactate Dehydrogenase Levels

Serum Transaminases

Normalization of serum alanine aminotransferase (ALT) was the pre-specified primary endpoint for the clinical trial of sebelipase alfa in patients with the CESD phenotype of LAL deficiency. However, the Agency noted at several stages during sebelipase alfa drug development that ALT does not directly measure clinical benefit of treatment (i.e., how a patient feels, functions, or survives), has not been shown to be on the causal pathway of the disease, and does it represent a surrogate endpoint reasonably likely to predict clinical benefit in patients with LAL deficiency. Therefore, the clinical significance of serum transaminase elevation in the patients with the early onset, rapidly progressive phenotype, like CESD, is not clear. For the patients with early-onset disease, it is also likely that liver injury is not cause of elevated serum transaminases in this patient group, particularly at initial disease presentation.

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Unlike LAL-CL02, elevated ALT level (>1.5 times the upper limit of normal, ULN) was not an inclusion criterion for LAL-CL03 eligibility. For 3 of the 9 (33%) patients in LAL-CL03, baseline ALT did not exceed 1.5 times ULN. (Two of the 3 were within the normal range). In 5 of the 9 (56%) LAL-CL03 patients [2 of the 6 (33%) surviving patients], ALT levels exceeded 3 times ULN. (It is important to note that, unlike LAL-CL02, serum transaminase measurements were not performed by a central laboratory, and therefore, normal reference ranges were determined by the individual local laboratories.)

By comparison, all 9 patients had elevated aspartate aminotransferase (AST) levels at baseline, ranging from 1.1 to 14.1 times ULN, median 2.1 times ULN. In 8 of the 9 patients, baseline AST levels were higher than ALT levels, and AST/ALT ratios were >2 in 5 of the 8 patients. These data suggest a non-hepatic etiology, such as a hematologic process, as the primary source for these patients' serum transaminase elevations.

Graphs of individual patient's serum ALT and AST levels over time are shown in Figure 9. Regardless of etiology, rapid improvements in transaminases were observed following initiation of sebelipase alfa treatment, and recrudescence in serum transaminases occurred in conjunction with other evidence of suboptimal treatment response, most notably in the 2 patients with clear disease exacerbations (Subject ⁽ᵇ⁾⁽⁶⁾ and ⁽ᵇ⁾⁽⁶⁾).

Figure 9: Serum Transaminase Levels [Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST)] Over Time in the Surviving Patients in LAL-CL03 (N=6)
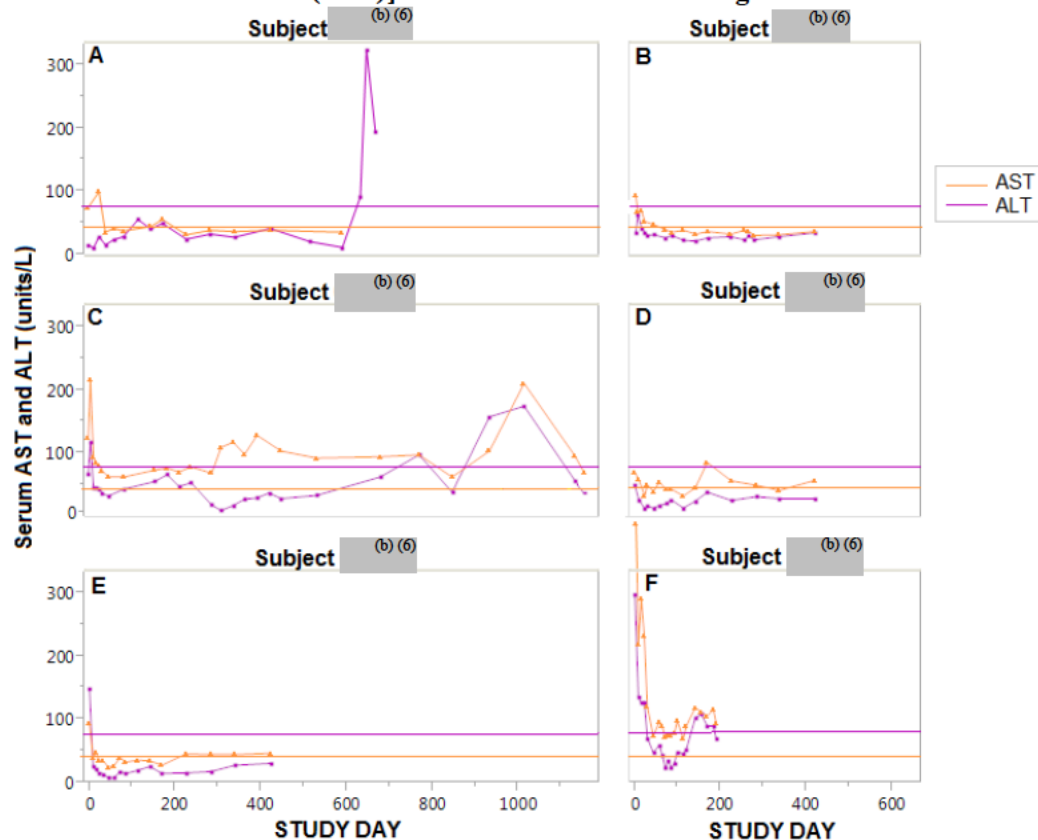
(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Serum Lactate Dehydrogenase and Serum Ferritin

Rapid improvements in serum lactate dehydrogenase (LDH) and ferritin were observed following treatment initiation. Of note, marked hyperferritinemia is a feature of hemophagocytic lymphohistiocytosis (HLH) [25,26], and as shown in Table 10, the highest baseline levels were observed in the patients with clinical presentations consistent with HLH [Subjects (b) (6) (not done in Subject (b) (6)]. Following initial improvements, recrudescence of these parameters were observed in Subjects (b) (6) along with worsening in other disease parameters, particularly serum AST.

Figure 10: Serum Lactate Dehydrogenase (LDH) and Ferritin Levels Over Time in the Surviving Patients in LAL-CL03 (N=6)

(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

Transfusion-free Hemoglobin Normalization (TFHN)

Individual plots of hemoglobin levels over time are provided in Figure 11. The timing of packed red blood cell transfusions received by patients during clinical trial participation is also noted in the figure.

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Hemoglobin data were analyzed in terms of transfusion-free hemoglobin normalization (TFHN) for which the Applicant pre-specified definitions. A patient was considered to have achieved TFHN if they met the following criteria:

➢ Two post-baseline measurements of hemoglobin, ≥4 weeks apart, above the age-adjusted lower limit of normal (LLN)

➢ No known additional measurements of hemoglobin were below the age-adjusted LLN during the ≥4-week period

➢ No transfusions administered during the ≥4-week period, or for 2 weeks prior to the first hemoglobin measurement in the ≥4-week period

Two sub-types of TFHN were pre-specified by the Applicant:

➢ Short-term TFHN: TFHN of ≥4 weeks at any time during the clinical trial (note: the date on which a patient achieved TFHN was reported as the date of the first hemoglobin assessment obtained in the 4-week period)

➢ Sustained early TFHN: Maintenance of TFHN for ≥13 weeks beginning at Week 6

At the time of enrollment, baseline hemoglobin levels ranged from 7.4 to 10.3 g/dL, with the exception of a questionable level of 1.4 g/dL reported in patient ⬚⬚ (b) (6), who had a screening level of 8.6 g/dL. Only 2 of the 9 patients (Subjects ⬚⬚ (b) (6) and ⬚⬚ (b) (6)) did not have a baseline hemoglobin level below the local laboratory's LLN or documentation of anemia in their medical history. Four (44%) subjects (⬚⬚⬚⬚⬚⬚⬚⬚⬚⬚ (b) (6)) received transfusions of red blood cells during the period between informed consent and initiation of sebelipase alfa treatment, and all 3 patients who died within the first 6 months of treatment were requiring frequent transfusion.

Five of the 6 surviving patients (83.3%) achieved short-term TFHN, and the estimated median time to achieve short-term TFHN (95% CI) by Kaplan-Meier analysis was 4.6 months (0.2 months, not estimable). Two patients (Subjects ⬚⬚⬚⬚⬚⬚ (b) (6)) also achieved sustained early TFHN.

After the first month of treatment, 3 patients required transfusions of packed red blood cells:
- Subject ⬚⬚ (b) (6): Required 2 transfusions—one on Study Day 120 (Week 17), 6 weeks prior to a dose increase to 3 mg/kg and one on Study Day 605 (Week 86), in the presence of neutralizing ADA and 2 weeks prior to a dose increase to 5 mg/kg.
- Subject ⬚⬚ (b) (6): Required a single transfusion on Study Day 104 (Week 14), 2 weeks after a dose increase to 3 mg/kg
- Subject ⬚⬚ (b) (6): Required 2 transfusions—one on Study Day 45 (Week 6), 2 days after a dose increase to 3 mg/kg and one on Study Day 98 (Week 13); from Week 6 through Week 15 this patient experience multiple catheter-related infections including bacteremia and sepsis

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Figure 11: Serum Hemoglobin Level (g/dL) Over Time and Packed Red Blood Cell Transfusions during LAL-CL03 in the Surviving Patients (N=6)
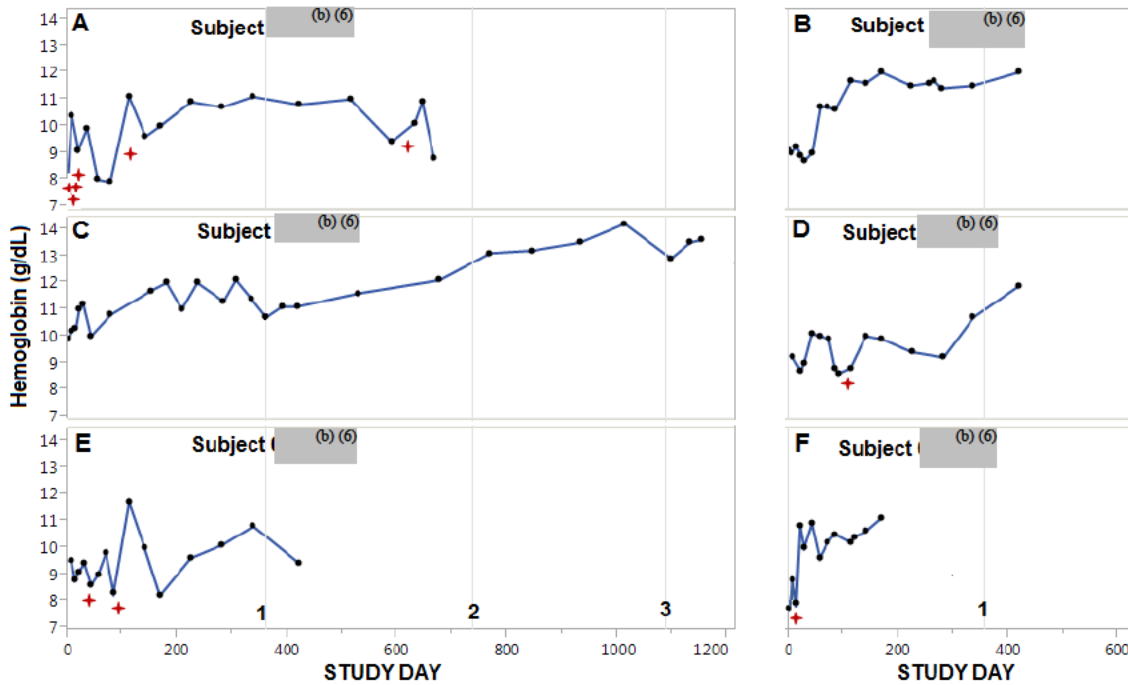
(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

+ Transfusion with packed red blood cells
Vertical lines indicate treatment duration in years (labeled 1, 2, etc.)

6.1.6   Other Endpoints

Serum Albumin

Individual plots of serum albumin over time are provided in Figure 12.

Rapid improvements were also observed in serum albumin levels (abnormal in 3 of the 6 surviving patients and all 3 of the deceased patients). There are many potential causes of hypoalbuminemia in these patients. Given the rapid rate of improvement, the most likely contributing factors are patient edema, malabsorption and the role of albumin rate of improvement in these patients, rather than liver dysfunction.

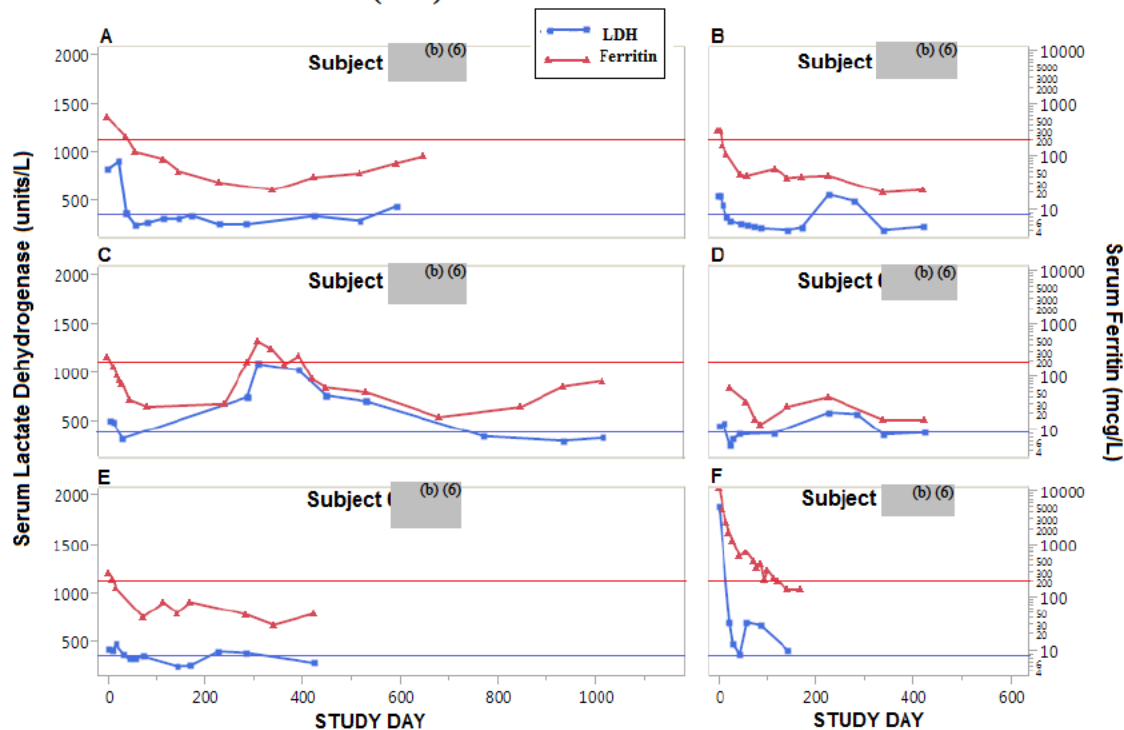**Figure 12: Serum Albumin (g/dL) Over Time for Surviving Patients in LAL-CL03 (N=9)**
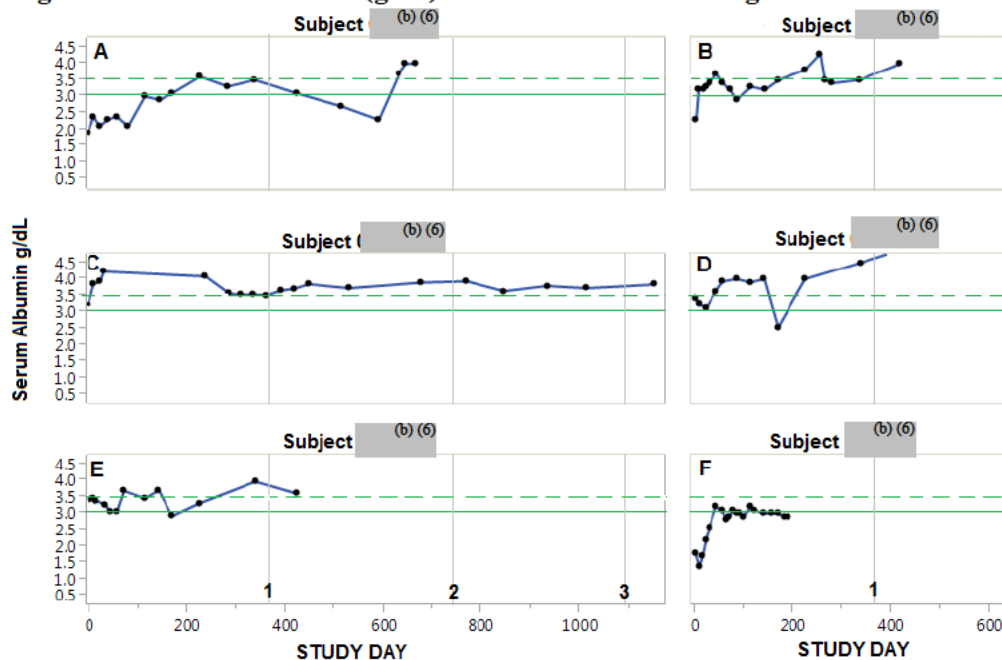
(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

Liver and Spleen Volume

Liver and spleen volume data were not consistently obtained during LAL-CL03 with respect to timing of assessments/missing assessments and variability in imaging modality. Of the 33 imaging studies obtained for the patients in LAL-CL03, central readings were performed in 14 studies. Results of imaging studies, regardless of imaging modality, are shown in Figure 13. (Modalities for each organ volume measurement are included in patient profiles, Figures 15 to 20)

Five of the 6 surviving patients in LAL-CL03 had liver and spleen volume data obtained at ≥2 study time points. In 3 of these patients, baseline measurements were available for both liver and spleen volume, and 1 patient had only a baseline liver volume measurement. Despite the inconsistencies in data collection and timing of assessments, these data demonstrate reductions in both liver and spleen volumes following treatment of sebelipase alfa. (Figure 13) Although the data are too limited to draw conclusions, reductions in liver size appear to be relatively consistent across patients following treatment initiation, while the greatest decreases in spleen volume were less consistent, with the greatest reductions after dose escalation to 3 mg/kg.

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Figure 13: Liver and Spleen Volumes (Multiples of Normal) in LAL-CL03.
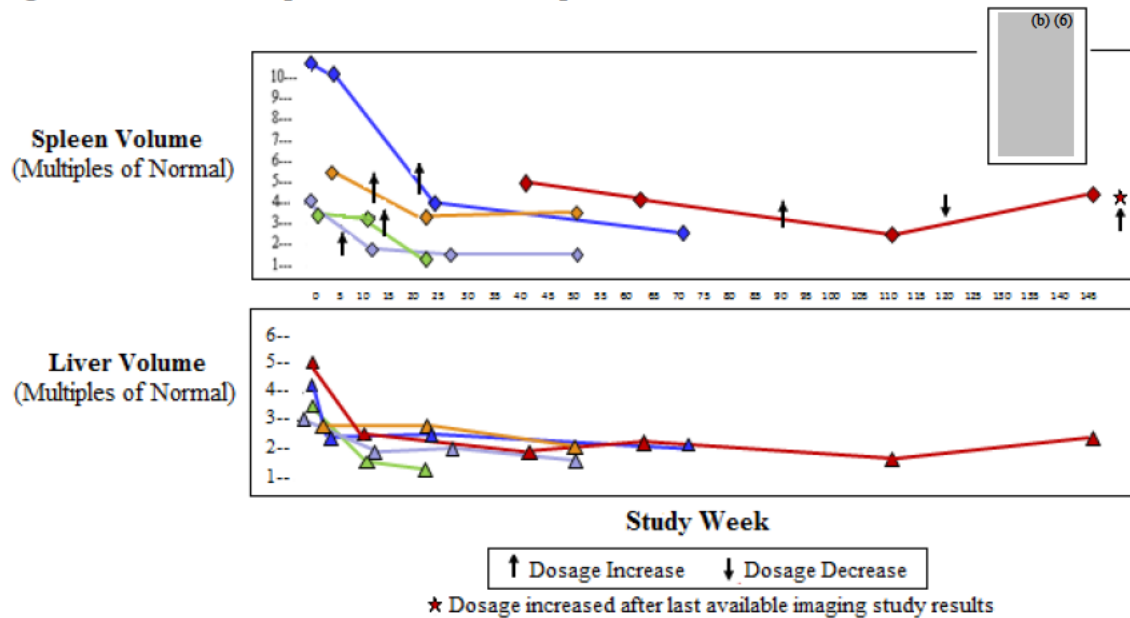
(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

Liver Histopathology

Because liver biopsies are considered too risky to undertake in most patients with rapidly progressive LAL deficiency, scheduled assessments of liver histopathology are not feasible in this population. However, because of the unmet need to better characterize the histopathological features of LAL deficiency and to assess the effects of sebelipase alfa treatment liver pathology, LAL-CL03 Protocol Amendment 10 added an optional liver biopsy after >12 months of sebelipase alfa treatment as an exploratory assessment. The BLA did not contain any centrally-read histopathological data for the patients in LAL-CL03. In response to an information request by the Agency, the Applicant later confirmed that, as of February 20, 2015, no patients with early-onset LAL deficiency in either LAL-CL03 or LAL-CL08 had undergone a liver biopsy as part of their clinical trial assessments.

6.1.7   Subpopulations

No subpopulation analyses were performed due to the small patient population size.

6.1.8   Analysis of Clinical Information Relevant to Dosing Recommendations

Early-onset, rapidly progressive LAL deficiency is a universally fatal disease. As such, adequate treatment is crucial to maximize the likelihood of survival. In addition, because no effective treatment has been available for this condition, the clinical course of treated, and the sequelae of suboptimal treatment are not known. To date, only 1 poor outcome has been reported in a

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patient receiving long-term sebelipase alfa treatment. Subject ░░░ (b) (6) had a sudden cardiac death after 28 weeks of sebelipase alfa treatment (18 doses at 3 mg/kg) and was noted on autopsy to have substantial evidence of active disease. Therefore, dosing recommendations should reflect the medications doses at which the greatest treatment benefit was observed without compromising patient safety.

Graphical Patient Profiles

To best inform sebelipase alfa dosing for this small patient population, evaluation of each individual patient's treatment response across several different clinical variables was required. This strategy was deemed necessary by this reviewer due to the differences in baseline disease-related abnormalities, variable response to initial sebelipase alfa dosing, variable timing of sebelipase alfa dose increases, dependence on secondary and exploratory outcome variables to assess treatment response, and the potential for ADA development to confound efficacy analyses. Therefore, individual graphical patient profiles were generated by this reviewer for the 6 surviving patients to facilitate the simultaneous comparison of multiple clinical variables in relation to patients' sebelipase alfa doses and ADA status/titers. The patient profiles are shown below in Figures 15-20, with a legend for interpretation of these profiles provided in Figure 14.

These profiles demonstrate that, although improvements in disease-related parameters were observed during weekly treatment with 1 mg/kg of sebelipase alfa, more consistent improvements of greater magnitude were observed in all patients during treatment with 3 mg/kg once weekly. One notable finding among these patient profiles is the striking simultaneous worsening of multiple disease-related clinical parameters in Subject ░░░ (b) (6) following the only reduction in infusion frequency attempted during LAL-CL03. A similar pattern of changes occurred in Subject ░░░ (b) (6), who experienced a decrease in efficacy in the presence of neutralizing ADA. Together, these patients provide greater insight into the clinical features associated with suboptimal treatment response and may help determine the most useful variables to assess treatment response.

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Figure 14: Legend for Interpretation of Graphical Patient Profiles for Surviving Patients (Figures 15-20)

LEGEND

———————	Timeline from birth to data cutoff
▪▪▪▪▪▪▪▪▪▪▪▪▪	Timeline from birth to enrollment
▬ ▬ ▬ ▬ ▬	First 12 months of life
0 5 10 15 20 …	Time from enrollment (weeks)
▼	First Sebelipase alfa infusion
▽ (S)	Onset of symptoms
▼	Data cutoff point
❘	Diagnosis of LAL deficiency
◆—	Birth Weight
●	ADA with negative neutralizing assay
●	ADA with positive neutralizing assay
[−]	ADA negative at last assessment prior to data cut-off
[+]	ADA positive with negative neutralizing assay at last assessment prior to data cut-off
[+]	ADA positive with positive neutralizing assay at last assessment prior to data cut-off

Sebelipase Dosages

———	<1mg/kg weekly
▬▬▬	1 mg/kg weekly
▬▬▬	3 mg/kg weekly
▬▬▬	5 mg/kg weekly
■ ■ ■ ■ ■	3 mg/kg every other week

Organ Volume: MN, Multiples of Normal; %, percent change from baseline

Measurement Methods
  MRI-C: Abdominal MRI, central reading
  MRI-L: Abdominal MRI, local reading*
    US: Abdominal Ultrasound
  *measurements from local reading used only when central reading not available

Other abbreviations: ADA, anti-drug antibody(ies); ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; HDL, high density lipoprotein; LDH, lactate dehydrogenase; LDL, low density lipoprotein; ND, not done; U, units

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Figure 15: Patient Profile for Subject (b) (6)
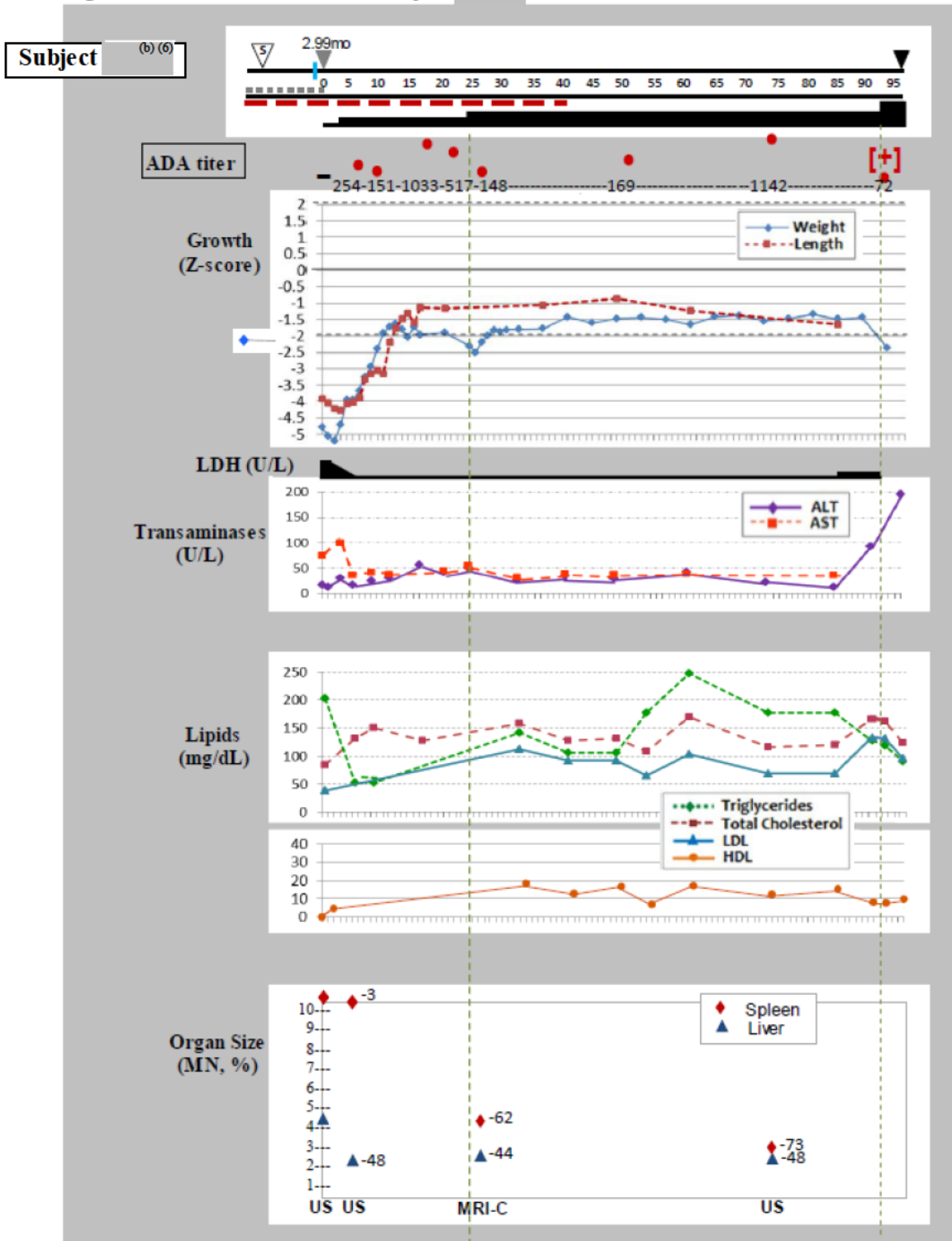
(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

Figure 16: Patient Profile for Subject (b) (6)

(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

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Figure 17: Patient Profile for Subject (b) (6)

(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

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Figure 18: Patient Profile for Subject (b) (6)

(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

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Figure 19: Patient Profile for Subject (b) (6)

(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

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Figure 20: Patient Profile for Subject (b) (6)
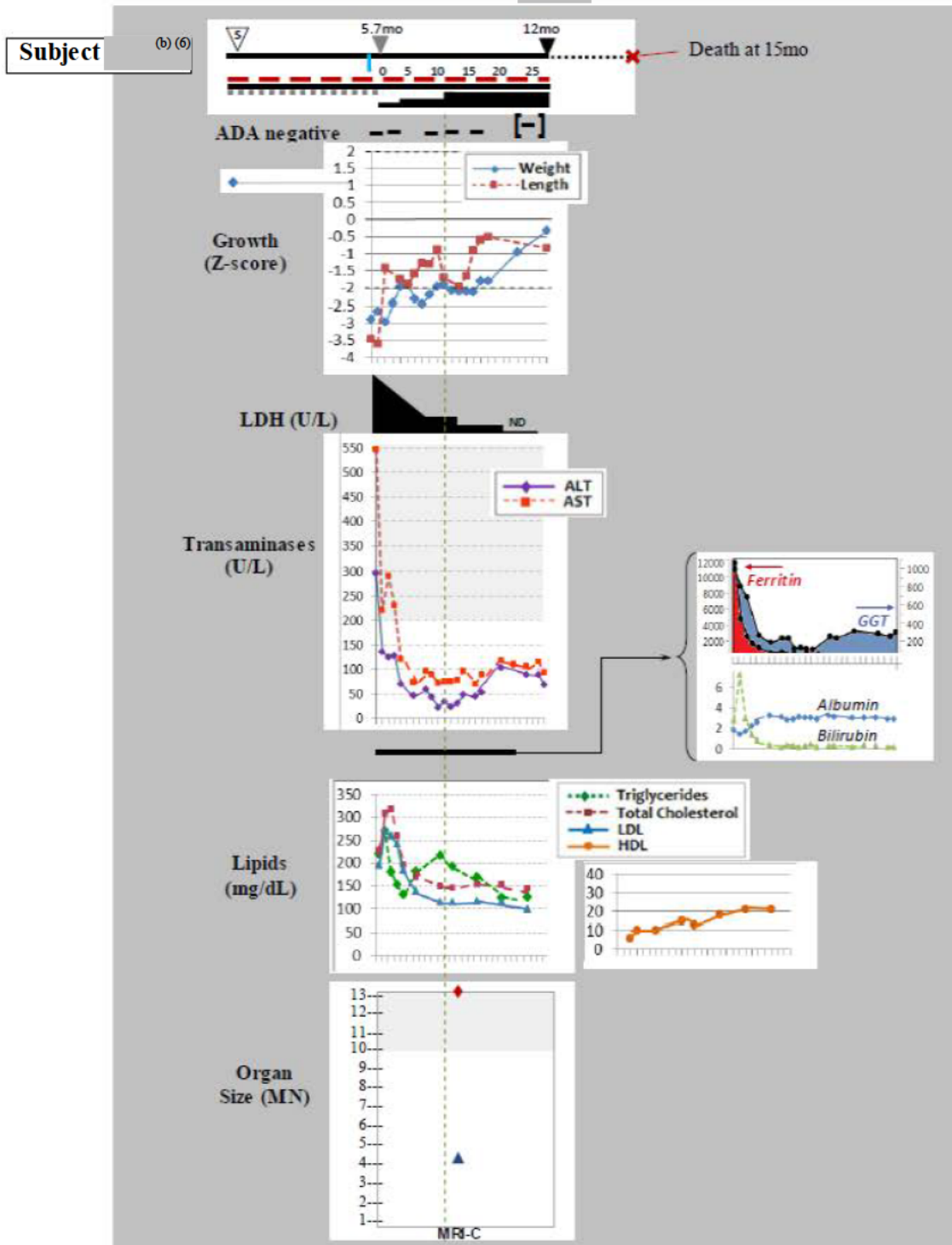
(Source: Reviewer's figure created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and tolerance effects could be affected by immunogenicity to enzyme replacement products. One of the 9 patients had neutralizing ADA and exhibited evidence of reduced sebelipase alfa efficacy. The conclusions that can be drawn from this information is limited due to the small patient population.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

LAL deficiency with early onset of rapidly progressive disease and growth failure is a fatal disease without available treatment. Like other enzyme replacement therapies, the primary safety concerns associated with sebelipase alfa are hypersensitivity reactions and the development of ADA. Hypersensitivity reactions occurred in 4 of the 6 (67%) surviving patients who received more than 4 infusions of sebelipase alfa. None of the patients discontinued treatment due to adverse reactions, and hypersensitivity reactions have been generally mild and manageable with treatment interruption, adjustment of infusion rates, and standard medical intervention.

ADA were detected in 4 of the 7 (57%) patients in whom post-treatment immunogenicity assessments were performed, all of whom were surviving patients. Three patients ((b) (6) , had multiple consecutive positive ADA assessments, while 1 patient had detectable ADA on a single immunogenicity assessment (Subject (b) (6) at Week 8. In addition, 2 of the 4 ADA-positive patients were positive for neutralizing ADA, and both of these patients were among those with detectable titers on multiple serial assessments. At the time of data cut-off, only 1 of the 3 patients with persistently positive ADA titers, Subject (b) (6) with positive neutralizing ADA, had a detectable level.

Three of the 4 patients with ADA, including both of the patients with neutralizing ADA, experienced hypersensitivity reactions, and recurrent reactions were noted for all 3 of these patients. By comparison, 1 of the 3 ADA-negative patients was reported to have a single hypersensitivity reaction. In addition to hypersensitivity reactions, a decrease in sebelipase alfa efficacy was observed in one patient with neutralizing ADA; however, the patient demonstrated improvement following a dose increase to 5 mg/kg without reported safety concerns associated with this dose adjustment.

Although the experience with sebelipase alfa in patients with early-onset LAL deficiency is limited to only 9 patients, the immunogenicity associated with sebelipase alfa treatment in this patient population appears to be less severe than findings in ERT-treated patients with infantile-onset phenotypes of other lysosomal storage disorders. This assessment is based on a generally

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lower rate of ADA development, lower magnitude of ADA titers, lower rate of neutralizing ADA development, higher rate of ADA resolution, milder severity of hypersensitivity reactions, lower percentage of patients demonstrating loss of efficacy due to ADA, and lack of patients with fatal outcome due to loss of treatment efficacy. Due to the extremely small patient population, these observations should be interpreted cautiously.

No other safety concerns with sebelipase alfa treatment were identified during LAL-CL03. Due to the variability of baseline serum lipid levels, very little data regarding the risk of transient exacerbation of hyperlipidemia due to mobilization of substrate following treatment initiation was obtained. However, no adverse events occurred which could be attributable to this phenomenon (e.g., pancreatitis or thromboembolic events).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary source of safety data for patients with infantile-onset phenotype of LAL deficiency (i.e., onset of rapidly progressive disease within first 6 months of life) is an ongoing, open-label, single-arm clinical trial, Study LAL-CL03, sebelipase alfa (data cut-off date June 10, 2014 for BLA submission). The LAL-CL03 safety population includes all patients who received at least 1 dose of sebelipase alfa (n=9).

The safety data from LAL-CL02 in pediatric and adult patients were reviewed by Dr. Juli Tomaino. For these results, please refer to the Clinical Review for BLA 122561, dated June 8, 2015.

7.1.2 Categorization of Adverse Events

Applicant Pre-Specified Definitions:
- Adverse event (AE)- any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject, whether or not causally related to administration of the study drug
- Serious adverse event (SAE)- any AE that was or led to any of the following: death; immediately life threatening; requires inpatient hospitalization or prolongation of existing hospitalization, congenital anomaly/birth defect; persistent or significant disability or incapacity; or an important medical event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the previously mentioned outcomes

  Because prolonged inpatient hospitalization during study participation would be expected in this patient population, continuation of patients' initial hospitalization during the study was not considered an SAE. In addition, hospitalizations required to perform study procedures, dictated by institutional policy, were not considered SAEs.

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All adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 13.1. This clinical reviewer compared verbatim terms with the applicant's coded/preferred term to ensure consistency in coding and revised as needed. Each AE verbatim term was assigned a preferred term (PT), low level term, high level term, and system/organ/class (SOC).

In general, this clinical reviewer's coding of AE verbatim terms was consistent with the terminology used by the Applicant. However, this reviewer grouped the PTs of "pyrexia", "fever", "increased body temperature", and "hyperthermia" and coded all of these events under the term "fever" (to be consistent with the product labeling), in order to perform tabulations. In addition, adverse events for which the clinical infectious process and pathogen were listed separately (e.g. central line infection and Staphylococcal bacteremia) were combined into single events.

Adverse events were obtained through spontaneous reporting or elicited by specific questioning or examination of the subject's parent or legal guardian, and were recorded from the date of informed consent until completion of the follow-up visit at approximately 30 days after the last dose of sebelipase alfa.

For each reported AE, the Investigator provided the following assessments:

➢ Severity: graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Adverse events not explicitly included in the CTCAE were graded on a 5-point scale as Grade 1 (mild), Grade 2 moderate), Grade 3 (severe), Grade 4 (life threatening), and Grade 5 (death)

➢ Causality: AEs were categorized as "related", "possibly related", "unlikely related", or "not related" based on the Investigators assessment of causality

➢ Relationship to sebelipase alfa infusion: an infusion-associated reaction (IAR) was defined as any AE that occurred during the sebelipase infusion or within 4 hours after the sebelipase alfa infusion and was assessed by the Investigator as at least possibly related to treatment. Events occurring outside of this time window could also be reported by the investigator as IARs if the symptoms were considered consistent with an IAR and related to administration of sebelipase alfa.

For labeling of enzyme replacement therapies (ERTs), categorization of AE as "infusion-associated reactions" or "infusion-related reactions" is no longer recommended. Instead, AEs which are temporally related to these medications and are likely immunologically-mediated should be categorized as "Hypersensitivity Reactions." Anaphylaxis represents a specific subgroup of hypersensitivity reactions which fulfill Sampson's criteria.[46] For the reactions categorized by the Applicant as IARs, the Applicant applied Samson's criteria to identify cases of anaphylaxis. This reviewer agrees with the Applicant's assessments of these cases. However, for the AEs categorized as IARs, this reviewer performed independent assessments to identify those which represent hypersensitivity reactions.

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

The Applicant provided an Integrated Summary of Safety, which included data from all completed and ongoing clinical trial patients. For this review, analyses were primarily based on LAL-CL03.

A 120-day safety update was submitted which also included updated safety data from LAL-CL02 and LAL-CL03, as well as safety data from 2 additional open-label clinical trials (LAL-CL06 in patients >8 months old and LAL-CL08 in patients <8 months old).

7.2 Adequacy of Safety Assessments

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

The dosing regimen specified by the LAL-CL03 clinical trial protocol consisted of 2 initial weekly doses of 0.35 mg/kg, followed by a planned dose escalation to 1 mg/kg once weekly if the lower doses were well-tolerated. Two patients died of disease-related complications after receiving a single dose of sebelipase alfa at 0.35 mg/kg, and 1 patient died after the 2nd weekly dose of 1 mg/kg. In all 7 patients who were treated with at least 3 doses of sebelipase alfa, the dose was successfully escalated to 1 mg/kg at Study Week 3 per protocol. The protocol called for an additional escalation to 3 mg/kg in patients who meet pre-specified criteria for suboptimal treatment response on the dosage of 1 mg/kg once weekly. Dose escalations to 3 mg/kg were performed in all 6 surviving patients in LAL-CL03. In one patient with loss of efficacy attributed to the presence of neutralizing ADA, the sebelipase dose was escalated to 5 mg/kg once weekly. In another patient (Subject (b) (6)), the frequency of sebelipase alfa infusions was decreased to every-other-week at Week 122 of treatment but was subsequently increased back to weekly infusions after worsening of disease manifestations.

As of the data cut-off for this Application, median duration of exposure was 60 weeks (range 0 to 165 weeks) for the LAL-CL03 patients. This represents a total of 462 administered sebelipase infusions for these 9 patients, including 141 infusions at a dose of 1 mg/kg and 295 infusions at a dose of 3 mg.

Table 17: Sebelipase Alfa Exposure in the LAL-CL03 Clinical Trial Patients (N=9)

Subject ID	Total number of infusions	Dose (mg/kg)/Infusion			
		<1 mg/kg#	1 mg/kg	3 mg/kg	5 mg/kg
(b) (6)	1	1	0	0	--
	95	2	21	64*	8
	62	2	10*	49*	--
	146	4	86*	56*	--
	65	2	10	53	--
	61	2	4	55	--
	28	2	8	18	--
	1	1	0	0	--
	4	2	2	0	--

(Source: Reviewer's table created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)
#All patients who initiated treatment in LAL-CL03 received 2 infusions at a dose of 0.35 mg/kg; Subject (b) (6) received 4 doses <1 mg/kg (0.2 mg/kg x 1, 0.3 mg/kg x 1, 0.5 mg/kg x 1, 0.75 mg/kg x 1)
* Missed doses: Subject (b) (6) (n=1): Week 73; Subject (b) (6) (n=4): Weeks 6, 10, 29, 37; (b) (6) (n=2): Weeks 13, 160

7.2.2 Explorations for Dose Response

Because of the small size of the patient population, graphical patient profiles were used to compare multiple clinical variables, including medication dose, simultaneously.

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

LAL-CL03 safety assessments included vital sign assessments, physical examinations, review of concomitant medications, and laboratory studies. Laboratory testing included specific assessments for binding and neutralizing anti-drug antibodies. The reader is referred to the memorandum by the Dr. Joao Pedras-Vasconcelos, Immunogenicity Reviewer, dated December 18, 2014 for a complete review of the immunoassays used for these assessments. The schedule of clinical trial safety procedures can be found in Table 5 and Table 6 in Section 5.3.1.

7.2.5 Metabolic, Clearance, and Interaction Workup

Due to the minimal available data, these assessments could not be performed for the infant patients in LAL-CL03. As an enzyme replacement therapy/ biologic agent, sebelipase alfa does not utilize drug enzymatic pathways and/or transporters for metabolism or clearance. Therefore, evaluations for drug-drug interactions are not performed for this class of medication. In addition, clearance from the systemic circulation occurs via distribution into target tissues and subsequent protein degradation. Thus, even if PK data were available, the usefulness these data for safety

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assessments would be limited. For overall population data, the reader is referred to the clinical pharmacology review by Dr. Jing Fang.

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

Safety monitoring included adequate evaluation for hypersensitivity and immune-mediated reactions, which are the known adverse reactions common to all ERT products. Laboratory assessments also included adequate measurements of serum lipids to monitor for transient elevations following treatment initiation due to mobilization of substrate and correlate with AE reports.

One product-specific concern not addressed by the Applicant during clinical trials is the risk of sebelipase alfa infusion in patients with hypersensitivity to egg protein. To date, patients with known allergy to eggs have been excluded from sebelipase alfa clinical trials. However, patients with sensitization to egg protein without documented clinical evidence of egg hypersensitivity are likely at increased risk for hypersensitivity reactions to sebelipase alfa, including anaphylaxis. However, this review focuses on a patient population who are likely too young to have prior exposure to egg protein and therefore, unlikely to be sensitized to egg protein.

7.3   Major Safety Results

7.3.1   Deaths

Three deaths were reported for patients in LAL-CL03 prior to data cut-off, all occurring within the first month of sebelipase alfa treatment. In all 3 cases, the Investigator considered cause of death to be unrelated to treatment with sebelipase alfa, and this reviewer concurs with these assessments. Patient deaths are listed in Table 18. *(Note: Because patient survival at 12 months of age was the pre-specified primary endpoint for Study LAL-CL03, deaths occurring during Study LAL-CL03 were relevant for both efficacy and safety assessments in this review.)*

Table 18: Listing of Deaths in LAL-CL03 Prior to Data Cutoff

Subject	Study Days of Infusion(s)	Number of Infusions Prior to Death	Dosing Regimen at Time of Death	Study Day of Death	Age at Death (months)	Cause of Death, as Reported by the Investigator
(b) (6)	1	1	0.35 mg/kg	6	2.79	Liver failure secondary to Wolman disease
	1	1	0.35 mg/kg	5	2.92	Massive intraperitoneal bleeding
	1, 6, 14, 20	4	1 mg/kg	26	4.27	Cardiac arrest

(Source: Adapted from Applicant's Table 18, entitled "Listing of Deaths in Study LAL-CL03", LAL-CL03 Clinical Study Report, page 180/233, amended based on Applicant's data in the Analysis Datasets, BLA 125561, Module 5.3.5.2)

Narratives of patient deaths (n=3, prior to data cut-off)

- Subject _____ (b) (6) - This patient is an _____ (b) (6) with onset of disease-related symptoms at 1.9 months of age. Diagnosis of LAL deficiency was made at 2.6 months of age. At the time of clinical trial enrollment, the patient was critically ill and required mechanical ventilation with high frequency oscillatory ventilation, inotropic support, and continuous blood products. (b) (6) received a single dose of sebelipase alfa on _____ (b) (6) at a dose of 0.35 mg/kg. (b) (6) developed worsening oliguria and abdominal distension on Study Day 5, and on Study Day 6, (b) (6) developed bradycardia, acidosis, hypotension, and a precipitous drop in hemoglobin level, followed by cardiac arrest. The cause of death reported by the Investigator was liver failure secondary to Wolman disease. This reviewer's assessment of cause of death is multi-system organ failure due to a hemophagocytic lymphohistiocytosis (HLH)-like syndrome affecting a subset of patients with early onset, rapidly progressive LAL deficiency (Wolman disease).

- Subject _____ (b) (6): This patient is _____ (b) (6) with onset of disease-related symptoms at 1.5 months of age. Diagnosis of LAL deficiency was made at 2.4 months of age. At the time of enrollment, the patient was noted to have abdominal distention and anasarca. (b) (6) also had persistent anemia, thrombocytopenia, and coagulopathy despite frequent blood product transfusions. (b) (6) received single dose of sebelipase alfa on _____ (b) (6) at a dose of 0.35 mg/kg. On Study Day 3, the subject developed compromised ventilation due to worsening ascites and abdominal distention. (b) (6) underwent abdominal paracentesis, which was complicated by intraperitoneal bleeding. Over the next 2 days, the patient developed bradycardia, metabolic acidosis, hypotension, and died on Study Day 5 of cardio-respiratory failure secondary to peritoneal hemorrhage.

- Subject _____ (b) (6) - This is a _____ (b) (6) with onset of disease-related symptoms at 3.0 months of age. Diagnosis of LAL deficiency was made at 3.3 months of age. At the time of study enrollment, the subject was being treated by the investigator for symptoms consistent with a hemophagocytic lymphohistiocytosis (HLH)-like syndrome, including persistent anemia, thrombocytopenia, and coagulopathy. (b) (6) received 4 weekly infusions of sebelipase alfa (2 infusions at 0.35 mg/kg and 2 infusions at 1 mg/kg), starting on _____ (b) (6) Death was 6 days after the last infusion. 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 authorisation".

One additional patient death (Subject _____ (b) (6)) occurred approximately 3 months after the data cutoff for this BLA submission. Subject _____ (b) (6) was almost 15 months at the time of death. The Subject is a _____ (b) (6) diagnosed with onset of disease-related symptoms at 0.5 months of age and diagnosis of LAL deficiency at 5.5 months of age. (b) (6) medical history was also notable for a diagnosis of Hemoglobin E disease. At the time of death, (b) (6) was receiving weekly outpatient infusions of sebelipase alfa at a dose of 3 mg/kg. (b) (6) last sebelipase alfa infusion was administered 6 days prior to (b) (6) death. The case was ruled a sudden cardiac death. The autopsy

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findings (summarized below) demonstrated a substantial disease burden, including significant pulmonary infiltration of lipid-laden macrophages, despite 27 weeks of sebelipase alfa treatment (18 doses of 3 mg/kg) and clinical improvement.

Summary of Subject ____(b) (6)____'s autopsy findings:

- General- non-dysmorphic ____(b) (6)____ infant Port-a-cath present on anterior chest; WFA <3rd percentile, LFA 50th percentile, and head circumference-for-age < 3rd percentile

- Cardiac- right atrial mural thrombus (1.5x 1.2 x 0.8 cm), mild left ventricular hypertrophy (consistent with the patient's history of hypertension), overall normal heart size for age, patent foramen ovale (0.2 cm), no cardiac myocyte abnormalities on microscopic examination

- Pulmonary- diffuse pulmonary edema, moderate-to-severe pulmonary congestion, xanthomatous changes with numerous intra-alveolar macrophages with prominent intracellular cholesterol clefts, subpleural fibrosis admixed with foamy macrophages

- Hepatic- hepatomegaly with pronounced passive hepatic congestion, preservation of parenchymal architecture, prominent fibrosis within portal triads and bile duct proliferation and areas of focal bridging fibrosis

- Gastrointestinal- Mesenteric thickening with dilated subserosal vessels; prominent submucosal fibrosis of the stomach, small intestine, colon; focal inflammation throughout the lamina propria; diffuse infiltration of the intestinal submucosa, muscularis, and serosa of jejunum with xanthomatous macrophages with prominent lipid vacuoles; granular subserosal fatty deposits mucosal; evidence of autolysis within pancreas

- Spleen- splenomegaly, minimal xanthomatous cell infiltration of splenic red pulp

- Lymph nodes- massive mediastinal, mesenteric/abdominal, retroperitoneal lymphadenopathy; cortical lymph node depletion and expansion of lymph node sinuses with foamy macrophages

- Bone marrow- extensive replacement of bone marrow by large lipid vacuoles and lipid-laden macrophage, residual bone marrow elements with

- Adrenal glands- fibrosis and dystrophic calcification of the inner adrenal cortex

- Normal brain and kidneys/urinary tract

7.3.2 Nonfatal Serious Adverse Events

Thirty-one serious adverse reactions (SAEs) were reported during Study LAL-CL03, and 8 of the 9 LAL-CL03 clinical trial patients experienced at least one SAE. As discussed in Section 7.1.2, investigators often reported multiple concurrent adverse events which represent signs, symptoms, or abnormal results of investigations for a single event. Of the 31 reported SAEs, this reviewer identified 26 unique events, occurring in 8 of the 9 LAL-CL03 patients. (Table 19) Of these 26 events, 3 (12%) events are considered to have a direct causal relationship to treatment with sebelipase alfa, and all 3 represent hypersensitivity reactions. A detailed review of hypersensitivity reactions in LAL-CL03 is located in Section 7.3.4.

This clinical reviewer identified an additional 10 (38%) SAEs which represent complications of sebelipase alfa treatment, although they were not directly caused by the drug and are not considered adverse reactions. All 10 events are complications related to venous access required for intravenous infusion of sebelipase alfa. As expected in this young population, indwelling central lines and/or permanent central venous access were required by all LAL-CL03 study patients. Because these AEs represent risks to patients incurred as a result of treatment (e.g., procedures performed for the purpose of administering sebelipase alfa infusions and complications of these procedures), this reviewer considers these events relevant to the overall benefit-risk profile of the drug.

Of the remaining 13 SAEs without a direct or indirect relationship to sebelipase alfa treatment, 7 (23% of all SAEs) were related to the patients' underlying LAL deficiency. These include 3 fatal events in Subjects   (b) (6)   , and   (b) (6)   , none of which are considered to be related to sebelipase alfa treatment (see Section 7.3.1).

Table 19: Serious Adverse Events in LAL-CL03 (n=26)

SUBJECT	STUDY DAY	DOSE (mg/kg)	SERIOUS ADVERSE EVENT
(b) (6)	6	0.35	*MULTISYSTEM ORGAN FAILURE*
(b) (6)	67	1	**CATHETER SITE INFECTION**
	134	1	**CENTRAL LINE INFECTION**
	233	3	FOOD INTOLERANCE
	408	3	VIRAL INFECTION
	594	3	RESPIRATORY INFECTION
	602	3	FEVER
(b) (6)	43	1	**CATHETER SITE INFECTION**
	73	1	**CATHETER SITE INFECTION**
	85	1	**CATHETER SITE INFECTION**
	99	3	**POOR VENOUS ACCESS**
	156	3	RESPIRATORY INFECTION
(b) (6)	521	1	LYMPHADENOPATHY
(b) (6)	32	1	FEVER
	93	3	WEIGHT LOSS
	103	3	**STAPHYLOCOCCUS AUREUS BACTEREMIA/SEPSIS**
	105	3	DIARRHEA/DEHYDRATION/ACIDOSIS
	270	3	ROSEOLA
(b) (6)	21	1	FAILURE TO THRIVE
	43	3	**CENTRAL LINE INFECTION**
	84	3	**HYPERSENSITIVITY WITH MULTIPLE SYMPTOMS**
	91	3	**STAPHYLOCOCCUS AUREUS BACTEREMIA/SEPSIS**
	168	3	BACTERIAL PYELONEPHRITIS
	240	3	**CENTRAL LINE INFECTION**
(b) (6)	5	0.35	*INTRAPERITONEAL HEMORRHAGE*
(b) (6)	26	1	*CARDIAC ARREST*

(Source: Reviewer's table based on Applicant data, LAL-CL03 Analysis Datasets, BLA 126651, Module 5.3.5.2)
Bolded items indicate SAEs either directly or indirectly related to sebelipase alfa treatment; bolded subject ID numbers indicate patients with ≥1 SAE directly or indirectly related to sebelipase alfa treatment

Items shaded gray represent adverse reactions events directly attributable to effects of sebelipase alfa)

Italicized items indicate fatal events.

7.3.3 Dropouts and/or Discontinuations

The Applicant reports that sebelipase alfa treatment was discontinued in one patient (Subject ^{(b) (6)}) after the first infusion due to the onset of bradycardia. The patient died prior to the day of the second scheduled infusion. No patients discontinued study treatment due to adverse reactions.

7.3.4 Significant Adverse Events

The majority of the AEs in LAL-CL03 belong to one of three categories—(1) hypersensitivity reactions, (2) disease-related manifestations and complications, and (3) concomitant illnesses. Hypersensitivity reactions are reviewed in Section 7.3.5.

In addition to the patients who died of disease-related complications, one additional patient experienced disease-related AEs which this reviewer considers of particular significance.

- Subject ^{(b) (6)}: An SAE of "lymphadenopathy" was reported at Day 521 (~Week 74) based on the MRI finding of worsening mesenteric lymphadenopathy (Week 63), as compared to the patient's baseline CT scan. The lymphadenopathy was determined to be due to the patient's underlying LAL deficiency, and was considered a sign of suboptimal treatment response; however, prior to this determination, the patient was hospitalized for evaluations to rule out potential malignancy, including bone marrow aspiration (Day 551 / Week 78) and hepatic and lymph node biopsies (Day 578 / ~Week 81). Histological examination of biopsied tissue revealed the presence of storage material. At Week 91 (Day 859), the patient's sebelipase alfa dose was escalated to 3 mg/kg once weekly. The SAE was considered resolved after the receipt of the patient's biopsy results.

7.3.5 Submission Specific Primary Safety Concerns

As with other ERT products, the primary safety concerns with sebelipase alfa are hypersensitivity reactions, including anaphylaxis, and the development of anti-drug antibodies (ADA).

Hypersensitivity Reactions Including Anaphylaxis

Forty-seven AEs with a temporal relationship to sebelipase alfa infusion were categorized by investigators as "infusion-associated reactions (IARs)." This tabulation does not include the reactions experienced by Subject ^{(b) (6)} while receiving sebelipase alfa treatment under the ATU. Because the Investigator was not required to report non-serious adverse events to the Applicant, minimal data are available regarding hypersensitivity reactions experienced by the

patient during this period, and these data are too limited to be included in LAL-CL03 safety analyses. The term IAR is relatively non-specific and does not distinguish between immune-mediated and non-immune mediated infusion-related events. For this class of medications, the Agency now recommends using the term "hypersensitivity reaction" to identify adverse reactions with both a temporal and specific causal relationship to the study drug. Of the 47 AEs labelled as IARs, 45 have been included in a subgroup of hypersensitivity symptoms. However, two of these 45 AEs (an episode of diarrhea in Subject (b) (6) and an isolated episode of vomiting in Subject (b) (6)), may not have been immune-mediated reactions. Gastrointestinal distress, particularly isolated diarrhea, can be a manifestation of a hypersensitivity reaction, and while these types of reactions have been recognized with other ERT products for lysosomal storage disorders, additional evidence such as response to antihistamine treatment and presence of anti-drug antibodies were useful to identify these as hypersensitivity reactions. For the purposes of this review, these 2 gastrointestinal reactions, which were categorized by the Applicant as "infusion-associated reactions" and for which a temporal relationship was clearly established, have been categorized as hypersensitivity reactions.

After accounting for multiple AEs reported for the same event, this reviewer identified 26 discrete hypersensitivity reactions occurring in 367 infusions (7%) administered in LAL-CL03 prior to data cutoff. Four of the 9 patients (44%) in LAL-CL03 [4 of the 6 (67%) surviving patients) experienced ≥1 hypersensitivity reaction. Three of the 4 patients (Subjects (b) (6) (b) (6)) experienced recurrent hypersensitivity reactions. Subject (b) (6) experienced a single episode of vomiting on Study 42, and as discussed above, it is not clear whether this represents a hypersensitivity reaction (Table 20).

All 3 of the patients with recurrent hypersensitivity reactions were ADA positive, and 2 of the 3 patients tested positive for neutralizing ADA. A discussion of the relationship between ADA and adverse events is discussed further in Section 7.4.6 (Immunogenicity).

Table 20: Summary of Hypersensitivity Reactions during LAL-CL03, by Patent, in Chronological Order

Subject ID	Study Day	Dose (mg/kg)	Description	Severity
(b) (6)	43	1	tachycardia, fever	Mild
	50	1	fever, irritability, tachycardia	Mild
	162	3#	urticaria	Moderate
	190	3	fever, retching, cough, agitation	Mild
	337	3	tachycardia, pallor	Mild
(b) (6)	(1-284)★	1	ATU reactions: ★ "fever, diarrhea, skin rash"	Unknown ("non-serious")
	285	1	fever	Mild
	291	1	fever	Mild
	306	1	fever	Mild
	348	1	fever	Mild
	355	1	diarrhea	Mild

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	377	1	urticaria	Mild
	614	1	vomiting	Mild
	621	1	vomiting	Mild
(b) (6)	*42*	*1*	*vomiting*	*Mild*
(b) (6)	14	1	vomiting	Mild
	43	3[#]	fever, tachycardia	Moderate/Severe[††]
	50	3	fever	Mild
	56	3	fever	Mild
	63	3	fever, vomiting	Mild
	84	3	fever, chills, pallor, tachycardia	Moderate/Severe[††]
	168	3	fever, chills	Mild
	203	3	fever	Mild
	240	3	fever, chills, decreased oxygen saturation	Moderate[‡]
	268	3	fever	Mild
	345	3	fever	Mild
	408	3	fever, tachycardia, chills, hypotonia, hypertension	Mild

(Source: Reviewer's table created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)
Italicized events represent the 2 reactions which may not be hypersensitivity reactions

★Until Week 40, Subject (b) (6) received sebelipase alfa treatment under an expanded access protocol in France, i.e., Autorisation Temporaire d'Utilisation (ATU). Because the Investigator was not required to report non-serious adverse events to the Applicant, information regarding hypersensitivity reactions experienced by the patient during this period is limited to data published by the Investigator. The available information includes only a list of symptoms without details of the number of hypersensitivity reactions, the timing of reactions, or the frequency and severity of individual symptoms.

[#] Reaction occurred during the patient's first sebelipase infusion at the dose of 3 mg/kg

[†] On Study Days 43 and 84, hypersensitivity symptoms experienced by Subject (b) (6) were assigned multiple levels of severity by the investigator. On Study Day 43, the patient experienced Grade 2 (moderate) fever and Grade 3 (severe) tachycardia, and on Study Day 84, the patient experienced Grade 2 (moderate) fever and chills and Grade 3 (severe) pallor and tachycardia.

[‡] The 3 moderate and severe reactions in Subject (b) (6) all occurred concurrently with episodes of moderate or severe infection.

As shown in Table 20, sebelipase alfa doses of both 1 mg/kg and 3 mg/g were associated with hypersensitivity events. The Applicant points out that 2 patients (Subject (b) (6) and Subject (b) (6)) experienced moderate/severe hypersensitivity reactions during their first infusion at the 3 mg/kg dose. However, for Subject (b) (6), all of the moderate/severe reactions occurred during periods of concurrent moderate- or severe-grade infections. In addition, Subject (b) (6) experience recurrent hypersensitivity events while receiving treatment with a dose of 1 mg/kg, but had no reactions reported during the approximately 500 days of treatment with 3 mg/kg. Thus, in this small patient population with variable timing of dose adjustments, an association between sebelipase alfa dose and risk of adverse events cannot be determined from these anecdotal observations.

Premedication was not routinely administered prior to infusions of sebelipase alfa in clinical trials. In LAL-CL03, 2 patients (22%) received scheduled premedication with antipyretics, antihistamines, and/or corticosteroids for prevention of hypersensitivity reactions. Details regarding the particular medications administered and the study time points of administration can are shown in Figure 22 in Section 7.4.6 (Immunogenicity).

Sebelipase infusion interruptions and/or modifications (e.g., rate slower than protocol procedures, rate escalation during infusion) were performed to treat and/or prevent hypersensitivity reactions in 5 of the 9 (56%) patients (5 of the 6 surviving patients). In 4 of the 5 patients, the majority of infusions were administered with these types of adjustments. (Table 21)

Table 21: Number of Sebelipase Alfa Infusions per Patient with Interruption and/or Modification to Treat and/or Prevent Hypersensitivity Reactions

Patient	n/Total	Percent
(b) (6)	0/1	0
	76/95	80
	49/61	80
	93/146	64
	1/65	2
	50/61	82
	0/28	0
	0/1	0
	0/4	0

Source: Reviewer's table created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most commonly reported adverse reactions in patients with early onset, rapidly progressive LAL deficiency are diarrhea, vomiting, fever, cough, and urticaria, and these reactions represent reported symptoms of hypersensitivity reactions. These are discussed in further details in Sections 7.3.4 and 7.4.6.

7.4.2 Laboratory Findings

Other than immunogenicity data, no safety concerns (i.e., evidence of drug toxicity) was identified from laboratory studies

7.4.3 Vital Signs

Sustained and/or recurrent episodes of elevated blood pressure were noted in 6 of the 9 patients in LAL-CL03. Normal ranges were defined based on sex-, age- and height-based normative data in infants and toddlers from the National Institute of Health.[47] Reference ranges for this

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patient population were 75 to 105 mmHg for systolic blood pressure and 37 to 66 mmHg for diastolic blood pressure.

Although elevated blood pressure was relatively common among these patients, no consistent pattern could be determined to identify a specific safety concern. Three patients with elevated blood pressures during study participation had a prior medical history of hypertension (Subjects   (b) (6)). In all 3 of these patients, blood pressures only mild changes were observed during sebelipase alfa infusions, and none of these patients experienced adverse events attributed to high blood pressure. Two patients experienced recurrent episodes of elevated blood pressures during sebelipase alfa (Subjects   (b) (6) and   (b) (6)), reported as "variable" and "substantial", none of which were associated with other adverse events. In both patients, blood pressures normalized after the infusion, though Subject   (b) (6) often maintained elevated blood pressure during the post-infusion monitoring period. In one patient (Subject   (b) (6)) without a prior medical history of hypertension, numerous substantially elevated systolic and diastolic blood pressures (pre-infusion, during infusion, and post-infusion) were recorded following initiation of sebelipase alfa treatment. Blood pressures were variable throughout study participation without a clear explanation for the high readings and no related adverse events occurred.

All other clinically significant vital sign abnormalities were reported as AEs, all of which were manifestations of hypersensitivity reactions. These events are reviewed in Section 7.3.4.

7.4.4 Electrocardiograms (ECGs)

Minimal ECG data were obtained in this population, and no abnormalities were identified which were attributable to the drug treatment.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

Anti-drug Antibody (ADA) Development

Seven of the 9 patients in LAL-CL03 patients had ≥1 assessment for anti-drug antibodies (ADA) following initiation of sebelipase treatment. Of these 7 patients, the 5 patients with available screening data were ADA negative at baseline. (Screening data were unavailable for   (b) (6) and   (b) (6)). Four of the 7 patients, all of whom were among the surviving patients, had detectable ADA on ≥1 post-treatment immunogenicity assessment. In the 3 patients who initiated sebelipase alfa treatment in LAL-CL03 and underwent protocol ADA assessments, measureable ADA titers were detected within the first 2 months of exposure (Weeks 5 to 8).

Two patients (Subjects   (b) (6) and   (b) (6)) tested positive for neutralizing antibodies that inhibit both LAL enzyme activity and LAL cellular uptake in Study LAL-CL03. In both patients,

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assessments for neutralizing antibodies were positive at all timepoints at which these patients had detectable ADA titers based on the binding antibody assay. Subject (b)(6) first tested positive for ADAs at Week 5 (titer 1/254), at which time neutralizing antibody activity was at a level of 18.9% enzyme inhibition. This patient remained ADA positive through data cutoff, and although ADA titers fluctuated throughout clinical trial participation, inhibition of LAL enzyme activity by neutralizing antibodies increased to 70.9% at Week 8 and remained above 80% on all subsequent assessments. This subject also tested positive for neutralization of cellular uptake on the single evaluation performed using this assay single (Week 72). The other patient with positive neutralizing antibodies (Subject (b)(6)) also had high levels of inhibition of LAL enzyme activity, ranging 82.1% to 89.8%, and starting within the first couple of months of exposure to sebelipase alfa (Week 8). This patient also tested positive for neutralizing antibody that inhibits cellular uptake at unscheduled assessments at ~Week 23 and Week 25. At the time of data cutoff, Subject (b)(6), as well as both of the ADA positive patients with negative neutralizing antibody assays (b)(6) and (b)(6)), patients with had negative ADA assessments. The one patient with detectable ADA titers through data cutoff, Subject (b)(6), experienced a reduction in sebelipase alfa efficacy which was attributed to the presence of neutralizing ADA. Peak ADA titers for this patient occurred at Week 16 (1/1032) and Week 72 (1/1141.6), the latter of which corresponded to the patient's loss of efficacy. Following a sebelipase alfa dose escalation to 5 mg/kg once weekly at Week 88, this patient was beginning to demonstrate evidence of clinical improvement at the time of data cutoff.

For all 6 surviving patients, antibody titers are shown graphically in Figure 21. For the 7 patients with at least 1 available post-treatment ADA assessment, immunogenicity data are summarized in

Table 22. In this small patient population, it is not feasible to draw definitive conclusions of the impact of ADA on the safety and efficacy of sebelipase alfa. However, it is notable that ADA titers were highest in the two patients with neutralizing ADA, recurrent hypersensitivity reactions occurred in the 3 patients prolonged periods of ADA positivity, and the only cases of loss of efficacy were associated with either neutralizing ADA or a failed attempt to decrease the frequency of sebelipase alfa infusions, both of which were improved with an increased dosage. The association between ADA and sebelipase alfa safety in LAL-CL03 is discussed in more detail below under the subheading "Impact of ADA on Safety of Sebelipase Alfa", along with a graphical representation of ADA titers, hypersensitivity reactions, and treatments of hypersensitivity (Figure 22 and associated Table 23).

Figure 21: Anti-Drug Antibody Titers Over Time for Surviving Patients in LAL-CL03 (N=6)
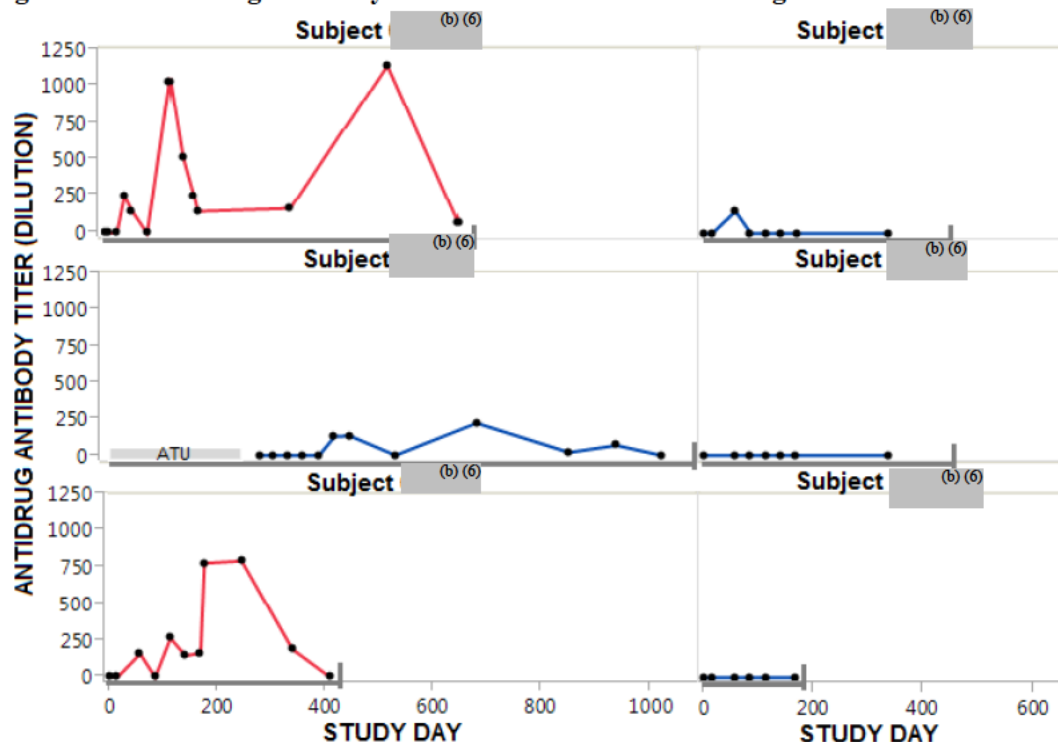
(Source: Reviewer's figure based on Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)
Duration of study participation with data cutoff are indicated by gray lines on X-axis.
Red lines indicate neutralizing ADAs, blue lines indicate ADA without neutralizing activity
ATU data not available for Subject ____ (b) (6) - 1st available immunogenicity result is from Week 40 of treatment

Table 22: Summary of Immunogenicity Data in Patients with ≥1 Post-Treatment Immunogenicity Assessment (N=7)

Patient ID	ADA Positive#	Baseline	Neutralizing ADA	ADA+ Weeks (of total)	Hyper-sensitivity	Decreased Efficacy
(b) (6)	Yes	Negative	Yes	5-92 (of 92)†	Yes	Yes
	Yes	Negative	No	10 (of 48)	No	N=
	Yes	Negative	No	59-132 (of 144)	Yes	No
	No	ND	N/A	N/A	Yes	No
	Yes	Negative	Yes	7-48 (of 60)	Yes	No
	No	Negative	N/A	N/A	No	No
	No	ND	No	N/A	No	N/A

(Source: Reviewer's table based on Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)
Abbreviations: ADA, anti-drug antibody(ies); N/A, not applicable; ND, not done (i.e., test not performed)

Patient ID in bolded font indicates ADA-positive patient

Italicized font indicates deceased patient

ADA positivity is defined as having ≥1 detectable ADA titer at any time point

†Subject ____ (b) (6) is the only patient with detectable ADA titer on the last assessment prior to data cut-off

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Impact of ADA on Safety of Sebelipase Alfa

Hypersensitivity reactions occurred in 3 of the 4 of the ADA-positive patients, whereas they occurred in only 1 of the 3 ADA-negative patients. (

Table 22) In addition, the 3 ADA-positive patients experienced recurrent hypersensitivity reactions, as compared to the ADA-negative patient who experienced a single, mild reaction which may not have been due to hypersensitivity. Both patients with neutralizing antibodies experienced recurrent hypersensitivity reactions, and were the only patients who experienced hypersensitivity reactions graded as moderate and/or severe.

Figure 22: Antibody Titers, Hypersensitivity Reactions, and Treatments for Hypersensitivity Reactions Over Time for the Patients with ≥1 Detectable ADA Titer or Hypersensitivity Event (N=5)
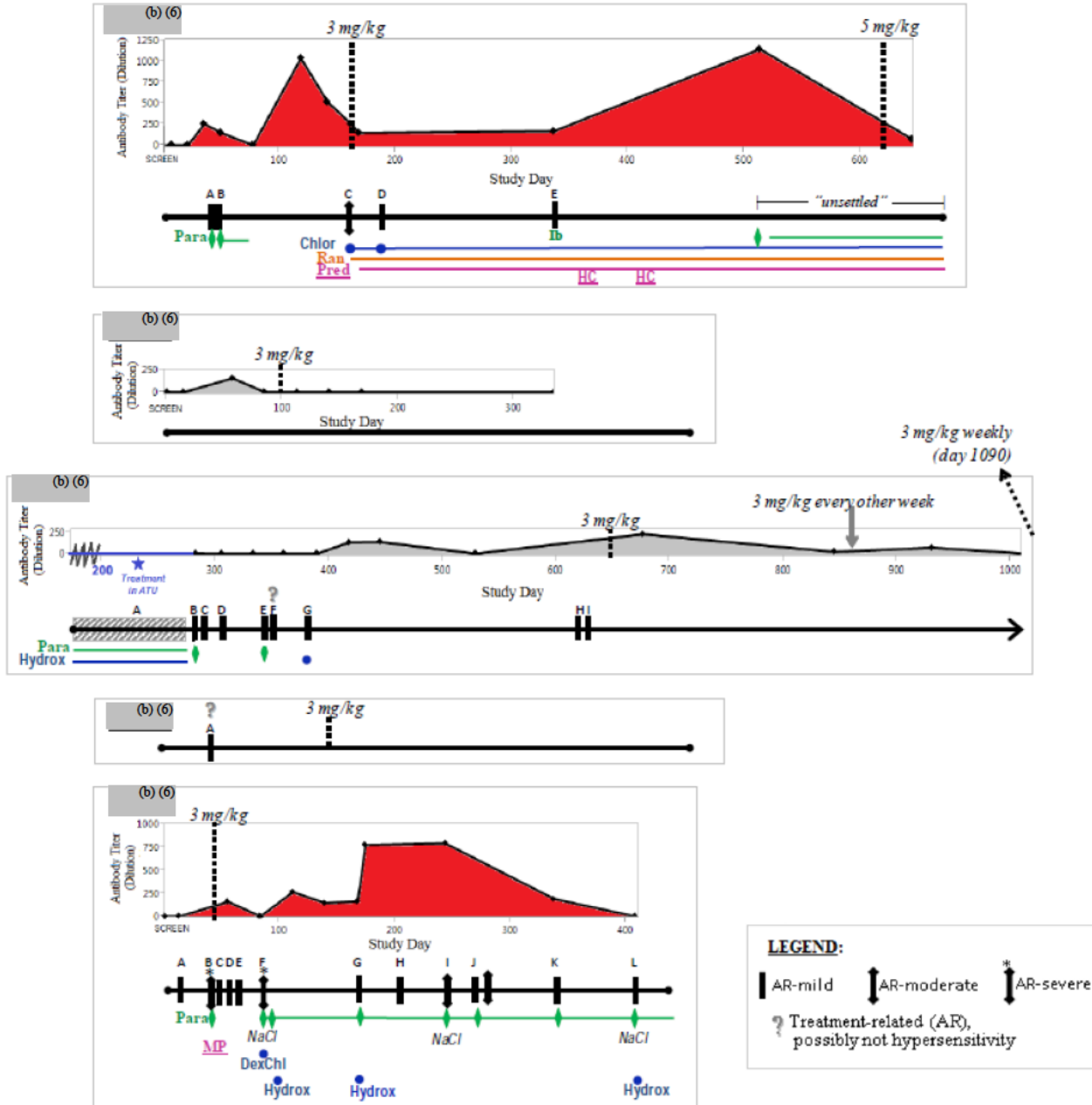
(Source: Reviewer's figure based on Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

Abbreviations- concomitant mediations:
- Antipyretics (green)-Ib, Ibuprofen; Para, paracetamol
- Antihistamine/H$_1$-receptor (blue)- Chlor, chlorphenamine.; DexChl, dexchlorphenamine; Hydrox, hydroxyzine
- H$_2$-receptor antagonist (orange)- Ran, ranitidine
- Corticosteroids (purple)- HC, hydrocortisone; MP, methylprednisolone; Pred, prednisolone
- Fluid resuscitation (black italics)- NaCl, normal saline

Table 23: Summary of Hypersensitivity Reactions during LAL-CL03 in Chronological Order (with Labels Corresponding to Figure 22)

Subject ID	AR "Label"[†]	Description	Severity
(b) (6)	A	tachycardia, fever	Mild
	B	fever, irritability, tachycardia	Mild
	C	urticaria	Moderate
	D	fever, retching, cough, agitation	Mild
	F	tachycardia, pallor	Mild
	G	urticaria	Mild
(b) (6)	A★	ATU reactions:★ fever, diarrhea, skin rash	Unknown ("non-serious")
	B	fever	Mild
	C	fever	Mild
	D	fever	Mild
	E	fever	Mild
	F	*diarrhea*	*Mild*
	G	urticaria	Mild
	H	vomiting	Mild
	I	vomiting	Mild
(b) (6)	*A*	*vomiting*	*Mild*
(b) (6)	A	vomiting	Mild
	B	fever, tachycardia	Moderate/Severe
	C	fever	Mild
	D	fever	Mild
	E	fever, vomiting	Mild
	F	fever, chills, pallor, tachycardia	Moderate/Severe
	G	fever, chills	Mild
	H	fever	Mild
	I	fever, chills, decreased oxygen saturation	Moderate
	J	fever	Mild
	K	fever	Mild
	L	fever, tachycardia, chills, hypotonia, hypertension	Mild

(Source: Reviewer's table created using Applicant's data in LAL-CL03 Analysis Datasets, BLA 125561, Module 5.3.5.2)

[†] AR "Label" is the letter code which corresponds to the reactions in Figure 22

★ Subject (b) (6) received 39 weeks of sebelipase alfa treatment in an expanded access program in France (ATU). Because the Investigator was not required to report information of non-serious AEs in the ATU, limited information is available regarding adverse events experienced by Subject (b) (6) during this time period. According to published information by the investigator referenced by the Applicant, the patient experienced episodes of fever, diarrhea, and skin rash associated with sebelipase alfa infusions and received pre-medication with hydroxyzine, paracetamol, and/or topical anesthetic duration treatment under the ATU. These medications were discontinued upon clinical trial enrollment.

Conclusions, Future Directions, Recommendations Regarding Immunotolerance

Based on the immunogenicity profile of sebelipase alfa in this small clinical trial population, this reviewer concludes that the available data do not support a recommendation to explore pre-emptive immunotolerance at this time. Despite the fact that early-onset LAL deficiency is a uniformly fatal disease loss of efficacy due to neutralizing ADA could be fatal, none of the patients in LAL-CL03 demonstrated ADA-related sequelae of this degree. On the other hand, several of these patients presented with multi-system organ dysfunction and evidence of severe immune dysregulation, which may make immunosuppression of these patients of immunosuppression highly risky.

It is possible that deficiency of LAL may lead to an inherent immunotolerance to ERT in this patient population. Studies in $LIPA^{-/-}$ knock-out mice have implicated LAL in the early development and maturation of T-cells.[31-34] These findings may provide an explanation for the overall lower rate and magnitude of ADA development and the transient nature of ADA positivity in patients who do develop ADA to sebelipase alfa, as compared to ERT treatment in patients with early-onset, fatal phenotypes of other lysosomal storage disorders. However, to date, no data in humans are available to provide supportive evidence that the observations in this small clinical trial population are the direct result of immunological effects of LAL deficiency as suggested by the preliminary animal studies.

7.5   Other Safety Explorations

None

7.5.1   Dose Dependency for Adverse Events

See discussion in Section 7.4.6.

7.5.3   Drug-Demographic Interactions

Due to the very small clinical trial population, subpopulation analyses were not performed based on demographics.

7.5.4   Drug-Disease Interactions

No specific studies were done to assess drug-disease interactions in this trial.

7.5.5   Drug-Drug Interactions

No specific studies were done to assess drug-drug interactions in this trial.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No assessments performed

7.6.2 Human Reproduction and Pregnancy Data

Not applicable to this patient population

7.6.3 Pediatrics and Assessment of Effects on Growth

Since growth retardation is a well-recognized clinical manifestation of early onset LAL deficiency, these assessments were performed as part of the efficacy evaluation. (Section 6.1.5) This review did not identify any evidence that concerns treatment with sebelipase alfa has a negative impact on somatic growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no concerns for overdose or drug abuse potential. No studies were conducted to investigate the effect of withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

There is no post-marketing experience with sebelipase alfa.

9 Appendices

9.1 Literature Review/References

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43. Yip PM, Chan MK, Nelken J, Lepage N, Brotea G, Adeli K. Pediatric reference intervals for lipids and apolipoproteins on the VITROS 5,1 FS Chemistry System. Clinical Biochemistry 39 (2006) 978–983.

44. Loh TP, Antoniou G, Baghurst P, Metz MP. Development of paediatric biochemistry centile charts as a complement to laboratory reference intervals. Pathology (June 2014) 46(4), pp. 336–343

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47. National Heart Lung and Blood Institute. A Pocket Guide to Blood Pressure Measurement in Children. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health; 2007.

9.2 Labeling Recommendations

This reviewer recommends the following revisions to the proposed label:

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- To ensure that prescribers are aware that Kanuma is not indicated for use in patients with dyslipidemia without concurrent evidence of LAL deficiency, the indication statement should be revised to state that Kanuma is a   (b) (6)

- Division of Section 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.

- Delineation of step-by-step preparation Instructions (input from the Division of Medication Error Prevention and Analysis (DMEPA) to calculate the total dose, number of vials, and volume of 0.9% Sodium Chloride for dilution.

- Addition of weight-based total infusion volumes for the 3 mg/kg dose to the table with recommended weight-based infusion volumes

- Inclusion of hypersensitivity reaction data from all ongoing and completed trials in Section 5.1 (Hypersensitivity Reactions Including Anaphylaxis)

- Addition of a separate subsection on "Hypersensitivity to Eggs or Egg Products."

- Deleted   (b) (6)

- Division of Section 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."

- Revision of Section 8 based to be consistent with the Pregnancy and Lactation Labeling Rule (PLLR) published on December 4, 2014

- Removal of   (b) (6)

- Revision of Section 14 to   (b) (6)
and revision of weight gain data to reflect changes in Z-scores

9.3 Advisory Committee Meeting

None.

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9.4   Clinical Investigator Financial Disclosure

Application Number: BLA 125561

Submission Date(s): January 8, 2015

Applicant: Alexion Pharmaceuticals, formerly Synageva

Product: Sebelipase alfa (SBC-102)

Reviewer: Lauren Weintraub, MD

Date of Review: September 8, 2015

Covered Clinical Study (Name and/or Number): LAL-CL03

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **68**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **1**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **8**		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)

- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Financial disclosure (FDA Form 3455) was provided for 1 of the 68 investigators participating in LAL-CL03 ((b) (6)*, a sub-investigator at site* (b)(6) *Certification (FDA Form 3454) was provided for 59 of the other 67 Investigators, and certification of due diligence was provided for 8 investigators.*

The Applicant disclosed that   (b) (6)*, Sub-Investigator at clinical trial site*   (b) (6) *received $25,012 for educational presentation/material and outreach activities. No subjects were enrolled in Study LAL-CL03 at this clinical study site.*

Complete financial disclosure information was provided for all Principal Investigators in LAL-CL03. The Applicant provided certification of due diligence for 8 sub-investigators in LAL-CL03 (b)(6)*from clinical trial site* (b)(6)*and* (b)(6)*from clinical trial site …) for whom they were unable to receive financial disclosure information.*

- *For the* (b)(6)*sub-investigators from clinical trial site*   (b) (6) *the Applicant reports that these investigators were included on FDA Form 1572, which was completed several months prior to site activation, and by the time the study started these investigators were no longer participating in clinical trial.* (b) (6) *was enrolled in LAL-CL03 at this site.*

- *For* (b)(6)*sub-investigator at clinical trial site*   (b) (6) *the Applicant states that this physician was inadvertently entered on Form FDA 1572 and never participated on the trial. No subjects were enrolled at LAL-CL03 at this site.*

This reviewer concludes that the disclosed financial interests/arrangements do not affect the approvability of this application or raise questions about the data integrity of Study LAL-CL03.

9.5 Additional Tables and Figures

Table 24: List of Assessment for the Natural History Study, LAL-1-NH01

Assessment Category	Assessment	Data Collection		
		Start	End	Frequency
Eligibility	Confirm study eligibility	Study entry		Once
Demographics	Date of birth	Study entry[a]		Once
	Gender, race, ethnicity	Study entry		Once
	Gestational age at birth and whether the patient was premature[b]	Study entry		Once
	Country of origin/nationality	Study entry		Once
	Treatment center[c]	Study entry		Once
	Date of diagnosis[d] of LAL Deficiency	Study entry		Once
	Name and specialty of treating physician at: Symptom onset Diagnosis Death, if deceased	Study entry or death, as applicable		Once for each
Clinical History	Date of death[d], if deceased	Study entry[a] or death, as applicable		Once
	Age at onset of first symptom(s)	Study entry		Once
	Consanguinity of patient's parents	Study entry		Once
	Family history of stillbirth	Study entry		Once
	Oligohydramnios during gestation	Study entry		Once
	First type of feeding (breast/bottle)	Study entry		Once
	Number of siblings with LAL Deficiency and their status (living/deceased)	Study entry		Once
	Date of first occurrence[d] and date of resolution[d] of first occurrence of: Vomiting Diarrhea Steatorrhea Other symptoms/diagnoses	First record	Last record, prior to treatment (as applicable)	Once for each symptom

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Table 24 (cont): List of Assessment for the Natural History Study, LAL-1-NH01

Assessment Category	Assessment	Data Collection		
		Start	End	Frequency
Diagnostic Testing	Date of test, test result, normal range (if available), and name of testing center for: LAL enzyme activity LIPA genetic analysis	Study entry [a]		Once for each test [h]
Clinical Chemistry	Date of test and test result for: AST/SGOT, ALT/SGPT, GGT, total bilirubin TC, TG, LDL, and HDL Albumin, CK, total protein, serum gamma globulins, and ferritin ACTH/ACTH stimulation tests Cortisol	First record	Last record, prior to treatment (as applicable)	First assessment of each day or, if hospitalized more than 7 days, first assessment of the week. (Monday was considered the start of the week.)
Hematology	Date of test and test result for (as available): Hemoglobin, hematocrit, Platelet count CD4/CD8 ratio PT, PTT Reticulocytes, WBC	First record	Last record, prior to treatment (as applicable)	First assessment of each day or, if hospitalized more than 7 days, first assessment of the week. (Monday was considered the start of the week.)
Physical Examination	Date and result for weight at birth (or first record) [e]	Study entry [a]		Once
	Date and result for weight ≥4 weeks after birth (or first record) and prior to treatment [e]	Study entry [a]		Once
	Date and result for weight at death, if deceased [e]	Study entry or death, as applicable		Once
	Date(s) and result(s) for other weight measurements [f]	First record	Last record, prior to treatment (as applicable)	First assessment of the week. (Monday was considered the start of the week.)

Assessment Category	Assessment	Data Collection		
		Start	End	Frequency
	Date(s) and result(s) for measurement of length	First record	Last record, prior to treatment (as applicable)	First assessment of the week. (Monday was considered the start of the week.)
	Date(s) and result(s) for measurement of core body temperature	First record	Last record, prior to treatment (as applicable)	First assessment of the week. (Monday was considered the start of the week.)
	Date(s) and result(s) for measurement of head circumference	First record	Last record, prior to treatment (as applicable)	First assessment of the week. (Monday was considered the start of the week.)
	Date(s) of first observation of: Abdominal distension Hepatomegaly Splenomegaly Skin rash	First record, as applicable		Once for each condition
Histopathology	Date(s) and result(s) for: Liver biopsy (including PAS staining) Small intestine biopsy Skin biopsy Bone marrow biopsy/ aspiration	First record	Last record, prior to treatment (as applicable)	As applicable

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Table 24 (cont): List of Assessment for the Natural History Study, LAL-1-NH01 (cont)

Assessment Category	Assessment	Data Collection		
		Start	End	Frequency
Radiology	Date(s) and result(s) of abdominal imaging, including presence of adrenal calcification, hepatomegaly, and/or splenomegaly, for: X-ray MRI Ultrasound CT	First record	Last record, prior to treatment (as applicable)	As applicable
Virology	Date(s) and result(s) of screening for: Hepatitis A Hepatitis B Hepatitis C	First record	Last record, prior to treatment (as applicable)	As applicable
Supportive Interventions	Date and type of nutritional support [f]	First record	Last record, prior to treatment (as applicable)	All available chart records
	Date, generic name, and highest daily dose of steroid replacement therapy	First record	Last record, prior to treatment (as applicable)	All available chart records
	Date, type, and volume of blood transfusion	First record	Last record, prior to treatment (as applicable)	All available chart records
	Date and description of any other significant interventions [g]	First record	Last record, prior to treatment (as applicable)	All available chart records
Treatments	Date of initiation of any HSCT, and description of procedure if not BMT or umbilical cord transplant	First record, as applicable		Once
	Date of initiation of any pre-transplant conditioning regimen	First record, as applicable		Once

Assessment Category	Assessment	Data Collection		
		Start	End	Frequency
	Date of first infusion of ERT for LAL Deficiency	First record, as applicable		Once
Autopsy	Date and results for: Liver (including weight) Spleen (including weight) Adrenal system Lipid aortic elastic fibers Endothelial system Central nervous system	Study entry [a] or death, as applicable		Once
Follow-up	For patients alive at the final record check, confirmation of survival or date of death	Overall study completion		Prior to database lock and annually for 5 years thereafter

Abbreviations: ACTH = adrenocorticotrophic hormone; ALT/SGPT = alanine aminotransferase; AST/SGOT = aspartate aminotransferase; BMT = bone marrow transplant; CK = creatine kinase; CT = computed tomography; ERT = enzyme replacement therapy; GGT = gamma-glutamyl transferase; HDL = high density lipoprotein; HSCT = hematopoietic stem cell transplant; LAL = lysosomal acid lipase; LDL = low density lipoprotein; MRI = magnetic resonance imaging; PAS = periodic acid-Schiff; PT = prothrombin time; PTT = partial thromboplastin time; TC = total cholesterol; TG = triglycerides; WBC = white blood cell

[a] Required for study eligibility.

[b] Prematurity was defined as < 37 weeks of gestation

[c] The center where the patient was being treated at the time of enrollment or, if the patient was deceased, the last center where the patient was receiving treatment prior to death.

[d] Age at the time of the event was collected, if the date of the event was unknown.

[e] Weight measurements were extracted from growth charts, where available.

[f] Nutritional support may have included supplements, changes in nutritional composition of the patient's diet, or changes in route of feeding.

[g] Significant interventions may have included medications given to treat or alleviate Wolman disease symptoms or other symptoms noted in the patient's clinical history.

[h] Data for at least 1 test was required for study eligibility. Data for both tests were recorded in the CRF, if available.

Figure 23: The Role of High Density Lipoprotein (HDL), ATP-binding cassette transporter A (ABCA1), and Lysosomal Acid Lipase (LAL) in Reverse Cholesterol Transport

Copyright Material Withheld
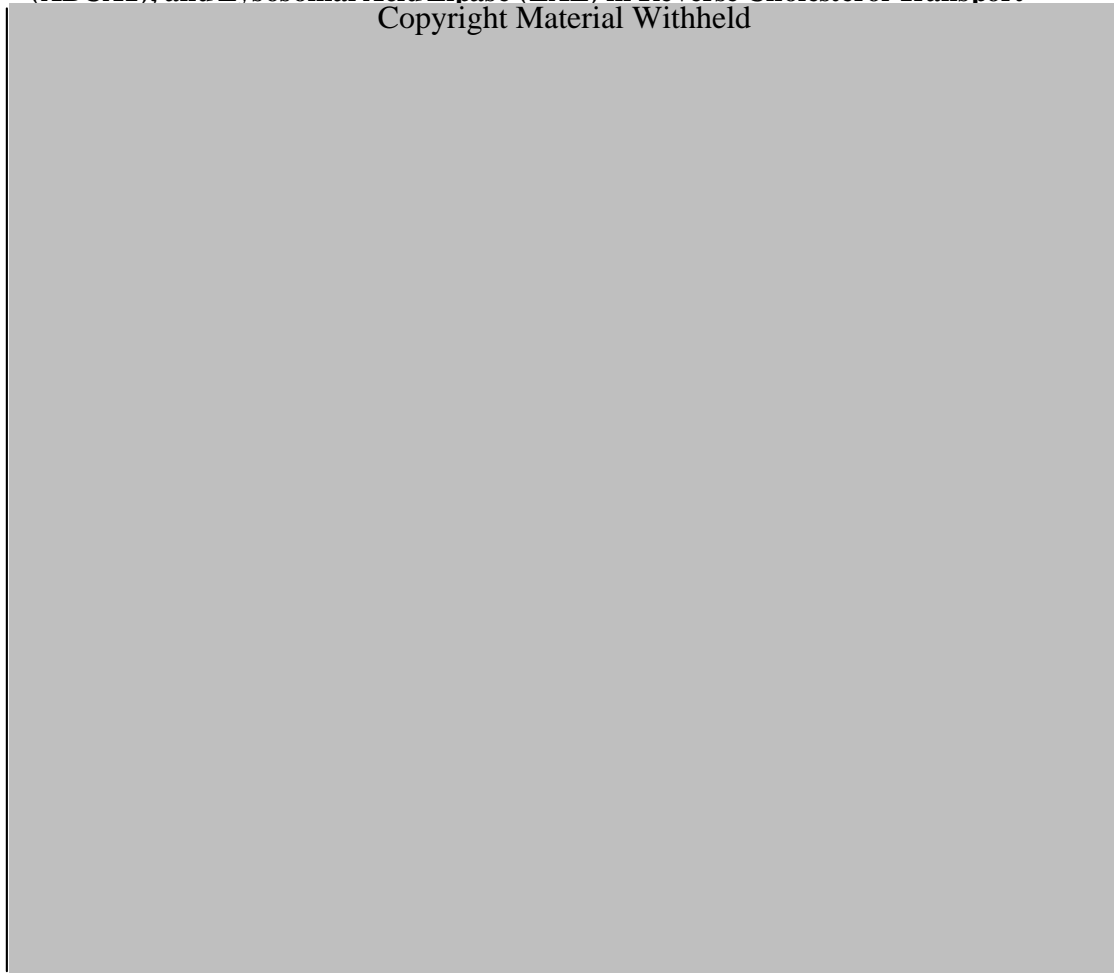
(Source: Reviewer's figure adapted from Zannis et al., J Mol Med 2006 and Tall et al., Cell Metabolism 2008)
The pathway of biogenesis and catabolism of HDL by liver, including key cell membrane or plasma proteins involved in HDL levels or composition

Abbreviations: ACAT1, Acyl-Coenzyme A:Cholesterol Acyltransferase; ABCA1, ATP-binding cassette transporter A; ABCG1, ATP-binding cassette sub-family G member 1; ApoA1, apolipoprotein A-I; CE, cholesteryl ester; CEH, cholesteryl ester hydrolase; FC, free cholesterol; FFA, free fatty acids; HDL, high density lipoprotein; LAL, lysosomal acid lipase; LDL, low density lipoprotein; SR-BI, scavenger receptor class B type I; TG, triglycerides; VLDL, very low density lipoprotein

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CLINICAL REVIEW

Application Type	New Molecular Entity for the treatment of lysosomal acid lipase deficiency
Application Number(s)	BLA 125561
Priority or Standard	Priority
Submit Date(s)	Rolling Review
Received Date(s)	January 8, 2015
PDUFA Goal Date	September 8, 2015
Division / Office	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer Name(s)	Juli Tomaino, MD, Medical Officer
	Jessica Lee, MD, Clinical Team Leader
Review Completion Date	June 8, 2015
Established Name	sebelipase alfa (SBC-102)
(Proposed) Trade Name	Kanuma
Therapeutic Class	Enzyme Replacement Therapy
Applicant	Synageva BioPharma Corp.
Formulation(s)	Intravenous infusion
Dosing Regimen	1 mg/kg every other week
Indication(s)	Lysosomal acid lipase deficiency
Intended Population(s)	Wolman's Disease and Cholesteryl Ester Storage Disease (CESD)

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1   Recommendations/Risk Benefit Assessment

1.1   Recommendation on Regulatory Action

This medical officer review evaluates BLA 125561 original application for Kanuma (sebelipase alfa). Kanuma 1 mg/kg intravenous (IV) infusion every other week is proposed for use as an enzyme replacement therapy for the treatment of pediatric and adult patients with lysosomal acid lipase (LAL) deficiency (i.e., cholesteryl ester storage deficiency [CESD]). Refer to the medical officer review by Dr. Lauren Weintraub for details of Study LAL-CL03, which enrolled infants with the more severe, rapidly progressive phenotype of LAL deficiency (Wolman Disease).

This document reviews the data submitted from Study LAL-CL02, a double-blind, randomized, placebo-controlled trial to evaluate the safety and efficacy of sebelipase alfa in patients ≥ 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 ≥ 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.

This reviewer considers BLA 125561 acceptable to recommend approval of Kanuma (sebelipase alfa) for the treatment of patients with lysosomal acid lipase deficiency with the requirement for a post-marking study to demonstrate the long-term clinical benefit of sebelipase alfa treatment on the progression of liver disease and cardiovascular events.

1.2   Risk Benefit Assessment

Kanuma 1 mg/kg every other week is proposed for the treatment of patients with lysosomal acid lipase (LAL) deficiency, a rare metabolic disease. Clinically, LAL deficiency is defined by two phenotypes: Wolman Disease (WD) (absence of LAL enzyme activity) and Cholesteryl Ester Storage Disease (CESD) (partial LAL enzyme activity). Since this document focuses on the

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results from Study LAL-CL02 in which enrolled patients ≥ 4 years of age with CESD, the risk benefit assessment will focus on that patient population. Clinical efficacy and safety data were also submitted from Study LAL-CL03, which evaluated sebelipase alfa in infants with Wolman disease, the most severe phenotype of LAL deficiency. Refer to medical officer review by Dr. Lauren Weintraub for details of Study LAL-CL03.

There are currently no available treatments for patients with LAL deficiency. The clinical manifestation of late-onset disease, CESD, is highly variable. While the majority of patients (80%) present in childhood with progressive liver disease, others go undiagnosed until complications (e.g., cirrhosis, liver failure, or atherosclerosis) manifest in late adulthood. Patients with CESD most frequently exhibit elevated serum transaminases, dyslipidemia (high LDL-cholesterol, high triglycerides, and low HDL-cholesterol), and hepatosplenomegaly; however, these are not universally manifested in all CESD patients. Kanuma (sebelipase alfa) is an enzyme replacement therapy that targets the underlying cause of the disease. Study LAL-CL02 provided efficacy and safety data to support the treatment of pediatric and adult patients with cholesteryl ester storage deficiency (CESD). As compared to placebo, patients treated with sebelipase alfa demonstrated significant improvement in low density lipoprotein cholesterol (LDL-c), and in other lipid parameters and liver-related pharmacodynamic measures.

The greatest risks associated with the class of enzyme replacement therapies are hypersensitivity reactions, including anaphylaxis. During the 20-week double-blind treatment period, no patients met the clinical criteria for anaphylaxis during Study LAL-CL02 and only 2/36 (6%) patients treated with sebelipase alfa experienced hypersensitivity reactions. These two patients experienced a total of 10 hypersensitivity reactions and 9/10 reactions occurred in one patient, who experienced a serious Grade 3 reaction and withdrew from the trial after Week 2. The other patient experienced a mild reaction that resolved without the need for additional treatment and had no recurrence of the reaction with subsequent infusions. The risks and mitigating strategies of anaphylaxis and hypersensitivity reactions will be described in the labeling.

Additionally, during the 20-week double-blind treatment period, only 5 patients developed low titers of anti-drug antibodies (ADA), which decreased to below detectable levels in 4/5 patients, and no patients tested positive for neutralizing antibodies during the double-blind treatment period. Only one patient with ADA experienced a hypersensitivity reaction reported as mild edema at the infusion site during the Week 12 infusion (7th study drug infusion). At the time, the ADA titer was low at 1:42. The infusion was stopped, no additional treatment was administered, and the patient was able to receive subsequent study drug infusions with no pre-medication and no recurrence of edema. No other ADA positive patient experienced a hypersensitivity reaction.

There were no deaths during Study LAL-CL02 and only one patient withdrew from the trial because of an adverse reaction, a serious hypersensitivity reaction. Overall, 59/66 (89%) patients experienced a treatment-emergent adverse event (TEAE) during the double-blind treatment period. Thirty-one out of the 36 (86%) SA-treated patients and 28/30 (93%) patients in the placebo group reported at least 1 TEAE. TEAEs reported in ≥ 8% of SA-treated patients (≥ 3 patients) where the frequency was higher in the SA group than in the placebo group included

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headache (10/36 [28%]), fever (9/36 [25%]), oropharyngeal pain (6/36 [17%]), nasopharyngitis (4/36 [11%]), constipation, nausea, asthenia, (3/36 [8%]) each.

There are no other available therapies for patients with LAL deficiency and the risks and mitigation strategies will be communicated through the label; therefore, Kanuma offers substantial clinical benefits compared to the risks that are associated with the product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no obligations for the Pediatric Research Equity Act (PREA) as orphan products are exempt from PREA requirements.

This reviewer recommends a postmarketing commitment study to further evaluate the long-term clinical benefit of Kanuma on liver and cardiovascular diseases. Of note, the applicant currently maintains a registry for patients with LAL deficiency and submitted the protocol upon request for our review.

- Evaluate the long-term, prospective clinical outcome of 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, weight z-scores). At a minimum, liver assessments will include liver biopsies, imaging, deterioration of liver synthetic function (i.e., increased bilirubin and IR), clinical progression to end stage liver disease (e.g., assessed by MELD score), receipt of liver transplantation, and death. Cardiovascular assessments will include incidence rates of stroke, myocardial infarction, and death. Additional evaluations will include dosing regimens and reasons for any dose modifications. This trial will also collect safety data including 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 follow for a minimum of 10 years from the time of enrollment or until death, whichever comes first. This trial may be conducted as a separate trial or as a sub-trial within the Lysosomal Acid Lipase registry.

Discussions regarding the goal date and final language of the study requirements were ongoing at the time of this review.

2 Introduction and Regulatory Background

Lysosomal acid lipase (LAL) deficiency is a rare multi-system disease in which mutations in the lysosomal acid lipase gene (*LIPA*) cause an absence or low levels of LAL enzyme activity.

The LIPA gene encodes lysosomal acid lipase (LAL), which is responsible for hydrolysis of cholesteryl esters and triglycerides in the lysosomes of the hepatocyte into free cholesterol and fatty acids. The low density lipoprotein (LDL) particle is comprised of proteins and lipids, including cholesteryl esters and triglycerides. Normally, LDL enters the hepatocyte via the LDL receptor and is transported to the lysosome where LAL hydrolyzes the cholesteryl esters and triglycerides into free cholesteryl and free fatty acids. The presence of free cholesterol in the cytosol of the hepatocyte results in decreased entry of cholesterol into the cell, decreased cholesterol synthesis, and inhibition of fatty acid synthesis. However, when LAL activity is deficient, the cholesteryl esters and triglycerides accumulate in the lysosomes. While the role of HMG-CoA reductase up-regulation is not completely understood in LAL deficiency, there may be a feedback inhibition of LDL receptor activity and reduced clearance of LDL-c.[1] Since the cholesteryl esters and triglycerides accumulate in lysosomes, the cells cannot access these lipids and must upregulate *de novo* cholesterol synthesis. Hepatomegaly or hepatosplenomegaly are common clinical findings in patients with CESD that occurs from the accumulation of cholesteryl esters and triglycerides in cell lysosomes of the gastrointestinal tract, liver, spleen, and cardiovascular system.[2]

Clinically, LAL deficiency is defined by two phenotypes: Wolman Disease (WD) (absence of LAL enzyme activity) and Cholesteryl Ester Storage Disease (CESD) (partial LAL enzyme activity). The estimated prevalence of WD is approximately 1:500,000.[3] Infants with WD exhibit massive hepatosplenomegaly, rapidly progressive liver dysfunction, fat malabsorption, steatorrhea, growth failure, profound weight loss, anemia, adrenal gland calcification, and death usually by 3 to 6 months of age; however, some may survive up to 12 months.

The diagnosis of late-onset disease, CESD, is highly variable. While the majority of patients (80%) present in childhood with progressive liver disease, others go undiagnosed until complications (e.g., cirrhosis, liver failure, or atherosclerosis) manifest in late adulthood.[2] The prevalence of CESD is estimated to be between 1/40,000 and 1/300,000, depending on the geographic location.[1] Patients with CESD most frequently exhibit elevated serum transaminases, dyslipidemia (high LDL-cholesterol, high triglycerides, and low HDL-cholesterol), and hepatosplenomegaly; however, these are not universally manifested in all CESD patients. Although many CESD patients are diagnosed with dyslipidemia, it is often misdiagnosed and is recognized less frequently than the complications of liver disease related to LAL deficiency.[1] Importantly, LDL-cholesterol 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. Premature accelerated atherosclerosis has been described in case reports of CESD patients, and

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[1] Reiner, Z., et al. Lysosomal acid lipase deficiency-An under-recognized cause of dyslipidaemia and liver dysfunction. Atherosclerosis 235 (2014) 21-30.
[2] Bernstein DL, Hülkova H, Bialer MG, Desnick RJ. Cholesteryl ester storage disease: Review of the findings in 135 reported patients with an underdiagnosed disease. J Hepatol. 2013 Feb 26.
[3] Meikle, P. J. et al. (1999). Prevalence of lysosomal storage disorders. *JAMA, 281*(3), 249.

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include coronary artery disease, aneurysm, stroke, atherosclerosis of the aorta and stenosis of femoral arteries.[4] Liver biopsies from patients with CESD have evidence of microvesicular steatosis, which progresses to fibrosis, cirrhosis and eventually, liver failure and death.[2] The life expectancy of patients with CESD depends on the severity of disease and associated complications.

Additionally, the clinical review team participated in a telephone call with patients with CESD, held February 27, 2015, to learn directly from patients and their caregivers about the most troublesome clinical signs and symptoms related to CESD to further inform the review of this product. All of the patients were monitored by physicians for abnormal liver- and lipid-related laboratory values. Patients/caregivers reported having normal BMI (or were "thin") despite being diagnosed with high cholesterol; one patient reported a diagnosis of atherosclerosis ("plaque") as an adult. Patients who were treated with lipid lowering medications stated that there was some improvement with medication and/or diet; however, they were not able to achieve and sustain normal or near-normal levels. The most notable clinical manifestations of disease described by the patients and their caregivers included fatigue and a large abdomen. Overall, the patients/caregivers did not describe feeling very symptomatic except for being aware of the abnormal blood work; however, they expressed concern about the presence of liver fibrosis and/or high cholesterol levels.

Currently, management of LAL deficiency is mainly supportive, and includes dietary modification and lipid lowering medication (e.g. HMG-CoA reductase inhibitors, cholestyramine). Statins, as monotherapy or combined with other lipid-lowering medications, often reduce LDL-c in patients with LAL deficiency but some patients have persistent elevations. However, these supportive medications do not address the underlying cause of disease.

2.1   Product Information

Sebelipase alfa (SA) is an enzyme replacement therapy (ERT), a recombinant human lysosomal acid lipase (rhLAL), that is purified from the egg whites of rhLAL transgenic gallus (hens). The enzyme has a terminal n-actelyglucosamine and mannose structures (e.g. mannose-6-phosphate) that allow binding to cell surface receptors and targeting of the enzyme to cell lysosomes. Sebelipase alfa cleaves cholesteryl esters and triglycerides that accumulate in LAL deficiency, thereby correcting the lipid abnormalities associated with LAL deficiency.

SA vials are for single-use only and intended for intravenous administration as a diluted solution, based on the patient weight, using a low-protein binding infusion set with an in-line, low-protein binding 0.2 micron filter. The total volume should be administered over 2 hours. SA contains no preservatives and should be used immediately after dilution.

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[4] Elleder M, et al. Subclinical course of cholesteryl ester storage disease in an adult with hypercholesterolemia, accelerated atherosclerosis, and liver cancer. Hepatol. 2000 Mar;32(3):528-34.

2.2   Tables of Currently Available Treatments for Proposed Indications

There are no approved therapies for LAL deficiency.

2.3   Availability of Proposed Active Ingredient in the United States

The active ingredient is not available in the United States.

2.4   Important Safety Issues with Consideration to Related Drugs

Enzyme replacement therapies are highly immunogenic; therefore, anti-drug antibody formation, including development of neutralizing antibodies, is the primary safety concern associated with this therapeutic class. Patients who develop antibodies may experience hypersensitivity reactions, including anaphylaxis, or decreases in efficacy, depending on the type of antibody (i.e., IgE vs. anti-drug IgG). The labels for most approved enzyme replacement therapies contain a boxed warning that states that life-threatening anaphylaxis and severe allergic and immune-mediated reactions are associated with these products.

2.5   Summary of Pre-submission Regulatory Activity Related to Submission

The initial IND application for sebelipase alfa was submitted on December 22, 2010 for the treatment of LAL deficiency. In July 2010, sebelipase alfa received Orphan Drug designation, and subsequently received Fast Track designation (June 14, 2011), followed by Breakthrough Therapy designation for LAL deficiency presenting in infants (May 13, 2013).

<u>Regulatory History Timeline: Key Clinical Meetings and Correspondences</u>

<u>June 12, 2012</u>: An End-of-Phase 1 (EOP1) meeting was held to discuss the clinical development plan of sebelipase alfa (SA). The Division generally agreed with the approach of evaluating patients with both Wolman and CESD and the plan to conduct two natural history studies, one for each phenotype. The Division recommended that data from the natural history studies be reviewed to inform the endpoints, target population, trial duration, and design of future clinical trials. In addition, the Division agreed based on the summary data provided from patients enrolled in Study LAL-CL01, that the approach of conducting a phase 2 dose-ranging study appeared acceptable, but there was inadequate data   (b) (4)
                                                The Division did not agree that the applicant provided
data to   (b) (4)

                                     Based on literature provided showing specific characteristic liver biopsy findings (i.e., birefringent cholesterol ester crystals), the Division recommended that the applicant consider evaluation of specific changes on liver biopsy in patients with CESD, as long as those changes can be correlated with clinical outcomes. Additional comments during this meeting included discussion of the appropriateness of using changes in ALT as the primary endpoint for a "registration" trial in patients with CESD. The Division did not agree that change

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in serum ALT could be used as a primary endpoint and recommended additional meetings to discuss the best path forward.

November 6, 2012: A Type C meeting was held as a follow-up to the EOP1 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 valid surrogate endpoint for clinical benefit in patients with CESD. The Division advised against using a "liver enzyme" endpoint as a primary endpoint in the proposed phase 3 trial, Study LAL-CL02. The Division stated that "to support the use of ALT as a primary endpoint, it is important that you demonstrate that the 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. For instance, 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 your drug or another drug are not at risk of developing onset of end-stage liver disease, you may have identified a surrogate worth considering as an endpoint."

May 13, 2013: Breakthrough Designation granted for Wolman disease ⬛⬛⬛⬛ (b) (4). The Breakthrough Designation was granted for the drug development program in infants with Wolman disease based on data that demonstrated survival to 10 months and 2 years of age in two sebelipase-treated infants, as compared to untreated patients in the applicant's natural history study, which showed that patients with Wolman disease and growth failure are expected to die by 6 months of age. An additional clinical benefit was demonstrated by the increase in weight-for-age percentile and resolution of growth failure (defined as weight below the 3rd percentile on a standard growth chart). ⬛⬛⬛⬛ (b) (4)

December 10, 2013: A Type C meeting (written response only) was held to further discuss the endpoints for phase 3.

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 these disease. The Division stated that in cases where there have been inadequate data to support the efficacy in certain disease subtypes, marketing

approval was granted only for those subtypes for which clinical trial data demonstrated clear evidence of improved clinical outcome. In this case, since differences in patient population, disease prognosis, and clinical trial endpoints will preclude integration of efficacy data for the infantile- and late-onset LAL patients, the efficacy results from clinical trials conducted in patients with infantile-onset disease will be reviewed separately from those conducted in patients with late onset disease to determine whether the data support a treatment indication in each subtype of LAL deficiency.

June 24, 2014: A Type C (written response only) meeting was held to address additional questions from the applicant regarding the planned components of the BLA.

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 remained concerned that the proposed clinical trial endpoints for late-onset LAL deficiency neither directly measure clinical benefit of treatment (i.e., how a patient feels, functions or survives) nor represent surrogate endpoints reasonably likely to predict clinical benefit. In addition, the Division stated that while a rolling review may permit early identification of issues that could delay or prolong the review process, 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) on the product (i.e., recombinant DNA construct engineered to express recombinant human lysosomal acid lipase) to conduct review of the New Animal Drug Application (NADA). After the Agency is notified of the complete application, a filing determination will be made within the usual time. The Division also reminded the applicant that NADA approval will be required prior to BLA approval. In addition, the applicant was reminded that justification for the proposed dosing regimen for each specific patient population with supporting data and data analyses needs to be provided; exposure-response should be provided for both efficacy and safety when possible. The Division recommended that the BLA should include data and analyses obtained from only blinded pathology interpretations of liver biopsy, rather than post-hoc unblinded evaluation of slides, as proposed.

October 21, 2015: BLA 125561 was submitted on a rolling review basis with key nonclinical, clinical, and quality components submitted on October 21, 2014 and November 21, 2014. Once the outstanding components required by the CVM were submitted, the BLA application was considered fully submitted on January 8, 2015.

2.6   Other Relevant Background Information

None.

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Appropriately organized data sets were provided for efficacy and safety populations.

3.2 Compliance with Good Clinical Practices

The applicant stated that the clinical trials were conducted in accordance with the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC), and in accordance with United States and international standards of Good Clinical Practice (GCP) as defined by the Food and Drug Administration [FDA] Title 21 part 312 and International Conference on Harmonization [ICH] guidelines.

Clinical Site Inspections: The clinical site inspection final reports were pending at the time of this review.

Protocol Deviations: No patient was withdrawn from the trial due to a protocol deviation. The applicant identified 7/66 (11%) patients with protocol violations that could potentially affect the analyses. Of the 7 patients with protocol violations, 5 patients were enrolled in the sebelipase alfa (SA) group and 2 patients were enrolled in the placebo group.

The full analysis set (FAS), all patients who were randomized to treatment and received at least one dose (or any portion of a dose) of sebelipase or placebo during the double-blind 20-week period was used for all efficacy and safety analyses. The efficacy analyses were repeated using the per-protocol (PP) population, which included all patients in the FAS who received at least 9 complete infusions during the double-blind period, had ALT measurements at both baseline and Week 20, had Week 20 assessments within 12 to 21 days of the preceding week (Week 18), did not change their lipid-lowering medications, and did not have any major protocol violations that would affect interpretation of the results for serum transaminases or serum lipids. Two patients were excluded from the PP analysis set: one patient (Subject ____(b) (6)____) in the SA group and one patient (Subject ____(b) (6)____) in the placebo group, due to a deviation in the time window between Week 18 and Week 20. One additional patient (Subject ____(b) (6)____) in the SA group was excluded from the PP analyses for receiving < 9 study drug infusions; however, the applicant did not consider this as a protocol violation since this patient withdrew from the double-blind treatment period after Week 2, due to a Grade 3 hypersensitivity reaction. The efficacy analyses were repeated using the PP population and the results were very similar to the analyses conducted using the FAS. Therefore, the analyses conducted using the FAS will be presented in this document. See statistical review by Dr. Benjamin Vali for further details.

The remaining 5 patients, 4/36 (11%) patients in the SA group and 1/30 (3%) patients in the placebo group, were determine to have the following protocol violations; however, these patients were not excluded from the PP analyses because the deviation was not considered to affect the

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interpretability of the results.

SA Group
- Subjects ▓▓▓ (b) (6) and ▓▓▓ (b) (6) were not fasting at the time of serum lipid collection at Week 0. Of note, both patients had elevated baseline total cholesterol and LDL-c with normal triglycerides and low HDL. At Week 20, an improvement in cholesterol parameters was seen in both patients; however, only patient ▓▓▓ (b) (6) achieved a LDL-c < 130 mg/dL at Week 20.
- Subject ▓▓▓ (b) (6) was included in the ALT ≥ 3x ULN stratum; however, he had a screening ALT < 3 × ULN (mean screening ALT for Subject ▓▓▓ (b) (6) was 82 U/L). However, in the baseline analyses, this patient is included in the correct category.
- Subject ▓▓▓ (b) (6) was included in the no prior LLM stratum; however, the patient had received prior LLM (simvastatin). However, in the baseline analyses, this patient is included in the correct category.

Placebo Group
- Subject ▓▓▓ (b) (6) was not fasting at the time of serum lipid collection at Weeks 0 and 2.

Additional deviations from planned protocol procedures included missed evaluations or sample collections, samples collected before or after the scheduled time, and rate of study drug infusion. These deviations were considered to be minor and were not considered by the applicant to affect analyses of the primary or secondary study endpoints, with the exception of one patient in the SA group (Subject ▓▓▓ (b) (6)). The Week 20 liver biopsy and MRI were performed after the completion of the double-blind period (i.e., 1 and 2 days after the Week 22 infusion, respectively). Therefore, this patient was excluded from the endpoint analyses that involved liver histopathology or MRI. She was included in the other primary and secondary endpoint analyses that were unrelated to the timing of liver biopsy or MRI. This reviewer agrees with excluding this patient from the endpoint analyses related to MRI and liver histopathology. Of note, this patient had an improvement in steatosis score, and liver volume and fat content as measured by MRI.

3.3   Financial Disclosures

The applicant adequately disclosed financial arrangements with the clinical investigators. These arrangements do not raise concern over the integrity of the data. Refer to Section 9.4 Supplementary Tables, Figure 13 for further details.

4   Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1   Chemistry Manufacturing and Controls

The CMC reviewers (Christopher Downey, Simon Williams, and Arulvathani Arudchandran) recommend approval of this application, pending resolution of outstanding information requests

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and the applicant's response to the 483 items from the facility inspections. Once submitted to the FDA, the review of these items will be filed as an addendum to the CMC review.

The CMC reviewers concluded that the data submitted in this BLA support the conclusion that the manufacture of sebelipase alfa is adequately controlled and yields a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. Therefore, the CMC reviewers recommend that KANUMA (sebelipase alfa) be approved for human use under conditions specified in the package insert.

Additionally, the CMC reviewers recommend an expiration-dating period of (b) (4) months for sebelipase alfa drug substance when stored at (b) (4) °C, and an expiration-dating period of 24 months for sebelipase alfa drug product when stored at 2 – 8°C.

Pending submission and review of the final negotiated specification limits, the CMC reviewers recommend approval of the proposed release and shelf life specifications for sebelipase alfa substance and drug product.

Refer to CMC review by Dr. Christopher Downey for the complete CMC review.

4.2   Clinical Microbiology

Sebelipase alfa drug product is a sterile, preservative-free 2 mg/ml solution for infusion. The drug product is manufactured by aseptically filling formulated sebelipase alfa drug substance into single-use vials. The most critical product quality microbiology issues that have yet to be resolved are listed below. These issues can be resolved through labeling revisions and post-marketing commitments. Although none of the issues identified as of May 2015 would preclude approval, responses to the following information request items are still pending at the time of this review:

- The endotoxin specification does not provide a sufficient margin of safety for the maximum dose (3 mg/kg) administered over the shortest time period allowed by the labeling (1 hour). (b) (4) , revising the specification may not be feasible prior to approval. (b) (4)

- The applicant has committed to perform additional studies to evaluate or improve the sensitivity of endotoxin test methods by the end of June 2015. All of the commercial drug product lots manufactured thus far have been tested for pyrogens in rabbits as an orthogonal assay for endotoxin detection, and there have been no failures. The applicant will implement this approach until an *in vitro* test is fully developed and validated. The endotoxin testing issue will be resolved through PMCs.

- ▓▓▓▓▓▓▓▓▓▓▓▓▓▓ (b) (4) There are outstanding issues regarding the design of the microbial retention study for the ▓▓▓▓▓▓▓▓▓▓ (b) (4) ▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓▓. The applicant will be asked to improve the study design and repeat the microbial retention study as a PMC.

Refer to the microbiology reviews by Dr. Colleen Thomas for additional details.
The product quality microbiology review by Dr. Bo Chi was ongoing at the time of this document.

4.3   Preclinical Pharmacology/Toxicology

In vivo primary pharmacology studies were conducted in the Donryu rat ("Yoshida") model of LAL deficiency at IV doses ranging from 0.2 to 5 mg/kg. Sebelipase alfa caused improvements in several disease related parameters in this rat disease model (e.g., body weight gain, reduction in organomegaly, reduction in cholesteryl esters and triglycerides in the liver and spleen, and in serum transaminase levels). Results also indicated that the benefits of sebelipase alfa require maintenance of regular dosing, as the animals showed general decline in the health associated with a progressive decrease in growth velocity and subsequent body weight loss following cessation of sebelipase alfa treatment.

Intravenous repeated dose toxicology studies have been conducted with sebelipase alfa in rats (4-week) and in Cynomolgus monkeys (4-week and 6-month). The no-observed-adverse-effect-levels (NOAELs) in 4-week toxicology studies in rats and monkeys were 50 mg/kg/day in both species. The NOAEL in the 6-month toxicity study in monkeys was 30 mg/kg/day. No significant organ toxicities were identified in these studies.

Sebelipase alfa at IV doses up to 60 mg/kg did not cause any adverse effect on fertility and reproductive performance of male and female rats. In embryofetal development studies in rats and rabbits at IV doses up to 60 and 50 mg/kg, respectively, sebelipase alfa did not cause any adverse effects on embryofetal development. A pre and postnatal development study in rats showed no evidence of any adverse effect on pre and postnatal development at IV doses of sebelipase alfa up to 60 mg/kg.

The nonclinical reviewer did not identify issues that would preclude approval and recommended approval for its proposed use as indicated in the labeling. Refer to nonclinical review by Dr. Tamal Chakraborti for details.

4.4   Clinical Pharmacology

The clinical pharmacology reviewer concluded that the information submitted in this BLA is acceptable to support a recommendation for the approval of Kanuma provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

The selected doses and dosing regimens for patients with infantile-onset LAL deficiency and late-onset LAL deficiency were based on the efficacy and safety data from the trials conducted in the respective patient population.

In patients with infantile-onset LAL deficiency, the exposure-response (E-R) relationship has not been established. The PK of sebelipase alfa in pediatric patients < 6 months of age has not been adequately characterized (Study LAL-CL03).

In patients with late-onset LAL deficiency, the E-R relationship (higher exposures appear to be associated with a greater LDL-c% change from baseline) provides supportive evidence of effectiveness. The clinical pharmacology reviewer evaluated the population PK model-derived PK parameters stratified by age groups for 47 pediatric patients and 18 adults enrolled in Study LAL-CL02 who received 1 mg/kg dose once every two weeks. The data show that the 4-11 year old pediatric group appeared to have lower exposure compared to the 12-17 year old pediatric and adults group. The efficacy data (% LDL-c change from baseline) showed that sebelipase alfa treated patients in all three age groups experienced a statistically greater response than placebo treated patients. There was no clear trend of differences in the sebelipase alfa treatment effect across the three age groups based on two subgroup analyses. The first subgroup analysis showed that the %LDL-c reduction was higher in sebelipase alfa treated subjects than in the placebo treated subjects by 16%, 23%, and 29% for 4-11 year-olds, 12-17 year-old, and adults, respectively. The second subgroup analysis showed that, among patients whose baseline LDL-c levels were ≥ 130 mg/dL, the proportion of patients who achieved LDL-c <130 mg/dL at Week 20 was greater in sebelipase alfa treated group than in the placebo group by 36%, 36% and 28% in 4-11 year-olds, 12-17 year-old, and adults, respectively. These data support the use of 1 mg/kg dosing regimen in all three age groups.

Refer to clinical pharmacology review by Dr. Jing Fang for additional details.

4.4.1   Mechanism of Action

Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) enzyme, purified from egg white of transgenic hens (*Gallus* species) with the same amino acid sequence as the native human enzyme. Sebelipase alfa binds via glycans expressed on the protein to macrophage mannose receptors or mannose-6-phosphate receptors on relevant cell types and is subsequently internalized and localized to the lysosomal compartment. In the lysosome, sebelipase alfa catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol, and free fatty acids.

4.4.2   Pharmacodynamics

Sebelipase alfa (SA) is an enzyme replacement therapy that reduces substrate accumulation of cholesteryl esters and triglycerides and improves lipid metabolism. Improvements in low density lipoprotein cholesterol (LDL-c) were demonstrated after 20 weeks of treatment with SA, including patients with elevated LDL-c at baseline (≥ 130 mg/dL) who achieved LDL-c < 130 mg/dL. Refer to clinical pharmacology review by Jing Fang for details.

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4.4.3 Pharmacokinetics

The pharmacokinetics of sebelipase alfa (SA) were determined using a population pharmacokinetic analysis of 79 patients with LAL deficiency who received intravenous infusions of SA at 1 mg/kg (once weekly and once every other week) or 3 mg/kg once weekly. Four patients were aged <1 years, 20 were aged 1-12 years, 28 were aged 12-18 years, and 27 were ≥18 years. Based on these data, the pharmacokinetics of SA appeared to be nonlinear with a greater than dose-proportional increase in exposure observed between the 1 and 3 mg/kg dosages. No accumulation was seen at 1 mg/kg (once weekly or once every other week) or 3 mg/kg once weekly. Refer to clinical pharmacology review by Dr. Jing Fang for details.

5   Sources of Clinical Data

This review will focus on the clinical data from Study LAL-CL02, a multi-center, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of sebelipase alfa in pediatric and adult patients with LAL deficiency (CESD phenotype). A review of the data from an open-label clinical trial, Study LAL-CL03, in patients with infantile-onset LAL-deficiency (Wolman disease) is located in the clinical reviewed by Dr. Lauren Weintraub. All studies/clinical trials conducted by the applicant in patients with LAL deficiency are summarized below in Table 1.

5.1 Tables of Studies/Clinical Trials

Table 1: Summary of Studies/Clinical trials

Study#	Objective	Study Design	Dosage regimen	N patients	Diagnosis of Patients	Duration of Treatment	Status
Trial for Efficacy and Safety Evaluation							
LAL-CL02	Safety, efficacy, PK	Randomized, double-blind, placebo-controlled period followed by open-label extension.	1 mg/kg every other week IV.	66	CESD Patients ≥ 4 years of age.	20 weeks of double-blind phase followed by open-label extension up to 130 weeks.	Double-blind phase complete. Open-label phase ongoing.
LAL-CL03	Safety, efficacy, PK	Single-arm, open-label, dose escalation.	0.35 mg/kg, 1 mg/kg weekly IV. Up to 3-5 mg/kg weekly	9	Wolman's disease. Patients ≤ 24 months of age.	Up to 208 weeks.	Primary analysis complete. Follow-up ongoing.
Natural History Studies							
LAL1-NH01	Natural history of children with LAL-deficiency.	Observational, chart review, non-interventional.	N/A	35	Wolman's disease (diagnosis before 2 years of age)	N/A	Complete.
LAL2-NH01	Natural history of children and adults with LAL-deficiency.	Observational, chart review, non-interventional. Sub-study: Abdominal imaging and lab sample collection.	N/A	49 (n= 24 in sub-study)	CESD (Patients ≥ 5 years of age at consent) (Patients ≥ 8 years of age for sub-study)	N/A	Complete.
Additional Clinical Trials							
LAL-CL01	Safety, tolerability, PK, PD	Single-arm, open-label, dose escalation.	0.35 mg/kg, 1 mg/kg, 3 mg/kg weekly IV.	9	CESD Patients ≥ 18 and ≤ 65 years of age	4 weeks	Complete.
LAL-CL04	Safety and efficacy.	Single-arm, open-label extension for patients who completed LAL-CL01.	0.35 mg/kg, 1 mg/kg, 3 mg/kg weekly for 4 weeks, then 1 mg/kg or 3 mg/kg every other week IV.	8	CESD	Up to 112 weeks.	Ongoing.
LAL-CL06	Safety, efficacy, PK	Single-arm, open-label trial for patients who do not meet inclusion criteria for other trials.	1 mg/kg every other week.	Planned: 20 patients Enrolled: 17 patients	LAL-deficiency. Patients > 8 months of age.	Up to 96 weeks.	Ongoing.

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Study#	Objective	Study Design	Dosage regimen	N patients	Diagnosis of Patients	Duration of Treatment	Status
LAL-CL08	Safety, efficacy, PK	Single-arm, open-label trial in infants.	1 mg/kg, up to 3-5 mg/kg weekly IV.	Planned: 10 Enrolled: 5 patients	LAL-deficiency. Patients < 8 months of age.	Up to 156 weeks.	Ongoing.

(Source: reviewer's table adapted from applicant's submission, BLA 125561)

5.2   Review Strategy

Study LAL-CL02 is the primary source of clinical data that will be reviewed in this document along with supportive information from the natural history study, Study LAL-2-NH01. Refer to clinical review, by Dr. Lauren Weintraub, for details of Study LAL-CL03.

Study LAL-CL02 provides the main source of clinical efficacy data to support the clinical benefit in patients with CESD who are treated with sebelipase alfa as compared to placebo. The primary objective of this trial is 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 does it represent a surrogate endpoint reasonably likely to predict clinical benefit in patients with late-onset LAL deficiency (i.e., patients with CESD). For these reasons, ALT normalization cannot serve as the basis to establish efficacy in the CESD patient population. Instead, the clinical review will focus on cholesterol parameters, including the first-ranked secondary endpoint, LDL-cholesterol (LDL-c), as LDL-c appears to be the most suitable endpoint to assess efficacy in patients with CESD. 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. Additionally, literature reports and data collected from the natural history study conducted by the applicant (Study LAL-2-NH01) describing the disease presentation and progression were reviewed to provide information on the expected disease progression without treatment. A review of the efficacy analysis will be provided in Section 6 of this document. A review of the safety analysis will be provided in Section 7 of this document.

5.3   Discussion of Individual Studies/Clinical Trials

5.3.1   LAL-CL02

The goal of this trial is to compare the efficacy and safety of sebelipase alfa as compared to placebo in patients with CESD. The 20-week double-bind treatment period was initiated on

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January 22, 2013 and completed on May 20, 2014. The open-label extension phase is ongoing and data available through May 30, 2014 were included in this submission.

Title: A multicenter, randomized, placebo-controlled study of sebelipase alfa (SBC-102) in patients with lysosomal acid lipase deficiency.

Study Objectives
Primary Objective:
To demonstrate efficacy of sebelipase alfa as compared to placebo based on normalization of ALT in patients with lysosomal acid lipase deficiency (LAL deficiency).

Secondary Objectives:
To demonstrate the efficacy of sebelipase alfa as compared to placebo based on the following parameters (in order of importance):
- Decrease in low-density lipoprotein cholesterol (LDL-c)
- Decrease in non-high-density lipoprotein cholesterol (non-HDL-c)
- Normalization of aspartate aminotransferase (AST)
- Decrease in triglycerides (TG)
- Increase in high-density lipoprotein cholesterol (HDL-c)
- 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.
- Improvement in hepatic histology in a subset of patients for whom biopsy was performed.
- Decrease in liver volume, as measured by MRI and reported in multiples of normal (MN) in a subset of patients for whom imaging was performed. Liver volume (MN) = subjects organ volume/(body weight [kg]*0.025).

Other endpoints included evaluating the safety, tolerability, and immunogenicity of sebelipase alfa therapy, and to further characterize the PK of sebelipase alfa.

Exploratory Objectives:
To evaluate the following:
- Effect of sebelipase alfa as compared to placebo on additional measures of efficacy, including macrophage activation markers.
- Effect of sebelipase alfa as compared to placebo on health-related quality-of-life (HRQOL) assessments.
- Effect of sebelipase alfa as compared to placebo on growth in pediatric patients.
- The durability of the clinical response to sebelipase alfa 1 mg/kg every other week (qow) in the open-label period.

Study Design: LAL-CL02 was a multicenter, randomized, placebo-controlled trial to evaluate the safety and efficacy of sebelipase alfa in patients with LAL deficiency (CESD phenotype). The trial consisted of a screening period of up to 6 weeks, a 20-week double-blind period, an open-label period of up to 130 weeks, and a follow-up phone call at least 4 weeks after the last dose of

study drug. Patients were randomized in a 1:1 ratio to receive sebelipase alfa 1 mg/kg or placebo intravenous (IV) infusion every other week during the 20-week double-blind period. After completing the double-blind period, each patient could begin the open-label treatment with sebelipase alfa at a dose of 1 mg/kg IV infusion every other week during the extension period.

Randomization was stratified by the following parameters:
- Age at randomization (< 12 years or ≥ 12 years)
- Average screening ALT level (< 3x ULN or ≥ 3x ULN)
- Use of lipid lowering medication (LLM) at baseline (yes/no).

Figure 1 below shows the study schema and stratification methods.

Figure 1: Study Schema

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8
Age (years)	<12	<12	<12	<12	≥12	≥12	≥12	≥12
Screening ALT (U/L)	<3x ULN	<3x ULN	≥3x ULN	≥3x ULN	<3x ULN	<3x ULN	≥3x ULN	≥3x ULN
Lipid-Lowering Medications	Yes	No	Yes	No	Yes	No	Yes	No

a – Subject meets the criteria for significant clinical progression (Section 6.1.3.1) at any time.
b – Subject meets the criteria for inadequate clinical response (Section 6.1.3.2) after at least 8 infusions of open-label SBC-102 1 mg kg⁻¹ qow.
c – A subject who was discontinued from the double-blind treatment period due to significant clinical progression continues to meet criteria for significant clinical progression (Section 6.1.3.1) after at least 4 infusions of open-label SBC-102 1 mg kg⁻¹ qow.

Note: The section numbers in the diagram footnotes refer to sections in the protocol.

(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, page 50/354)

Study Population: Patients with a confirmed diagnosis of LAL deficiency, who were ≥ 4 years of age and had ALT ≥ 1.5x ULN (based on age- and sex-specific normal ranges of the central lab) on 2 consecutive measures obtained at least 1 week apart were eligible for enrollment into the trial. Sixty-six patients were enrolled and randomized.

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Inclusion Criteria

Patients were included if the following criteria were met:

- Patient and/or patient's parent or legal guardian provided informed consent prior to any study procedures.
- Age ≥ 4 years on the date of informed consent.
- LAL enzyme deficiency confirmed by dried blood spot (DBS) testing at screening, based on the definition of deficiency provided by the central laboratory performing the assay.
- ALT ≥ 1.5x ULN (based on age- and sex-specific normal ranges of the central lab) on 2 consecutive screening ALT measurements obtained at least 1 week apart.
- Females of childbearing potential had 1) a negative serum pregnancy at screening, 2) not breastfeeding, 3) agreed to use a medically acceptable method of contraception from the screening visit until 4 weeks after the last dose of the study medication.
- Patients receiving lipid lowering medications (LLM) at stable doses for at least 6 weeks prior to randomization must be willing to remain on a stable dose for at least the first 32 weeks of treatment in the trial.
- Patients receiving stable doses of medications for the treatment of non-alcoholic fatty liver disease (NAFLD) (e.g., glitazones, high-dose vitamin E, metformin, ursodeoxycholic acid [UDCA]) for at least 16 weeks prior to randomization must be willing to remain on a stable dose for at least the first 32 weeks of treatment in the trial.

Exclusion Criteria

Patients were excluded for the following reasons:

- Severe hepatic dysfunction (Child-Pugh Class C).
- Presence of any medical conditions or comorbidities that would interfere with study compliance or data interpretation, including but not restricted to severe intercurrent illness, known causes of active liver disease other than LAL deficiency (e.g., chronic viral hepatitis, autoimmune hepatitis, alcoholic liver disease, or physician concerns about excess alcohol consumption), human immunodeficiency virus (HIV), poorly-controlled diabetes, or cancers other than non-melanoma skin cancer.
- History of hematopoietic or liver transplant procedure.
- Treatment with "high-dose" corticosteroids (acute or chronic) within 26 weeks prior to randomization. However, patients receiving maintenance therapy with "low-dose" oral, intranasal, topical, or inhaled corticosteroids were considered eligible for this trial.
- Participation in a study where they received an investigational medical product within 4 weeks prior to randomization.
- Known hypersensitivity to eggs.

Study Treatments: During the double-blind placebo period, patients were randomized to receive either sebelipase alfa (SA) 1 mg/kg or a matched placebo intravenous (IV) infusion every other week. The study drug was diluted in 0.9% sodium chloride for injection to a final infusion volume of between 100 and 300 mL, depending on the patient's weight. Other products were not

infused in the same infusion tubing. It was recommended that all infusions of study drug be administered using in-line filtration with a low protein binding 0.2 µ filter. From Week 0 to Week 22, infusions were administered at an infusion rate between 50 mL/hr and 150 mL/hr, depending on the patient's weight, and were completed in approximately 2 hours. Beginning at Week 24, infusions were administered over approximately 1 hour, if well tolerated. Dose modifications were allowed only during the open-label extension period, starting at Week 22.

Dose Modification and Escape Therapy During the Double-Blind Period
Since dose modification was not permitted during the double-blind treatment period, patients who met the pre-specified criteria for significant clinical progression were allowed to discontinue from the double-blind period and transition into the open-label extension period, during which time the schedule of assessments for the open-label period (Week 22 through trial completion) was followed. The treatment assignment was not unblinded except in the event of a medical emergency. Such "escape therapy" was considered only if a patient exhibited evidence of significant clinical progression of liver disease (see definition below) after receiving a minimum of 5 consecutive infusions every other week of blinded study drug, and there was no clear alternative etiology for the deterioration in clinical status.

Definition of Significant Clinical Progression of Liver Disease:
- Elevation of ALT or AST > 5x ULN and at least 2x the highest pre-treatment value
  AND
- Presence of one of the following
  - Increase of total bilirubin to > 3x ULN and at least 2x the highest pretreatment value
  - Prolongation of prothrombin time (PT) ≥ 4 seconds above baseline
  - Development or worsening of ascites
  - Development of encephalopathy

Dose Modification During the Open-Label Extension Period
During the open-label period, sebelipase was initially administered at a dose of 1 mg/kg every other week. Dose increases to 3 mg/kg every other week were allowed if the patient continued to meet criteria for significant clinical progression (definition above) after at least 4 consecutive open-label infusions at a dose of 1 mg/kg every other week. If the patient met the criteria for inadequate clinical response (see definition below), dose escalation to 3 mg/kg was permitted after at least 8 consecutive open-label infusions at a dose of 1 mg/kg every other week.

Definition of Inadequate Clinical Response:
- ALT or AST remained abnormal, and either did not improve from baseline or worsened from the previously achieved lowest value over the preceding 8 consecutive infusions, OR
- LDL-c or TG remained abnormal, and either did not improve or worsened over the preceding 8 consecutive infusions, OR
- Patients < 18 years of age at the time of assessment for inadequate clinical response and had a weight-for-age (WFA) z-score that was 2 standard deviation (SD) below the mean and either did

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not improve or worsened during the preceding 6 months and the patient did not miss more than 20% of study infusions during the preceding 6 months.

Patients also qualified for transition to the open-label extension and dose de-escalation to sebelipase alfa 0.35 mg/kg every other week if he/she discontinued the double-blind period because of hypersensitivity reactions or elevated lipid levels that could not otherwise be managed by interruption of the study drug and/or through initiation of adjustment of the lipid lowering medication.

Procedures/Safety Considerations/Monitoring
For additional details of the study schedule of events, refer to the Appendix at the end of this document, Figure 11 and Figure 12.

The following assessments were performed during the trial:
- Safety assessments included documentation of AEs, SAEs, and hypersensitivity reactions [note that the applicant refers to hypersensitivity reactions as infusion-associated reactions (IARs)], 12-lead ECGs, and clinical laboratory tests (hematology, serum chemistry, lipid panel, urinalysis), vital signs, physical exam, use of concomitant medications/therapies, and measurements of anti-drug antibodies (ADAs).
- Physical exam was performed at Weeks 0, 6, 14, and 20 during the double-blind treatment period and at Weeks 28, 36, 42, and 52 during the open-label period. The exam included general assessment, liver size, spleen size, lymphadenopathy, arterial disease, and skin manifestations.
- Clinical laboratory tests are listed below. Laboratory assessments were performed in a central lab with the exception of the urinalysis and coagulation parameters.
  - Hematology: white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean hemoglobin and hematocrit concentration (MCH, MCHC), platelet count, lymphocytes, monocytes, eosinophils, basophils, peripheral blood smear
  - Liver panel: ALT, AST, alkaline phosphatase, GGT, albumin, total, direct, and indirect bilirubin.
  - Serum lipids: LDL-c (calculated using the Friedewald formula), total non-HDL-c, TG, HDL-c.
  - Other chemistry: Serum electrolytes, glucose, creatinine, bicarbonate, total protein, blood urea nitrogen (BUN), glycosylated hemoglobin (HbA1c).
  - Macrophage activation markers: Serum chitotriosidase and serum ferritin
  - Urinalysis
  - Viral hepatitis screen
  - Carbohydrate deficient transferrin (CDT) for alcohol use

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- o Coagulation parameters: Partial thromboplastin time (PTT), prothrombin time (PT), international normalized ratio (INR)
- o Serum and urine pregnancy tests
- o Exploratory biomarkers
- o LAL enzyme activity
- o Pharmacogenetics

Note that exploratory biomarkers were not included by the applicant in this submission and will be reported when available.

Because of the limitations on acceptable blood volume limits in young children, the laboratory assessments were divided into two tiers. Tier 1 was considered mandatory and Tier 2 labs were collected based on the permissible blood volume threshold for each patient's weight and clinical status.

- Tier 1: safety laboratory tests, including serum chemistry, liver panel, serum lipids, hematology, coagulation panel, serum hCG, anti-drug antibodies (ADA), dried blood spot (DBS) LAL enzyme activity (spotted at local site). These tests also included all laboratory tests for primary and secondary efficacy endpoints.
- Tier 2: all other lab tests including PK, exploratory biomarkers, macrophage activation markers, viral hepatitis screen, CDT, HbA1c, DBS LAL enzyme activity (spotted at the central lab).

Efficacy Endpoints:
Primary Efficacy Endpoint
The proportion of patients who achieved ALT normalization, based on the age- and sex-specific ULN provided by the central lab, at the end of the 20-week double-blind period (i.e., last double-blind (DB) assessment).

If the final assessment of ALT was less than 10 weeks (70 days) after the first dose, the patient was considered as a non-responder in the analysis. The last double-blind assessment for safety was defined as the last measurement prior to the first open-label infusion. The open-label period is ongoing at the time of this report. Data are available from the open-label period through Week 36 of treatment for the SA group and Week 14 of treatment with SA for the placebo/SA group (i.e., the last time points at which > 5 patients in each treatment group had data available).

Secondary Efficacy Endpoints
Secondary efficacy outcome measures below were analyzed in a hierarchical fashion and included the following changes or normalization or improvement rates, as applicable, from baseline to the end of the 20-weel double-blind period:

- Relative reduction in LDL-c.
- Relative reduction in non-HDL-c.

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- Proportion of patients with an abnormal baseline AST (i.e., > ULN) who achieved normalization of AST, based on age- and sex-specific normal ranges provided by the central laboratory performing this assay.
- Relative reduction in TG.
- Relative increase in HDL-c.
- Relative reduction in liver fat content, using multi-echo gradient-echo proton density fat fraction (MEGE PDFF) MRI, in the subset of patients for whom this assessment was performed.
- Proportion of patients who showed improvement in liver histopathology (in the subset of patients for whom this assessment was performed). An improvement in liver histopathology (responder) was defined as a decrease in liver fat (measured in the H&E stained section) ≥5% at the end of the double-blind period compared to baseline.
- Relative reduction in liver volume (in the subset of patients for whom this assessment was performed) using MRI, measured in multiples of normal (MN): normal liver volume in liters was set as 2.5% of the body weight (kg). Liver volume (MN) = subjects organ volume/(body weight [kg]*0.025).

Supportive/Exploratory Efficacy Endpoints
Supportive efficacy outcome measures included the following changes or normalization, as applicable, from baseline to the end of the 20-week double-blind treatment period:
- Proportion of patients with an abnormal baseline gamma glutamyl-transferase (GGT) (i.e., > ULN) who achieved normalizations, based on age- and sex-specific normal ranges provided by the central laboratory performing this assay.
- Proportion of patients with a baseline bilirubin > 1.5 x ULN who achieved normalizations, based on age- and sex- specific normal ranges provided by the central laboratory performing this assay.
- Absolute reductions in ALT, AST, and GGT.
- Relative reduction in spleen volume using MRI as measured in multiples of normal (MN): normal spleen volume was set as 0.2% of the body weight (kg). Spleen volume (MN) = subjects organ volume / (body weight [kg]*0.002).
- Relative reduction in spleen fat content using multi-echo gradient-echo proton density fat fraction (MEGE PDFF) MRI in the subset of patients for whom this assessment was performed.
- Measures of growth failure (a prominent manifestation in affected infants which has also been noted in some affected children and adults with LAL deficiency), including:
  - Z-scores and percentiles for weight-for-age (WFA) and stature-for-age (SFA) (based on Centers for Disease Control and Prevention [CDC] child growth standards) in patients ≤ 18 years of age on the date of informed consent.
- Markers of macrophage activation, including absolute reductions in serum ferritin and serum chitotriosidase.

Given the potential for anti-drug antibodies (ADAs) to alter treatment response for a biological product, the effect of ADAs on the efficacy of sebelipase alfa was also explored.

Note that the central laboratory did not have pre-specified normal ranges for ferritin or non HDL-c. As such, another central laboratory facility [redacted] (b) (4) was consulted to provide normal ranges for these parameters for reference. The normal range provided for ferritin was 10 to 291 μg/L for females and 22 to 322 μg/L for males, and the normal range for non-HDL-c was 65 to 165 mg/dL.

Planned Methods of Analysis:
A planned total of 50 randomized patients would have provided 97% power to detect a statistically significant difference between sebelipase alfa and placebo for the primary endpoint (ALT normalization), using Fisher's exact test at α=0.05, and also would have provided over 90% power to detect statistically significant differences between sebelipase alfa and placebo for reduction in LDL-c, reduction in non-HDL-c, normalization of AST, and reduction in TG.

If the primary analysis was statistically significant at α=0.05, then statistical hypothesis tests of the secondary endpoints would be performed in a fixed sequence as outlined below. If the first-ranked secondary analysis was statistically significant at α=0.05, then the next statistical hypothesis in the sequence was tested at α =0.05. If at any point in the sequence a particular hypothesis did not achieve statistical significance at α=0.05, then formal statistical hypothesis testing was to be stopped, and none of the remaining tests would be considered statistically significant (in the confirmatory analysis). The sequence of hypothesis tests compared sebelipase alfa and placebo with respect to:

1. Primary endpoint: Proportions of patients who achieved ALT normalization at the end of the double-blind period;
2. Relative reduction (percentage change from baseline) in LDL-c at the end of the double-blind period;
3. Relative reduction (percentage change from baseline) in non-HDL-c at the end of the double blind period;
4. Proportion of patients with an abnormal baseline AST (i.e., >ULN) who achieved normalization of AST, based on age- and sex-specific normal ranges provided by the central laboratory performing this assay at the end of the double-blind period;
5. Relative reduction (percentage change from baseline) in TG at the end of the double-blind period;
6. Relative increase (percentage change from baseline) in HDL-c at the end of the double-blind period;
7. Relative reduction (percentage change from baseline) in liver fat content using MEGE PDFF MRI in the subset of patients for whom this assessment was performed at the end of the double-blind period;
8. Proportion of patients with improvement in liver histopathology (in the subset of patients for whom this assessment was performed) at the end of the double-blind period;
9. Relative reduction (percentage change from baseline) in liver volume using MRI (in the subset of patients for whom this assessment was performed) at the end of the double-blind period.

Analysis datasets:
- Consented Subject Set (Consented Set): All patients who signed informed consent.

- Full Analysis Set (FAS): All patients in the Consented Set who were randomized to treatment and received at least one dose (or any portion of a dose) of sebelipase or placebo during the double-blind 20-week period. The FAS was a modified Intent-to-Treat (ITT) dataset. The FAS was used for all efficacy analyses and for the presentation of patients in all subject listings. Safety analyses were performed for the FAS.
- Per-Protocol (PP) Set: All patients in the FAS who received at least 9 complete infusions during the double-blind period, had ALT measurements at both baseline and Week 20, had Week 20 assessments within 12 to 21 days of the preceding week (Week 18), did not change their lipid-lowering medications, and did not have any major protocol violations that would affect interpretation of the results for serum transaminases or serum lipids. The efficacy analyses were repeated using the PP population to assess whether the results were similar to the analyses conducted using the FAS.
- For the open-label period, an Extension Analysis Set (EAS) was used, since the FAS was limited to the double-blind treatment period. The EAS was comprised of patients in the Consented Set who were randomized to treatment and received at least 1 dose (or any portion of a dose) of sebelipase alfa during the open-label phase.
  - For patients who were originally randomized to sebelipase alfa and received at least 1 dose of sebelipase alfa (SA/SA), all assessments from both the double-blind and the open-label period were included in the EAS.
  - For patients who were originally randomized to placebo and received at least 1 dose of sebelipase alfa in the open-label period (PBO/SA), assessments from the open-label period were included in the EAS.

Subgroup Analyses:
The following subgroup analyses were performed:
- Age at Randomization (age $\geq$ 12 years as compared to < 12 years)
- Sex
- Race and Ethnicity
- Japanese Patients
- Baseline Liver Volume measured by MRI in multiples of normal (MN) (< 1.25 MN, $\geq$ 1.25 to < 1.58 MN, $\geq$ 1.58 MN). Multiples of normal is the same method used in the key secondary efficacy analyses to measure liver volume.
- Baseline ALT (< 3x ULN as compared to $\geq$ 3x ULN)
- Baseline LDL-c (< 190 mg/dL as compared to $\geq$ 190 mg/dL)
- Lipid Lowering Medication (LLM) Use
- Exploratory analyses of the impact of cirrhosis and genotype on baseline disease characteristics and clinical response

Safety Analysis:
Severity of all adverse events (AEs)/serious adverse events (SAEs) was assessed as mild, moderate, or severe, based on the established definitions (developed from Clinical Data

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Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standard terminology v3.1.1).

Variables selected to characterize the safety profile of sebelipase alfa in patients with LAL deficiency included the following:
- The incidence of AEs, SAEs, and infusion-associated reactions (IARs).
- Changes from baseline in 12-lead electrocardiograms (ECGs), and clinical laboratory tests (hematology, serum chemistry [including lipid panel], urinalysis).
- Changes in vital signs during and post-infusion, relative to pre-infusion values.
- Physical examination findings.
- Use of concomitant medications/therapies.
- Characterization of ADAs, including proportion of patients who are antibody positive, patients who were neutralizing antibody positive, time to antibody positivity, ADA titer by time point, peak ADA titer, and time to peak ADA titer.

Since enzyme replacement therapies are known to be associated with hypersensitivity reactions, these types of reactions were considered to be AEs of special interest. Instead of hypersensitivity reaction, the applicant used the term, "infusion-associated reaction (IAR)", defined as any AE that occurred during the 2-hour infusion or within 4 hours after the end of the infusion and was determined to be at least possibly related to the study drug. AEs occurring outside of this time period may also have been determined to be IARs. However, the Agency is moving away from using the term "infusion reaction" and is currently recommending that the term "infusion reaction" be replaced with "hypersensitivity reaction" or "anaphylaxis," as appropriate. Although the term "infusion reaction" implies a temporal relationship, infusion reactions are not well defined and may encompass a wide range of clinical events, including anaphylaxis. Therefore, in this document, signs and symptoms that are associated with the infusion and are likely to be related to sebelipase alfa will be described and the term "hypersensitivity reaction" will be used.

Pharmacokinetic (PK) Parameters
PK parameters included clearance (CL) and volume (V) estimates along with secondary parameters of area under the concentration time curve (AUC), maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), and terminal elimination half-life ($t_{1/2}$). The effect of ADAs on the PK profile of sebelipase alfa was also evaluated.

Quality of Life Assessments
Changes from baseline in the following survey responses were evaluated for patients $\geq$ 5 years of age at the time of randomization:
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale[5]

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[5] Webster, Kimberly and Cella, David. The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT) Measurement System: properties, applications, and interpretation. Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare and Northwestern University Feinberg School of Medicine, Evanston, Illinois, United States. *Health and Quality of Life Outcomes* 2003, 1:79.

- o 13-item FACIT-Fatigue scale, measures levels of fatigue in people living with a chronic disease. This scale has been evaluated primarily in patients with cancer but also in other chronic diseases (e.g., multiple sclerosis, HIV/AIDS, rheumatoid arthritis).
    - o The total score ranges from 0-52. A score of < 30 indicates severe fatigue.
    - o The FACIT-Fatigue total score was calculated if more than 50% of the items were answered (a minimum of 7 of 13 items).
    - o Administered to patients ≥ 17 years of age.
- Chronic Liver Disease Questionnaire (CLDQ)[6]
    - o Disease-specific instrument designed to assess health-related quality of life in patients with chronic liver disease.
    - o The CLDQ includes 29 items related to fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry.
    - o Each response is scaled using seven points (1=all of the time, 7=none of the time). Higher values indicate better quality of life.
    - o Administered to patients ≥ 17 years of age.
- Pediatric Quality of Life Inventory (PedsQL™) Generic Core Scales[7]
    - o PedsQL™ 4.0 is a 23-item scale designed to measure core dimensions of health, as delineated by the World Health Organization (WHO).
    - o The scale includes 4 multidimensional scales of physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items). In addition to the total scale score (all 23 items), 2 summary scores, the Physical Health Summary (8 items) and Psychosocial Health Summary (15 items), were reported.
    - o Administered to patients 5 to 18 years of age through Week 20 only. Parent proxy reports were not used.
- Additionally, for patients ≥ 18 years of age, a history of alcohol consumption was obtained at screening and during the trial duration via the Alcohol Use Disorders Identification Test (AUDIT) questionnaire.[8] The total score ranges from 0 to 40 with higher scores indicating a greater likelihood of harmful drinking habits.

5.3.2 LAL-CL03

A brief summary of Study LAL-CL03 is provided in this section. Refer to clinical review by Dr. Lauren Weintraub for details of this trial. Study LAL-CL03 is an open-label, multi-center, dose escalation trial to evaluate the safety, tolerability, efficacy, pharmacokinetics (PK),

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[6] Younossi ZM., et al. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut 1999;45:295-300.
[7] Varni JW. The PedsQL™ 4.0 Generic Core Scales Young Adult Version: Feasibility, reliability, and validity in a university student population. J Health Psychol. 2009;14:611- 622.
[8] Saunders, JB., et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction. 1993 Jun;88(6):791-804.

pharmacodynamics (PD) of sebelipase alfa in infants with growth failure due to lysosomal acid lipase deficiency. The primary efficacy endpoint was survival at 12 months of age. Secondary endpoints included safety, survival beyond 12 month of age, effects of sebelipase alfa on growth parameters, hepatomegaly, splenomegaly, serum transaminases, serum lipids, hematologic parameters, and PK. Nine patients who were ≤ 8 months of age, and met the criteria for growth failure within the first 6 months of life, on the date of the first study infusion were enrolled. Eight patients received a starting dose of sebelipase 0.35 mg/kg , escalated to a dose of 1 mg/kg, and then to 3 mg/kg weekly based on clinical status. One patient was found to have neutralizing antibodies and suboptimal clinical response and therefore, the dose was escalated to 5 mg/kg weekly.

Clinical signs and symptoms of enrolled patients included hepatosplenomegaly, abdominal distension, vomiting, diarrhea, adrenal calcification, and failure to thrive. Biochemical abnormalities included elevated AST, ALT, total bilirubin, GGT, and alkaline phosphatase. Hepatosplenomegaly was found on baseline physical exam in 8 patients with available data. At the time of the BLA submission, 6 patients continued to receive treatment and 3 patients died prior to 12 months of age. The median age at death was 2.9 months (range: 2.8 to 4.3 months) for the 3 patients who died. Therefore, 6/9 (67%) patients survived to 12 months of age as compared to 0/21 (0%) untreated patients in a natural history study conducted by the applicant. Refer to clinical review by Dr. Lauren Weintraub for a full clinical review of this trial and the natural history study in patients with infantile-onset LAL deficiency (Wolman disease).

5.3.3   Natural History Study: LAL-2-NH01 and Sub-study

Title: An Observational Study Of The Clinical Characteristics And Disease Progression Of Patients With Lysosomal Acid Lipase Deficiency / Cholesterol Ester Storage Disease Phenotype and Associated Sub-Study: An Abdominal Imaging, Substrate Analysis And Laboratory Sample Collection Sub-Study For Participants Who Have Enrolled In LAL-2-NH01.

Study Objectives
Primary Objective:
To characterize key aspects of the clinical presentation, disease phenotype, and progression of patients with Lysosomal Acid Lipase (LAL) deficiency, including, but not limited to, age of presentation, onset of hepatomegaly, progression of liver function over time, and stability of lipid abnormalities.

Secondary Objectives, as defined in the sub-study protocol:
* To determine abdominal organ size and lipid content via magnetic resonance imaging (MRI) and 1H and 13C-magnetic resonance spectroscopy (MRS), if available, in children and adult patients presenting with LAL deficiency.
* To investigate the within-patient variability of key clinical laboratory parameters.
* To obtain blood samples for analysis of LAL deficiency using new and existing diagnostic methods.

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Study Design:
An observational, multinational, multicenter, retrospective review of the clinical charts and prospective evaluations of quality of life (QoL), alcohol consumption history, and current virology status at a single time point for living patients ≥ 18 years of age to evaluate the natural history of patients with CESD.

After the main study was initiated, as a result of new insights on the potential for non-invasive assessment of hepatic lipid and cholesterol ester content, additional prospective evaluations were conducted for patients who consented to participate in a sub-study protocol, including abdominal MRI, ^{1}H MRS, and/or ^{13}C-MRS, at a single time point and collection of blood samples for clinical laboratory tests at up to 3 time points, each at least 1 week apart.

Study Population: Data were collected from 49 patients and analyzed for 48 patients, including 24 patients who participated in the sub-study. Patients with LAL deficiency, either alive or deceased, who were ≥ 5 years of age at the time of consent and had a documented diagnosis of LAL deficiency (based on LAL enzyme activity or molecular genetic testing) were eligible to participate in the study. A minimum age of 5 years was chosen to distinguish from the rapidly progressive form of LAL deficiency presenting in infants. Patients who met the eligibility criteria for the main study could be considered for participation in the sub-study. To be eligible for the sub-study, a patient had to be ≥ 8 years of age, willing to undergo abdominal MRI and MRS, and could not have had any known contraindications to MRI (e.g., cardiac pacemakers, active medical implants).

Patients were included if the following data were available to be assessed through chart review:
- LAL enzyme activity and/or LAL molecular genetic test results (to confirm the diagnosis of LAL deficiency).
- Demographics (date of birth, sex)
- First reported dates for hyperlipidemia, abnormal serum transaminases, and documentation of a potential clinical diagnosis of LAL deficiency.
- Presence/absence of hepatomegaly and/or splenomegaly on a documented physical examination.
- Clinical laboratory tests from at least 3 time points spanning a period of at least 12 months, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, and triglycerides.
- If the patient was deceased, date and cause of death.

The applicant notes that some of these data were difficult to obtain due to inconsistencies in documentation (i.e., types of assessments performed during patient follow-up, amount of time that had passed since the data were generated). Therefore, patients who met other eligibility criteria, but were missing some mandatory data, were still considered eligible for inclusion in analyses, provided he/she had sufficient data available for a particular analysis. However, all patients were required to provide written informed consent/parental consent with assent and documentation of a confirmed diagnosis of LAL Deficiency.

The following information was collected prospectively from living patients ≥18 years of age:
- Alcohol use, as assessed using the Alcohol Use Disorder Identification Test (AUDIT)
- QoL data, as assessed using the Chronic Liver Disease Questionnaire (CLDQ)
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale
- Short Form -36, version 2 (SF-36 V2)

The following additional data were collected, if available:
- Country of origin, race, and ethnicity
- Genotype
- Dates of and findings from abdominal imaging (computed tomography [CT], MRI, ultrasound, and/or X-ray)
- Additional clinical laboratory data, including activated partial thromboplastin time (aPTT), adrenocorticotrophic hormone (ACTH) and/or ACTH stimulation testing, albumin, bilirubin, cortisol, creatine kinase, gamma-glutamyl transferase (GGT), hematocrit, hemoglobin, low-density lipoprotein (LDL-c) (≥ 3 measurements with a minimum of 12 months between the first and last), neutrophil count, platelet count, prothrombin time, serum amylase, serum ferritin, serum gamma globulin, serum protein level, and white blood cell (WBC) count.
- Last known AST and ALT, and last known normal high-density lipoprotein (HDL), LDL-c, total cholesterol, and triglyceride value.
- Consanguinity and familial history of LAL deficiency.
- History of angina, aortic aneurysm, cardiovascular death, cholecystectomy and/or gallstones, coronary artery disease, diarrhea, hospital admissions related to fever or infection, lymphadenopathy, non-fatal stroke or transient ischemic attack, persistent abdominal pain, persistent unexplained fever, pulmonary hypertension, recurrent infections, splenectomy, and other significant concomitant conditions.
- Dates and findings from liver, lymph node, skin, small intestine, and/or bone marrow biopsy as well as Periodic acid–Schiff (PAS) staining of liver biopsy and result.
- Liver transplantation (duration on waiting list, date of procedure, and pathology of removed liver).
- Minimum of 2 height measurements before and after initiation of any interventions before age 18 years as well as longitudinal height and weight values. For patients between 5 and 20 years of age, longitudinal assessments were made using Z-scores and percentiles based on CDC standards.
- History of investigation or treatment for cancer.
- History of interventions, including low-fat diet and lipid-lowering medication (LLM) (e.g., statin and ezetimibe use).

For patients participating in the sub-study, the following assessments were to be performed after written informed consent or parental permission with assent:
- Blood collection at a minimum of 1 time point and up to 3 time points for AST, ALT, alkaline phosphatase (ALP), GGT, bilirubin (direct and total), total cholesterol, triglycerides, HDL-c, and LDL-c.

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- Abdominal MRI and ^{1}H and ^{13}C-MRS, where possible, with assessment of hepatic and spleen fat content.

Statistical Methods:
Summaries for continuous endpoints included the number of patients with non-missing values (n), mean, standard deviation (SD), minimum, first quartile (Q1), median, third quartile (Q3), and maximum observed values. Summaries for categorical endpoints included the number and percent of patients within each category.

Sample Size:
No formal sample size calculation was performed. In light of the low prevalence of LAL deficiency, a sample size of approximately 30 patients was considered achievable within a reasonable time frame. It was anticipated that 20 patients who participated in the main study would participate in the associated sub-study. No formal sample size calculation was performed for the sub-study.

Analysis Sets Definitions:
- All Patients Set: All patients in the study.
- Full Analysis Set (FAS): All patients with a confirmed diagnosis of LAL deficiency for whom informed consent was obtained.
- Dietary Intervention Set (DIS): All patients in the FAS who had at least 1 dietary intervention (DI), and at least 1 recorded pre-intervention value and at least 1 recorded post-intervention value for one outcome variable of interest (ALT, AST, total cholesterol, LDL-c, HDL-c, or triglycerides). DIs were considered specialized low-fat or low-cholesterol diets; high-protein or low-sodium diets were not considered DIs for the purpose of this study.
- Lipid-Lowering Medication Set (LLMS): Patients in the FAS who received at least 1 LLM, at least 1 recorded premedication value, and at least 1 recorded post-medication value for one outcome variable of interest (see above).
- Complete Medical History Set (CMHS): Patients in the FAS who had full documentation of all mandatory clinical data.

6   Review of Efficacy

Efficacy Summary

Synageva submitted two phase 3 trials (LAL-CL03 and LAL-CL02) to support the effectiveness of sebelipase alfa (SA) for the treatment of patients with LAL deficiency. Refer to the medical officer review by Dr. Lauren Weintraub for details of Study LAL-CL03, which enrolled infants with the more severe, rapidly progressive phenotype of LAL deficiency (Wolman Disease). This

document focuses on the review of Study LAL-CL02, which enrolled patients ≥ 4 years of age with late-onset LAL deficiency (i.e., cholesteryl ester storage disease [CESD]). Study LAL-CL02 compared SA 1 mg/kg IV infusion every other week to placebo over a 20-week double-blind treatment period. At the end of the 20 weeks, patients were allowed to enroll in an open-label extension period to continue treatment with SA or switch to SA if they were enrolled in the placebo group during the double-blind period. The primary efficacy endpoint for the trial was normalization of ALT; however, the Division communicated to the applicant during pre-submission meetings and the review cycle that ALT normalization could not serve as the primary endpoint since 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 children and adults with CESD. While elevated serum transaminases usually represent liver injury, ALT is not on the causal pathway of disease and not specific to injuries due to accumulation of cholesteryl esters and triglycerides in the liver of patients with CESD. Furthermore, normal ALT does not necessarily exclude the presence or progression of liver disease.[9,10] Therefore, normalization of ALT does not reliably represent a clinical benefit (b) (4) in this patient population. Secondary endpoints evaluated by the applicant include low density lipoprotein cholesterol (LDL-c), non- high density lipoprotein (non-HDL-c), high density lipoprotein (HDL-c), AST normalization, triglyceride (TG), liver fat content (%) as measured by MRI, liver histology based on liver biopsy, and liver volume (multiples of normal) as measured by MRI.

Based on the data collected during Study LAL-CL02, LDL-cholesterol (LDL-c) appears to be the most suitable endpoint to assess efficacy in patients with CESD. 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. Over half of the patients enrolled in Study LAL-CL02 had a baseline LDL-c ≥ 190 mg/dL, placing them at high risk for coronary heart disease. Therefore, the assessment of efficacy will focus on the change from baseline in LDL-c in patients with CESD who are treated with SA. There are limited data on CESD patients with cardiovascular disease (CVD), which may be due to many patients being diagnosed as children and usually not developing CVD until later in life. Of the five cases of CVD reported in the literature, the patients were mostly asymptomatic and the diagnosis was made at a later age.[2,11] This reviewer recommends requesting additional data as a post-marketing study to demonstrate the long-term clinical benefit of sebelipase alfa on liver- and cardiovascular-related outcomes in patients with CESD.

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[9] Kyrlagkitsis, I., et al. Liver Histology and Progression of Fibrosis in Individuals with Chronic Hepatitis C and Persistently Normal ALT. Am J Gastroenterol 2003;98(7):1588-93.

[10] Feld, JJ., and Liang, TJ.. Hepatitis C- identifying patients with progressive liver injury. Hepatology. 2006;43:S194-206.

[11] Fouchier, S., Defesche, J., Lysosomal acid lipase A and the hypercholesterolaemic phenotype. Curr Opin Lipidol 2013, 24:332–338.

Of the 66 patients enrolled, 18/36 (50%) patients in the SA group and 20/30 (67%) patients in the placebo group had a baseline LDL-c $\geq$ 190 mg/dL, placing them at high risk for coronary heart disease. The mean change from baseline in LDL-c was a decrease of $28 \pm 22\%$ in the SA group and a decrease of $6 \pm 13\%$ in the placebo group (p < 0.0001). For patients with baseline LDL-c $\geq$ 130 mg/dL, 13/32 (41%) patients in the SA group achieved an LDL-c of < 130 mg/dL as compared to only 2/30 (7%) patients in the placebo group. Therefore, a substantially larger proportion of patients treated with SA experienced decreases in LDL-c over the 20-week double-blind treatment period, and 41% of patients were able to achieve LDL-c levels < 130 mg/dL. Improvements were demonstrated in both the patients receiving treatment with stable doses of lipid lowering medications as well as those who were not treated with lipid lowering medications.

The 2001 National Cholesterol Education Program Adult Treatment Panel III (ATP III) recommends LDL-c as the primary target of lipid-lowering therapy.[12] Since LDL receptor function is normal in patients with CESD with an overproduction of ApoB lipoproteins, a common feature in the general population with hyperlipidemia, reduction of LDL-c in patients with CESD is also likely to be associated with reduction in cardiovascular risks.[13] Additionally, the American College of Cardiology/American Heart Association Task Force on Practice Guidelines 2013 Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Risk in Adults identified groups of individuals most likely to benefit from statin therapy. The guidelines state that based on results from randomized clinical trials evaluating statin therapy, there is extensive evidence to support the treatment of individuals with elevations in LDL-c $\geq$ 190 mg/dL to reduce events of arteriosclerotic cardiovascular disease (ASCVD).[14] In Study LAL-CL02, 38/66 (58%) patients enrolled had baseline LDL-c $\geq$ 190, and 9/38 (24%) were receiving lipid-lowering medication, thereby placing them at high risk for cardiovascular disease. CESD patients who do not have evidence of severe liver disease or liver failure may remain asymptomatic until a cardiovascular event occurs.[2] Therefore, given the widely known association of elevated LDL-c with cardiovascular risks, observed reduction of LDL-c in patients with CESD who are treated with SA represents a clinical benefit.

Additionally, unlike lipid lowering medications that 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. Patients treated with sebelipase alfa in Study LAL-CL02 also experienced improvements in other biochemical and

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[12] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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) final report. Circulation. 2002 Dec 17;106(25):3143-421.

[13] Graham, I., et al. Dyslipidemias in the Prevention of Cardiovascular Disease: Risk and Causality. Curr Cardiol Rep (2012) 14:709- 720.

[14] Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;00:000–000.

pharmacodynamic measures as compared to placebo. For patients treated with sebelipase alfa as compared to placebo, statistically significant changes from baseline were demonstrated in mean percent reduction in non-HDL-c, triglycerides, and liver fat content, as measured by MRI, and mean percent increases were demonstrated in HDL-c.

Finally, efficacy of SA in patients with CESD is further supported through the results of Study LAL-CL03, which revealed improved survival in infants with the Wolman phenotype as compared to untreated patients in a natural history study conducted by the applicant. The two phenotypes share a common pathophysiology as disease in both phenotypes result from a mutation in the LIPA gene. The LIPA gene encodes lysosomal acid lipase (LAL), which is responsible for hydrolysis of cholesteryl esters and triglycerides within LDL particles into free cholesterol and fatty acids. When LAL activity is deficient, the cholesteryl esters and triglycerides accumulate in the lysosomes, thereby contributing to disease manifestations seen in patients with LAL deficiency. Since SA has demonstrated efficacy in infants with Wolman disease, the more severe and rapidly progressive form of LAL deficiency, SA is expected to be also effective in the less severe CESD population. Therefore, based on the review of data obtained from Study LAL-CL02, supported by the results of Study LAL-CL03 in infants with Wolman disease, this reviewer concludes that the effectiveness of SA has been established in the patient population with CESD.

6.1   Indication

The applicant's proposed indication is "Kanuma (sebelipase alfa) is   (b) (4) indicated   (b) (4) for patients with Lysosomal Acid Lipase (LAL) Deficiency."

6.1.1   Methods

See section 5.3 Discussion of Individual Studies/Trials for details.

Since there are no accepted surrogate or biomarkers for CESD, the totality of the data collected from Study LAL-CL02 were reviewed to determine the effects of treatment with SA as compared to placebo in patients with CESD. Additionally, the clinical review team participated in a telephone call with patients with CESD, held February 27, 2015, to learn directly from patients and their caregivers about the most troublesome clinical signs and symptoms related to CESD to further inform the review of this product. Refer to Section 2 for details of the telephone call.

6.1.2   Demographics

Sixty-six patients were enrolled into Study LAL-CL02. The mean age of the patient population was 16 ± 11 years (median: 13 years, range 4-58 years); 24/66 (36%) patients were < 12 years and 42/66 (64%) patients were $\geq$ 12 years of age. Of the 42 patients who were $\geq$ 12 years of age at randomization, 23 patients were between 12 and < 18 years and 19 patients were $\geq$ 18 years.

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Overall, the baseline disease characteristics were similar between the patients randomized to the sebelipase alfa (SA) treatment group and patients randomized to the placebo group. However, the SA group had fewer patients between ages 12 and 18 years and more patients < 12 years of age and adult patients than the placebo group. This reviewer is not aware of evidence to suggest that adolescent patients would have more severe disease than patients < 12 years; therefore, does not believe that the slight imbalance between the groups with respect to number of patients between 12 and 18 years of age would impact the overall results of the trial. When the treatment groups were divided using age 12 as a cut-off (i.e., < 12 years of age vs. ≥ 12 years of age), the proportions of patients in the SA group and placebo groups were similar, as shown below in Table 2. Since CESD generally presents during childhood, the age distribution for this trial is consistent with characteristics of the broader CESD population that is described in the review of 135 patients with CESD by Bernstein et al. 2013.[2]

The distribution of patients based on ethnicity/race in this patient population is also consistent with the review by Bernstein et al.[2] that described the most common ethnicity reported for CESD patients as European or North American, with fewer Latin American, Asian or Indian patients. In Study LAL-CL02, the patient population was mostly Caucasian (55/66 [83%]), with the remaining patients being Japanese (2/66 [3%]), other Asian or African-American (1 each [2%]), and 7/66 [11%] patients were categorized as "other" (i.e., mixed race (n=4), Hispanic (n=2), and middle-eastern (n=1)). The population was balanced between male (n=33, 50%) and female patients (n=33, 50%). Table 2 below describes the demographics for the trial population.

Table 2: Demographics (Full Analysis Set, Double-Blind Treatment Period)

	Sebelipase Alfa (SA) (N= 36)	Placebo (N = 30)	Total (N = 66)
Age* (years)			
Mean ± SD	17 ± 12	15 ± 10	16 ± 11
Median	14	13	13
Range	4 - 55	4 - 58	4 - 58
Age subgroup*, n (%)			
< 12 years	14 (39)	10 (33)	24 (36)
≥ 12 - < 18 years	9 (25)	14 (47)	23 (35)
≥ 18 years	13 (36)	6 (20)	19 (29)
Sex, n(%)			
Male	18 (50)	15 (50)	33 (50)
Ethnicity, n(%)			
Hispanic or Latino	6 (17)	4 (13)	10 (15)
Not Hispanic or Latino	30 (83)	26 (87)	56 (85)
Race, n(%)			
Asian	1 (3)	0	1 (2)
Japanese	2 (6)	0	2 (3)
Black or African American	1 (3)	0	1 (2)
White	27 (75)	28 (93)	55 (83)
Other	5 (14)	2 (7)	7 (11)

*Age at randomization was used in all analyses of age.
(Source: summarized from applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 152-153/354)

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In the review by Bernstein, et al., the median age of disease onset was 5 years for both males and females; of the 131 patients with a documented age of diagnosis, 35 (27%) presented between birth and 2 years of age, 81 (62%) presented between 3 and 12 years of age, and 15 (11%) presented during adolescence or adulthood. Of note, the patients who presented younger than 2 years of age were more severely affected.[2] The clinical presentation of CESD is variable, but patients usually present with elevated serum transaminases (ALT, AST), hepatomegaly, splenomegaly, elevated serum LDL-cholesterol (LDL-c) and triglycerides (TG), and normal to low HDL-cholesterol (HDL-c) (type IIb hyperlipoproteinemia).[2] As shown in Table 3 below, the age of onset and clinical presentation for the trial population are consistent with the literature reports; therefore, the overall demographics of the patient population of this clinical trial appears to be representative of the general patient population with CESD that has been previously described in the literature.

Table 3: LAL Deficiency Diagnostic History (FAS, Double-blind Treatment Period)

	Sebelipase Alfa (SA) (N= 36)	Placebo (N = 30)	Total (N = 66)
Age at First Onset of LAL Deficiency-related Symptom			
Mean ± SD	8 ± 8	5 ± 5	7 ± 7
Median	5	4	4
Range	0 - 42	0 - 20	0 - 42
First LAL Deficiency-related Abnormality, n (%)			
Elevated Transaminases	17 (47)	14 (47)	31 (47)
Hypercholesterolemia	6 (17)	2 (7)	8 (12)
Hypertriglyceridemia	1 (3)	0	1 (2)
Low HDL	0	0	0
Splenomegaly	0	1 (3)	1 (2)
Complications of Liver Disease	0	0	0
Cardiovascular Disease Events	0	0	0
Other	12 (33)	13 (43)	25 (38)
Method of Initial Diagnosis, n(%)			
Enzyme Activity	23 (64)	20 (67)	43 (65)
Genetic Sequencing	2 (6)	3 (10)	5 (8)
Other	11 (31)	7 (23)	18 (27)

(Source: Summarized from applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 154/354)

Disease Presentation
The age of LAL-deficiency-related clinical symptoms may vary depending on the residual LAL activity, which generally ranges from 1% to 12% of normal in patients with CESD.[2] The median age of symptom onset was similar between the SA and placebo groups (5 years and 4 years of age, respectively). However, the SA group included a larger range of ages (0 to 42 years) than placebo group (0 to 20 years). Almost half of the patients in both groups initially presented with elevated transaminases: 17 (47%) patients in the SA group and 14 (47%) in the placebo group. Hypercholesterolemia was the initial presenting symptom in 6 (17%) patients in the SA group and 2 (7%) in the placebo group. There were 12 patients in the SA group whose first presenting symptom was categorized as "Other" and included the following symptoms: hepatomegaly (7

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patients), hepatosplenomegaly and diarrhea (2 patients), and microvesicular steatosis, hypertriglyceridemia, and abdominal pain (1 patient each). Two of the patients with hepatomegaly had additional symptoms: 1 patient had jaundice, diarrhea, and vomiting and another patient had failure to thrive. There were 13 patients in the placebo group whose first presenting symptom was categorized as "Other" which included the following: hepatomegaly (8 patients) and hyperlipidemia, hepatitis, diarrhea, and splenomegaly (1 patient each).

As shown above in Table 3, the initial presenting sign/symptoms most often included elevated transaminases, hypercholesterolemia, or other liver-related complications related to cholesteryl ester or triglyceride accumulation due to LAL deficiency. Cutaneous stigmata of hyperlipidemia, including xanthelasma and tuberous xanthomas, were not reported in any patient. Although only 6 patients were over the age of 30 years, no patient had a medical history of atherosclerosis, with the exception of a 21-year-old ⁽ᵇ⁾ ⁽⁶⁾ patient (Subject ⁽ᵇ⁾ ⁽⁶⁾ in the placebo group with a history of a vascular graft.

Concurrent associated conditions were reported based on the medical history. Overall, the most common hepatic conditions that were reported in the medical history and were considered to be ongoing at baseline in the trial included hepatomegaly in 38/66 (58%) patients, increased transaminases in 25/66 (38%) patients, and hepatic steatosis and hepatosplenomegaly in 7/66 (11%) patients. A palpable liver was detected on physical examination in 48 (73%) patients and was greater than 5 cm below the costal margin in 19 (29%) patients. A palpable spleen was noted in 11 (17%) patients and was greater than 5 cm in length in 2 (3%) patients. Seven of 66 (11%) patients had abnormally low platelet counts at baseline, with the abnormally low counts ranging from 37 to 125×10^9/L.

Cirrhosis History
Of the 66 patients enrolled, a history of cirrhosis and/or portal hypertension was reported in 7 (11%) patients. Spider nevi were reported for 9 (14%) patients; however, despite this finding, cirrhosis and/or portal hypertension was reported in only 3/9 patients with spider nevi. Other cutaneous manifestations of increased portal venous pressure captured in medical history were seen in 5 (8%) patients; only 2 of these 5 patients had a history of cirrhosis and/or portal hypertension reported in the medical history. Twelve (18%) patients had a history of either hyperbilirubinemia and/or jaundice reported in the medical history. Of these 12 patients, 1 patient had a history of Gilbert's Disease and 1 patient had a history of cholelithiasis, both of which are associated with increased bilirubin and jaundice.

The applicant identified patients with evidence of "medically important chronic liver disease" at baseline, defined by the applicant as the presence of cirrhosis on baseline biopsy or in the medical history, medical history of portal hypertension, or history of coagulopathy. Twenty-nine (44%) patients were identified, of which 18 patients were female and 11 were male. The mean age was 14 years, median age 12 years, and ranged from 4 to 41 years of age. Of the 10 patients with histologically demonstrated cirrhosis based on the baseline liver biopsy, only 4 patients had documented cirrhosis or portal hypertension in their medical history. A summary of patients with evidence of medically important chronic liver disease is presented in the Appendix, Table 30.

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LAL Enzyme Activity

All 66 patients had a confirmed diagnosis of LAL deficiency, based on dried blood spot (DBS) LAL enzyme testing. Traditionally, LAL activity has been determined in cultured fibroblasts, peripheral leukocytes, and liver tissue using various substrates but was not specific for LAL enzyme. In contrast, the DBS method has the ability to distinguish between normal controls, carriers, and affected patients.[2,15] Hamilton, et al reported on LAL activity in DBS samples obtained from 140 normal controls as 0.50 - 2.30 nmol/punch/h and in 11 patients with CESD as < 0.03 nmol/punch/h.[16] In the LAL-CL02 patient population, the mean LAL activity was 0.009 nmol/punch/hr, with a range of 0.000 to 0.016 nmol/punch/hr. Low LAL activity was seen in all patients, regardless of genetic mutation category (i.e., homozygous for common mutation, heterozygous for common mutation, or other mutation). Patients with no measurable LAL activity (i.e., values of 0.000) were observed across all 3 mutation categories.

Genotype

Currently, a clear genotype/phenotype relationship has not been described for CESD[2] since there are a limited amount of data on siblings and unrelated affected patients with the same genotype for comparison. The most common genotype is a donor-splice site mutation (i.e., c.894 G>A, also known by the former nomenclature E8SJM[-1G>A]), and patients homozygous for this mutation are found across a spectrum of age of onset, disease severity, disease progression, and clinical manifestations.[2] The genetic mutations detected for the patient population enrolled in LAL-CL02 are shown below in Table 4.

Table 4: LIPA Gene Analysis (FAS, Double-blind Treatment Period)

Genetic mutation category	Sebelipase Alfa			Placebo			Total		
	All	< 12 years	≥ 12 years	All	< 12 years	≥ 12 years	All	< 12 years	≥ 12 years
	N=36	N=14	N=22	N=30	N=10	N=20	N=66	N=24	N=42
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Homozygous for common mutation, i.e., c.894 G>A	11 (31)	3 (21)	8 (36)	10 (33)	4 (40)	6 (30)	21 (32)	7 (29)	14 (33)
Heterozygous for common mutation	17 (47)	8 (57)	9 (41)	18 (60)	5 (50)	13 (65)	35 (53)	13 (54)	22 (52)
Other mutation[1]	8 (22)	3 (21)	5 (23)	2 (7)	1 (10)	1 (5)	10 (15)	4 (17)	6 (14)

[1] Other mutation: At least one of the alleles had an identified mutation but neither allele had the common mutation (i.e., c.894 G>A).

(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, page 157/354)

Overall, 85% of patients had at least one copy of the c.849G>A common exon 8 splice junction mutation (32% homozygotes and 53% compound heterozygotes), resulting in the common exon 8 splice junction mutation allele frequency of 60% in this trial, which is consistent with literature

[15] Hamilton, J., Jones, I., Srivastava, R., Galloway, P.. G78 A Simple Screening Method For the Measurement of Lysosomal Acid Lipase Using Dried Blood Spots. Arch Dis Child 2013;98:A40 doi:10.1136/archdischild-2013-304107.090.

[16] Hamilton, J., Jones, I., Galloway, P. A new method for the measurement of lysosomal acid lipase in dried blood spots using the inhibitor Lalistat 2. Clin Chim Acta. 2012 Aug 16;413(15-16):1207-10.

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reports.[17] This mutation was identified in at least 1 patient in 93% of the 15 countries from which patients were enrolled. Both patients from Japan had mutations other than c.849G>A, and only 1 of the 7 patients at the centers in Mexico had the c.849G>A mutation (compound heterozygote).

Baseline Disease-Related Laboratory Characteristics

Serum Transaminases
To be eligible for inclusion in the trial, patients were required to have ALT ≥ 1.5x ULN (based on age- and sex-specific normal ranges of the central lab) on 2 consecutive screening ALT measurements obtained at least 1 week apart. The baseline measurement was defined as the last measurement prior to the first infusion of the study drug. However, in cases of multiple pre-treatment measurements, the average of the last (up to 3) measurements was used as the baseline value.

Of note, to ensure that using the average of the last (up to 3) pre-treatment values as the baseline did not influence the results, the clinical review team requested that the applicant also conduct the primary efficacy analysis using one baseline ALT value, defined as the last ALT value prior to the first infusion of the study drug, even if multiple pre-treatment ALT values were available. The baseline values, using the applicant's definition are shown below in Table 5. Using the alternate definition, defined as the last ALT value prior to the first infusion, the baseline ALT mean for the total population was 101 ± 46 U/L, median was 87 U/L, and range was 39 – 270 U/L, suggesting that there are only minor differences from the values shown in Table 5 when the alternate definition is applied. The results of the reanalysis of the primary efficacy endpoint using the alternate definition were unchanged from the original analysis of the primary efficacy endpoint using the applicant's definition. Baseline ALT, AST, and GGT values are shown below in Table 5.

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[17] Scott, SA., et al. Frequency of the cholesteryl ester storage disease common LIPA E8SJM mutation (c.894G>A) in various racial and ethnic groups. Hepatology. 2013 Sep;58(3):958-65.

Table 5: Baseline Serum ALT, AST, GGT (FAS)

	Sebelipase Alfa (SA) (N= 36)	Placebo (N = 30)	Total (N = 66)
ALT (U/L)			
Mean ± SD	105 ± 45	99 ± 42	102 ± 44
Median	90	87	87
Range	52 - 212	50 - 237	50 - 237
ALT category, n(%)			
< 3x ULN	26 (72)	22 (73)	48 (73)
≥ 3x ULN	10 (28)	8 (27)	18 (27)
AST (U/L)			
Mean ± SD	87 ± 33	78 ± 35	83 ± 34
Median	75	71	74
Range	41 - 173	39 - 220	39 - 220
AST category, n(%)			
< 3x ULN	29 (81)	28 (93)	57 (86)
≥ 3x ULN	7 (19)	2 (7)	9 (14)
GGT (U/L)			
Mean ± SD	52 ± 47	52 ± 60	52 ± 53
Median	38	34	35
Range	14 - 239	13 - 333	13 - 333

Baseline: Last measurement prior to first study drug infusion. In case of multiple pre-treatment measurements, the average of the last (up to 3) measurements.
(Source: Adapted from applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, page 164/354)
Refer to Table 32 in the Section 9 Appendix for a table of normal laboratory values as defined by the central lab.

Baseline Alanine Aminotransferase (ALT)
The upper limit of normal (ULN) for ALT used by the central laboratory in this trial was dependent on age and sex. The ULN specified by the central laboratory was 34 U/L for females 4 to 69 years of age and males 1 to 10 years of age, and 43 U/L for males 10 to 69 years of age. The mean baseline ALT was 105 ± 45 U/L in the SA group and 99 ± 42 U/L in the placebo group, both higher than the normal range for ALT. The majority of patients in each treatment group had ALT values < 3x ULN: 26/36 (72%) patients in the SA group and 22/30 (73%) patients in the placebo group. Ten out of 36 (28%) patients in the SA group and 8/30 (27%) patients in the placebo group had ALT values ≥ 3x ULN at baseline. Therefore, only a small number of patients had markedly elevated ALT values at baseline.

Baseline Aspartate Aminotransferase (AST)
For AST, the central laboratory specified the ULN for females 4 to 7 years of age as 48 U/L, females 7 to 18 years of age as 40 U/L, and females 18 to 59 years of age as 34 U/L. The ULN for males 4 to 7 years of age was 59 U/L, males 7 to 18 years of age was 40 U/L, and males 18 to 59 years of age was 36 U/L. The mean baseline AST was 87 ± 34 U/L in the SA group and 78 ± 35 U/L in the placebo group, both above the ULN for AST. All patients, except for 1 patient in the placebo group, had abnormal AST values at baseline. Similar to ALT, most patients also had AST values < 3x ULN: 29/36 (81%) patients in the SA group and 28/30 (93%) patients in the placebo group. Seven out of 36 patients (19%) in the SA group and 2/30 (7%) patients in the placebo group had AST values ≥ 3x ULN at baseline.

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Baseline Gamma Glutamyl-transferase (GGT)

The central laboratory specified the ULN for GGT in females 4 to 10 years of age as 24 U/L, females 10 to 18 years of age as 33 U/L, and 49 U/L for females 18 to 59 years of age. For males 4 to 10 years of age, the ULN was 24 U/L, 51 U/L for males 10 to 18 years of age, and 61 U/L males 18 to 59 years of age. As shown in Table 5 above, the mean GGT at baseline was 52 ± 47 U/L in the SA group and 52 ± 60 U/L in the placebo group. Of the patients with elevated baseline GGT values, 13/36 (36%) patients were in the SA group and 12/30 (40%) patients were in the placebo group. However, of the 25 patients with GGT > ULN, only 9 patients in the SA group and 6 patients in the placebo group had baseline elevations > 1.5x ULN, as specified by the central lab. These findings are consistent with the observations made in the natural history study conducted by the applicant (Study LAL-2-NH01); the majority of patients (36/45 [80%]) had GGT values within the normal range at baseline and over 24 months post-baseline, 50-100% of patients had GGT values within the normal range.

Additional baseline lab assessments included alkaline phosphatase (ALP), albumin, bilirubin, and coagulation parameters (i.e., PT, PTT, and INR).

Baseline Alkaline Phosphatase (ALP)

At baseline 27/66 (41%) patients had ALP levels above the ULN. Of the 27 patients with abnormal/high ALP at baseline, the range was 116 - 519 U/L. There were only 11 patients with baseline ALP values > 100 U/L above the ULN (range: 105 - 219 U/L above the ULN for age and sex). Of the 11 patients with elevated ALP values at baseline, 10/11 were ≤ 15 years of age and 1 patient was 18 years of age. Higher levels of ALP are expected in growing children since the ALP isoenzyme from bone contributes to elevated total serum levels.[18] Elevations above the ULN for ALP are likely not clinically meaningful since they are not considerably outside of the normal range and contribution from the bone isoenzyme is possible.

Baseline Albumin

The lower limit of normal (LLN) for albumin specified by the central lab was 29 g/L for males and females 4 to 16 years of age, and 33 g/L for males and females 16 to 58 years of age. At baseline, no patient had an albumin value below the LLN.

Baseline Bilirubin

As per the central lab, the ULN for total bilirubin and indirect bilirubin was 21 μmol/L and the ULN for direct bilirubin was 7 μmol/L. In both the SA and placebo groups, the mean total, direct, and indirect bilirubin was below the ULN. Only 1/66 (2%) patient in the SA group had a direct bilirubin of > 1.5x ULN; of note, this patient had evidence of cirrhosis as indicated by an Ishak score of 6 on baseline liver biopsy.

Baseline Coagulation Parameters

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[18] Fleisher GA, Eickelberg ES, Elveback LR. Alkaline phosphatase activity in the plasma of children and adolescents. Clin Chem. 1977;23:469–472.

Coagulation parameters (e.g., PTT, PT and INR) were evaluated at local laboratories. PTT was reported as abnormal at baseline in 5/61 (8%) patients that had PTT reported in seconds; the mean baseline PTT was 31.6 seconds and ranged from 21.0 to 48.8 seconds. PT was reported as abnormal at baseline in 12/50 (24%) of patients that had PT reported in seconds; the mean baseline PT was 13.6 seconds and ranged from 9.7 to 26.0 seconds. INR was reported as abnormal at baseline in 17/65 (26%) patients with a mean baseline INR of 1.1 (range of 0.9 to 2.2). There were only 11 patients with 2 or more abnormal clotting tests (PTT, PT, or INR) at baseline; 4 patients in the SA group and 7 patients in the placebo group.

Of the 17 patients with abnormal baseline INR, the abnormal values were modestly elevated with the three highest values in Subjects   (b) (6) with INR values of 1.35, 1.58 and 2.15, respectively. Since elevated INR is considered to be reflective of hepatic synthetic dysfunction, [19] the ALT values for these 3 patients were reviewed. Interestingly, despite having elevated INR values, the ALT values of Subjects   (b) (6) were < 3x ULN with values of 87, 89, and 57 mg/dL, respectively. Subject   (b) (6) had the highest INR of 2.15 and the lowest ALT of 57 mg/dL. Of note, there was no documentation of cirrhosis on baseline biopsy that might explain the discrepancy between the INR and ALT values. Of these 3 patients, 2 patients had no documentation of cirrhosis on baseline biopsy; however, Subject   (b) (6) did not have a baseline biopsy performed but had documented portal hypertension in the medical history. Of note, coagulation parameters were not evaluated in the central lab, and significant interlaboratory variability in INR has been described.[19,20] Therefore, it is difficult to make conclusions and comparisons since the coagulation parameters were obtained in local labs, likely resulting in some variation among the local labs performing the assessment.

While ALT was elevated in all 66 patients at baseline, as required by the inclusion criteria for the trial, only 25 patients had elevated GGT > ULN, no patients had abnormally low albumin, only 1 patient had a direct bilirubin of > 1.5x ULN, and 1 patient had an INR > 2, suggesting that overall, patients did not have evidence of hepatic synthetic dysfunction based on other liver-related biochemical parameters. Therefore, while elevated ALT may represent liver injury, ALT is not on the causal pathway of disease and not specific to injuries due to accumulation of cholesteryl esters and triglycerides in the liver of patients with CESD. Therefore, improvement or normalization of ALT does not reliably represent a clinical benefit to support product labeling in this patient population. Additional long-term data will be requested as a post-marketing study to further evaluate the effect of sebelipase alfa on the progression of liver disease and liver-related outcomes.

<u>Serum Lipids</u>
Serum lipids including LDL-c, non-HDL-c, TG, and HDL-c were measured at baseline and are shown below in Table 6. The baseline mean LDL-c and TG values were higher in the placebo group than in the SA group. However, the differences between groups were not statistically

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[19] Northup, P., and Caldwell., S.. Coagulation in Liver Disease: A Guide for the Clinician. Clinical Gastroenterology and Hepatology 2013; 11: 1064-1074.
[20] Porte, RJ., et al. The International Normalized Ratio (INR) in the MELD Score: Problems and Solutions. American Journal of Transplantation 2010; 10: 1349-1353.

significant. Statistically significant differences between groups were seen in baseline cholesterol and non-HDL-c, with higher mean values seen in the placebo group than in the SA group.

Table 6: Baseline Serum Lipids (FAS)

	Sebelipase Alfa (SA) (N= 36)	Placebo (N = 30)	Total (N = 66)
LDL-c (mg/dL)			
Mean ± SD	190 ± 57	230 ± 70	208 ± 66
Median	193	213	204
Range	70 - 280	135 - 378	70 - 378
LDL-c category, n(%)			
< 130	4 (11)	0	4 (6)
≥ 130 - < 190	14 (39)	10 (33)	24 (36)
≥ 190	18 (50)	20 (67)	38 (58)
non-HDL-c (mg/dL)			
Mean ± SD	221 ± 61	264 ± 75	240 ± 71
Median	224	242	231
Range	90 - 332	155 - 408	93 - 408
Triglyceride (TG) (mg/dL)			
Mean ± SD	153 ± 54	174 ± 66	163 ± 60
Median	138	170	160
Range	65 - 307	66 - 361	65 - 361
TG category, n (%)			
< 200	30 (83)	22 (73)	52 (79)
≥ 200 - < 500	6 (17)	8 (27)	14 (21)
HDL-c (mg/dL)			
Mean ± SD	32 ± 7	33 ± 7	33 ± 7
Median	32	34	33
Range	18 - 48	16 - 47	16 - 48

(Source: Adapted from applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 167-168/354)
Refer to Table 32 in the Section 9 Appendix for a table of normal laboratory values as defined by the central lab.

The baseline pattern of dyslipidemia is consistent with what has been described in the review of 135 CESD patients by Bernstein et al., where the lipid values were observed over a range, including some values in the normal range: LDL-c 119 - 360 mg/dL, HDL-c 8 - 50 mg/dL, and TG 69 - 425 mg/dL. However, the majority of patients described in this review were found to have elevated LDL-c values > 200 mg/L in 79% of patients, including 49% of patients treated with HMG-CoA reductase inhibitors who continued to have elevated LDL-c. [2]

Baseline LDL-c
The baseline LDL-c values ranged from 70 - 378 mg/dL with mean baseline LDL-c values of 190 ± 57 mg/dL in the SA group and 230 ± 70 mg/dL in the placebo group. Overall, the baseline LDL-c was elevated in the majority of the 66 enrolled patients; 62 patients had an elevated LDL-c ≥ 130 mg/dL and 38/66 (58%) patients had a markedly elevated LDL-c ≥190 mg/dL. Baseline LDL-c values ≥190 mg/dL were found in 18/36 (50%) patients in the SA group and 20/30 (67%) patients in the placebo group. Only 4/66 (6%) patients had LDL-c values < 130

mg/dL at baseline; all 4 patients were randomized to the SA group and all 4 patients were receiving lipid lowering medications (LLM).

Baseline non-HDL-c
Non-high-density lipoprotein cholesterol (non-HDL-c) is the difference between the total cholesterol and the HDL cholesterol. The baseline non-HDL-c values for the overall patient population ranged from 93 - 408 mg/dL with a mean of 221 ± 61 mg/dL in the SA group and 264 ± 75 mg/dL in the placebo group.

Baseline HDL-c
Overall, the HDL-c values ranged from 16 - 48 mg/dL with a mean of 32 ± 7 mg/dL in the SA group and 33 ± 7 mg/dL in the placebo group. All 33 (100%) female patients had HDL-c values < 50 mg/dL and 28/33 (70%) male patients had HDL-c values < 40 mg/dL. Markedly low HDL-c levels, defined as values < 30 mg/dL, were seen in 24/66 (36%) patients.

Baseline Triglycerides
The baseline triglyceride (TG) values ranged from 65 - 361 mg/dL with a mean baseline TG value of 153 ± 54 mg/dL in the SA group and 174 ± 66 mg/dL in the placebo group. Hypertriglyceridemia, defined as TG levels ≥ 200 mg/dL, was seen in only 6/36 (17%) patients in the SA group and 8/30 (27%) in the placebo group.

Baseline Concomitant Lipid-Lowering Medication Use
Of the 66 patients, 26 (39%) were being treated with at least 1 prior lipid -lowering medication (LLM), including 15/36 (42%) in the SA group and 11/30 (37%) patients in the placebo group. Of the 26 patients receiving LLM at baseline, 4 (15%) patients were < 12 years of age, 22 (85%) patients were ≥ 12 years of age. Twenty-four of the 66 (36%) patients were treated with a statin. Other types of LLM were less common: 3/66 (5%) patients previously received bile acid sequestrants, and 1/66 (2%) each previously received fibrates and HMG-CoA reductase inhibitors in combination with ezetimibe. Baseline use of medication for non-alcoholic fatty liver disease (NAFLD) was less common since only 3/66 (5%) patients received medication for the treatment of NAFLD (e.g., glitazones, high-dose vitamin E, metformin, and UDCA). Patients receiving lipid lowering medications (LLM) must have been on stable doses for at least 6 weeks prior to randomization and must remain on a stable dose for at least the first 32 weeks of treatment in the trial. Patients receiving therapy for NALFD must have been on a stable dose for least 16 weeks prior to randomization must be willing to remain on a stable dose for at least the first 32 weeks of treatment in the trial. No patient had a change in LLM or NAFLD-related treatment during the trial.

Since diet can also influence serum lipid values and liver fat content, a diet history was obtained at baseline. Of the 66 patients, 38 (58%) were on a low cholesterol and/or low saturated fat diet at screening. There were no major differences in diet between the SA and placebo groups. The characteristics of the patient diets included diets that were low in fatty dairy products, low in animal-derived fatty foods, or higher in cholesterol-lowering foods.

Baseline Liver and Spleen Volume and Fat Content
Liver and spleen volume and fat content were assessed by MRI at baseline prior to the double-blind treatment period. Fat content is reported by percentage and organ volume is described using multiples of normal (MN) where the normal liver volume in liters was set as 2.5% of the body weight (kg), and normal spleen volume was set as 0.2% of the body weight (kg).[21]

Liver and spleen fat content was assessed using multi-echo gradient-echo proton density fat fraction (MEGE PDFF) MRI. MEGE-MRI has been evaluated in patients with NAFLD to quantify liver fat content.[22] The relationship between steatosis on liver biopsy and as measured by MRI in patients with NALFD has been reported in the literature; however, the correlation was weaker when fibrosis was present.[23] The relationship between hepatic fat quantification, as measured by MEGE-MRI, and hepatic fat, as measured by liver biopsy, has not been described in patients with CESD prior to this drug development program.

Thirty-five patients in the SA group and 26 patients in the placebo group underwent this assessment. There were 5 patients without MRI results. Two patients in the placebo group did not have MRI performed; Subjec   (b) (6) due to procedural-related anxiety, and Subject   (b) (6) due to the presence of internal metal device previously placed to correct a clavicular fracture, which is a contraindication to MRI. The other 3 patients without MRI results underwent the MRI but the results were not readable; 1 patient (Subject   (b) (6)) in the SA group and 2 patients (Subjects   (b) (6) and   (b) (6)) in the placebo group. Table 7 below shows the baseline liver and spleen volume and fat content, as measured by MRI.

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[21] Liver volume (MN) = subjects organ volume/(body weight [kg]*0.025). Spleen volume (MN) = subjects organ volume / (body weight [kg]*0.002).

[22] Noureddin, M., et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. Hepatology 2013; 58 (6): 1930-1940.

[23] Idilman IS., et al. Hepatic steatosis: quantification by proton density fat fraction with MR imaging versus liver biopsy. Radiology. 2013;267(3):767-75.

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Table 7: Liver and Spleen Volume and Fat Content at Baseline (Patients in the FAS with Assessment Performed, Double-Blind Treatment Period)

	Sebelipase Alfa (SA) (N= 36)	Placebo (N = 30)	Total (N = 66)
Liver fat content (%)			
n*	35	26	61
Mean ± SD	9 ± 4	8 ± 3	8 ± 3
Median	8	8	8
Range	3 - 25	2 - 13	2 - 25
Tertiles liver fat content, n(%)			
< 7.35	11 (31)	9 (35)	20 (33)
≥ 7.35 - < 9.72	13 (37)	7 (27)	20 (22)
≥ 9.72	11 (31)	10 (38)	21 (34)
Liver volume (MN)			
n*	36	28	64
Mean ± SD	1.4 ± 0.4	1.5 ± 0.3	1.5 ± 0.4
Median	1.4	1.4	1.4
Range	0.8 - 2.9	1.1 - 2.2	0.8 - 2.9
Tertiles liver volume (MN)			
< 1.25	14 (39)	7 (25)	21 (33)
≥ 1.25 - < 1.58	11 (31)	10 (36)	21 (33)
≥ 1.58	11 (31)	11 (39)	22 (34)
Spleen fat content (%)			
n*	35	26	61
Mean ± SD	1 ± 2	1 ± 1	1 ± 2
Median	1	1	1
Range	1 – 10	-0.6 – 3	-0.6– 10
Spleen volume (MN)			
n*	36	28	64
Mean ± SD	3.4 ± 2.7	3.3 ± 1.3	3.3 ± 2.2
Median	2.5	2.8	2.6
Range	0.7 - 16.2	1.9 - 6.7	0.7 - 16.2

N= number of patients in the treatment group.
n*= number of patients with quality data to permit analyses.
Multiples of normal (MN): normal liver volume in liters is set as 2.5% of the body weight (kg), and normal spleen volume is set as 0.2% of the body weight (kg). Liver volume (MN) = subjects organ volume/(body weight [kg]*0.025). Spleen volume (MN) = subjects organ volume / (body weight [kg]*0.002).
(Source: Adapted from applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 170-171/354)

Liver fat content (%) as measured by multi-echo gradient-echo proton density fat fraction (MEGE PDFF) MRI
A cut-off value of ≥ 5% has been used in the literature to define hepatic steatosis, based on liver biopsy and MRI findings in pediatric and adult patients with NAFLD and NASH.[24,25,26,27] At

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[24] Brunt, EM., et al. Nonalchoholic steatohepatitis: a proposal for grading and staffing the histological lesions. Am J Gastroenterol. 1999 Sep;94(9):2467-74.
[25] Reeder, S. B. (2013), Emerging quantitative magnetic resonance imaging biomarkers of hepatic steatosis. Hepatology, 58: 1877–1880.
[26] Shin, HJ., et al. Normal Range of hepatic fat fraction on dual- and triple-echo fat quantification in MR in children. PLoS One. 2015; 10(2): e0117480.

baseline in Study LAL-CL02, the mean percent liver fat content was $9 \pm 4\%$ in the SA group and $8 \pm 3\%$ in the placebo group. The percent fat content was categorized into low, middle and high tertiles, $< 7.35\%$, $\geq 7.35\%$ and $< 9.72\%$, and $\geq 9.72\%$, respectively. The applicant determined the cut-off values for the tertiles based on the 33rd and 67th percentiles, each containing a third of the population for a study population of 66 randomized patients, as outlined in the statistical analysis plan (SAP).

Eleven out of 35 (31%) patients in the SA group and 10/26 (38%) patients in the placebo group were found to have baseline liver fat content in the highest tertile (i.e., liver fat content $\geq 9.72\%$). Only 1 patient (Subject   (b) (6)) had a markedly elevated baseline fat content as compared to the overall patient population. This patient was a 41-year-old female who had a liver fat content of 25%, and was 1 of the 2 patients with the highest amount of macroscopic fat on liver biopsy. In contrast, this reviewer identified 12 patients, 6 in the SA group and 6 in the placebo group, with baseline liver fat content of less than 6%. These patients were between 6 and 18 years of age and baseline fat content ranged from 2% to 5%. Since the patients were balanced between the SA and placebo groups, the inclusion of patients with low fat content is unlikely to impact the overall results. Furthermore, changes in liver fat as measured by MRI are considered to be pharmacodynamic measures rather than a clinical outcome since a reduction in liver fat content has not been correlated with improvements in liver disease in patients with CESD.

Liver Volume in Multiples of Normal (MN) as Measured by MRI
Liver volume, as measured by MRI and reported as multiples of normal (MN), was available in 36 patients in the SA group and 28 patients in the placebo group. As discussed above, 2 patients in the placebo group did not have MRI performed: Subject   (b) (6) due to procedural-related anxiety and Subject   (b) (6) due to a contraindication for the procedure (presence of internal metal device previously placed to correct a clavicular fracture). The overall mean baseline liver volume, as assessed by MRI, was 1.46 ± 0.37 MN, with a mean liver volume of 1.44 ± 0.41 MN in the SA group and 1.50 ± 0.31 MN in the placebo group. Baseline liver volume (MN) was categorized into low, middle, and high tertiles, defined as < 1.25 MN, ≥ 1.25 MN and < 1.58 MN, and ≥ 1.58 MN, respectively. The applicant determined the cut-off values for the tertiles based on the 33rd and 67th percentiles, each containing a third of the population for a study population of 66 randomized patients, as outlined in the statistical analysis plan (SAP).

Eleven of the 36 (31%) patients in the SA group and 11/28 (39%) patients in the placebo group had baseline liver volume in the high tertile (i.e., ≥ 1.58 MN). While 21 (33%) patients had baseline liver volumes < 1.25 MN, there were 43 (67%) patients with baseline liver volumes ≥ 1.25 MN; of these 43 patients, all except 4 patients had palpable livers (i.e., evidence of liver enlargement/ hepatomegaly) on baseline physical exam. Hepatomegaly or hepatosplenomegaly are common clinical findings in patients with CESD that occurs from the accumulation of cholesteryl esters and triglycerides in cell lysosomes of the gastrointestinal tract, liver, spleen,

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[27] Pacifico L, Martino MD, Catalano C, Panebianco V, Bezzi M, et al. (2011) T1-weighted dual-echo MRI for fat quantification in pediatric nonalcoholic fatty liver disease. World J Gastroenterol 17: 3012–3019.

and cardiovascular system.[2] Hepatomegaly is consistent with what patients discussed as one of the few noticeable physical findings during the patient listening call, held February 27, 2015.

Spleen Fat Content and Volume
Baseline spleen fat content, measured by percent fat, and spleen volume, measured in multiples of normal (MN) were also assessed at baseline using MRI. The mean baseline spleen fat content was similar between the SA group (1 ± 2%) and placebo group (1 ± 1%). The mean spleen volumes were also similar between the SA (3.4 ± 2.7 MN) and placebo groups (3.3 ± 1.3 MN). However, spleen volumes in the SA group spanned a larger range than in the placebo group (0.7-16.2 MN vs. 1.9 - 6.7 MN). Of note, patients with large baseline spleen volumes also had lower platelet counts. The majority of patients had baseline spleen volumes ≥ 2 MN in both the SA and placebo groups (29/36 [81%] vs. 26/28 [93%]). However, of the 55 patients with spleen volume ≥ 2 MN, the spleen was palpable on physical exam in only 10 (18%) patients. Of the 14 patients with spleen volumes > 4 MN, the spleen was palpable on physical exam in only 6 (43%) patients. Therefore, on physical exam, splenomegaly was not identified as frequently as hepatomegaly in patients with evidence of enlarged spleen or liver seen on MRI.

Baseline Liver Histopathology
Baseline liver pathology, assessed by a blinded central reader, was available for 32 patients: 19 patients in the SA group and 13 patients in the placebo group. All 32 (100%) patients had evidence of fibrosis at baseline. Fifteen of the 19 (80%) patients in the SA group and 10/13 (77%) patients in the placebo group had Ishak scores of > 2 (fibrous expansion of more than 50% portal tracts). Ten patients, 5/19 (25%) patients in the SA group and 5/13 (38%) patients in the placebo group, were found to have Ishak scores of 5 (indicating early or incomplete cirrhosis) or a score of 6 (indicating probable or definite cirrhosis). Refer to Appendix Table 33 for a description of the Ishak scores.

All patients had biopsy evidence of lobular inflammation at baseline: minimal inflammation (1 focus per 10x field) was seen in 10/19 (53%) patients in the SA group and 8/13 (62%) patients in the placebo group, mild inflammation (2 to 4 foci per 10x field) was seen in 8/19 (42%) patients in the SA group and 5/13 (38%) patients in the placebo group, and moderate inflammation (5 to 10 foci per 10x field) was seen in 1/19 (5%) patients in the SA group and 0 patients in the placebo groups.

Only one patient (Subject ____(b) (6)____) in the placebo group had evidence of a cirrhotic scar without hepatocytes. All other patients had evidence of microvesicular steatosis at baseline, and fat vacuoles were seen in all or nearly all of the hepatocytes in 18/19 (95%) patients in the SA group and 10/13 (77%) patients in the placebo group. In contrast, macroscopic steatosis was not demonstrated in the majority of patients; 16/19 (84%) patients the SA group and 11/13 (85%) patients in the placebo group did not have evidence of macroscopic steatosis. The presence of microvesicular steatosis is consistent with the histopathology findings described for this patient population in the literature.[2]

Baseline Anthropometric Data

Given the age range of the enrolled patients in this study comparison of the absolute values for weight, height, and BMI between the treatment arms has limited value. However, age- and sex-adjusted percentiles for height and weight for patients ≤ 18 years of age were evaluated. Of the 50 patients ≤ 18 years of age, 29 (58%) were ≤ 50th centile for height at baseline but only 6 (12%) were ≤ 5th centile. Of the 50 patients ≤ 18 years of age, 29 (58%) were ≤ 50th centile for weight but only 5 (10%) were ≤ 5th centile for weight. Since only a small number of patients were below the 5th centile for height and/or weight at baseline, growth failure was not a common finding in enrolled patients with CESD.

6.1.3   Subject Disposition

Sixty-six patients from 15 countries were enrolled over a 9-month period between March and December 2013. Of these 66 patients, 36 were randomized to the SA group and 30 were randomized to the placebo group. There were no significant differences in the proportion of patients in each stratum between the SA and placebo groups based on age at randomization, average screening ALT, and use of LLM.

All 66 patients enrolled met all protocol entry criteria. Of the 66 patients enrolled, all 66 (100%) received at least 1 study drug infusion and were included in the Full Analysis Set (FAS). Sixty-five out of the 66 patients (98%) completed the double-blind period and continued in the open-label period. As of the data cutoff date of May 30, 2014, 65 patients entered the open-label period to continue in the study. One patient in the SA group (Subject   (b) (6)) did not complete the double-blind period. This patient, a 13-year-old   (b) (6), experienced a Grade 3 hypersensitivity reaction approximately 8.5 hours after completion of the second study drug infusion, and did not resume double-blind treatment. Since this patient received only 2 study drug infusions, (b)(6) was excluded from the Per-Protocol (PP) set, defined as all patients in the FAS who received at least 9 complete infusions during the double-blind period, had ALT measurements at both baseline and Week 20, had Week 20 assessments within 12 to 21 days of the preceding week (Week 18), did not change their lipid-lowering medications, and did not have any major protocol violations that would affect interpretation of the results for serum transaminases or serum lipids. The FAS was used for all efficacy and safety analyses. The efficacy analyses were repeated using the PP population and the results were very similar to the analyses conducted using the FAS. Therefore, the conclusions were unchanged and the analyses conducted using the FAS will be presented in this document. See statistical review by Dr. Benjamin Vali for further details. The overall disposition for patients screened, enrolled, and randomized is shown below.

Figure 2: Disposition
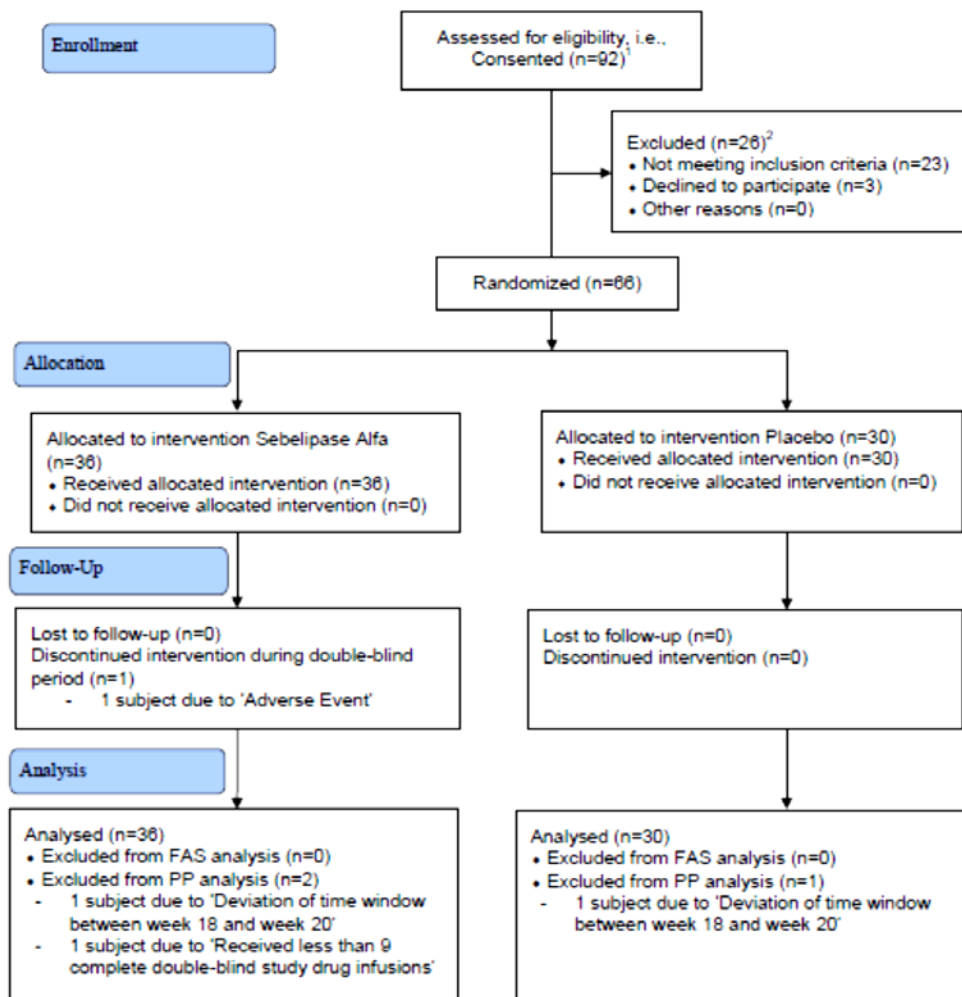
Source: Figure 14.1.1.6.
1   There were 92 screenings across 86 unique subjects.
2   There were 26 exclusions across 20 unique subjects.

(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 147/354)

The last double-blind assessment for the efficacy analyses was conducted at Week 20 for the majority of patients. The patients whose last double-blind assessment occurred at a time point other than Week 20 for ALT and lipid parameters are listed below.

- Subject ⬚ (b) (6) discontinued from the double-blind treatment period due to a hypersensitivity reaction at Week 2; therefore, the last double-blind assessment for all labs was conducted at Week 2.
- The last double-blind assessment of ALT for Subject ⬚ (b) (6) in the SA group occurred at Week 18 because the Week 20 chemistry sample was hemolyzed ("beyond stability") and was unable to be interpreted; however, this patient had all other labs collected and recorded at Week 20.

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- The last double-blind assessment of LDL-c, HDL-c, and non-HDL-c for Subject [(b) (6)] occurred at Week 14 and all other laboratory assessments occurred at Week 20. This patient had no significant changes from baseline in HDL-c or LDL-c at Week 14.

Of note, there were 3 patients in the SA group whose last double-blind assessment of AST occurred at time points other than Week 20: Week 2 (1 patient) and Week 18 (2 patients).

6.1.4 Analysis of Primary Endpoint(s)

As discussed previously in this document, ALT normalization is not an appropriate primary endpoint to assess the efficacy of sebelipase alfa in this trial since 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 children and adults with late-onset LAL deficiency (i.e., cholesteryl ester storage disease [CESD]). While elevated serum transaminases usually represent liver injury, ALT is not on the causal pathway of disease and not specific to injuries due to accumulation of cholesteryl esters and triglycerides in the liver of patients with CESD. Therefore, normalization of ALT does not represent a clinical benefit [(b) (4)] in this patient population. However, the relevant clinical and laboratory parameters for which there are pre- and on-treatment data were reviewed in this document with a focus on reductions in LDL-cholesterol, the first-ranked key secondary endpoint.

Since the applicant's pre-specified primary efficacy endpoint was ALT normalization over the 20 week double-blind treatment period, ALT will be briefly reviewed in this section. The planned secondary endpoints were subject to a fixed sequence testing and are presented along with the primary endpoint in Table 8 below.

Table 8: Primary and Secondary Efficacy Endpoints by Treatment Group (FAS, Double-blind Treatment Period)

Efficacy Endpoint	SA (N=36)	Placebo (N=30)	Statistically significant in fixed sequence test
ALT normalization n Yes, n (%)	36 11 (31)	30 2 (7)	Yes
Difference p-value	24% 0.03		
LDL-c percent change from baseline n Mean ± SD Q1, Q3 Median Range	36 -28 ± 22 -46, -12 -29 -59- 46	30 -6 ± 13 -12, 5 5 -33 - 16	Yes
Difference p-value	-22 < 0.0001		

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non-HDL-c percent change from baseline				Yes
n	36	30		
Mean ± SD	-28 ± 19	-7 ± 11		
Q1, Q3	-44, -17	-16, 3		
Median	-26	-6		
Range	-53 - 35	-31 – 7		
Difference	-21			
p-value	< 0.0001			
AST normalization				Yes
n	36	29		
Yes, n (%)	15 (42)	1 (3)		
Difference	39%			
p-value	0.0003			
Triglyceride percent change from baseline				Yes
n	36	30		
Mean ± SD	-25 ± 29	-11 ± 29		
Q1, Q3	-46, -12	-36, 5		
Median	-32	-15		
Range	-67 – 59	-51 – 56		
Difference	-14			
p-value	0.04			
HDL-c: percent change from baseline				Yes
n	36	30		
Mean ± SD	20 ± 17	-0.3 ± 12		
Q1, Q3	10, 28	-10, 7		
Median	19	1		
Range	-24 – 66	-25 – 21		
Difference	20			
p-value	< 0.0001			
Liver fat content percent change from baseline				Yes
n	32	25		
Mean ± SD	-32 ± 27	-4 ± 16		
Q1, Q3	-50, -19	-13, 9		
Median	-35	-4		
Range	-75 – 52	-37 – 25		
Difference	-28			
p-value	< 0.0001			
Improvement in liver histopathology				No
n				
Yes, n (%)	16	10		
	10 (63)	4 (40)		
Difference	23%			
p-value	0.4			

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Liver volume percent change from baseline (multiples of normal)			No
n	33	27	
Mean ± SD	-10 ± 11	-3 ± 10	
Q1, Q3	-16, -2	-10, 3	
Median	-12	-5	
Range	-36 – 12	-22 – 19	
Difference	-8		
p-value	0.007		

N: number of patients in the treatment group. n: number of patients with available data. Difference: difference between the mean or percentage for SA- placebo. p-value: Fisher's exact test for normalization and liver histology endpoints and Wilcoxon rank sum test for all other endpoints.

ALT and AST normalization: abnormal values at baseline that became normal (below the age- and sex-specific ULN) at the end of the double-blind treatment period. If the final assessment of ALT was < 10 weeks (70 days) after the first dose, the patient was considered as ALT normalization = No in the analysis. Patients with normal AST values at baseline were excluded from the AST normalization endpoint analysis. Abnormal baseline ALT and AST values were defined as exceeding the ULN as defined by the central lab.

Abdominal MRI was required for all patients except 1) those with internal or otherwise non-removable metal medical items, and 2) children for whom sedation was required but contraindicated.

Multi-echo gradient echo assessments of liver fat content were not required in children who could not hold their break for 15-30 seconds.

For patients ≥ 18 years of age, biopsies were required unless contraindicated.

MN: multiples of normal. A value of MN > 1.0 indicated an organ volume which was greater than the expected normal size.

(Source: adapted from applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 182-184/354)

Of note, the normal range for ALT was based on age- and sex-specific normal values provided by the central laboratory performing the assay. The normal ranges for ALT were 6 to 34 U/L for females aged 4 to 69 years and males aged 4 to 10 years and 6 to 43 U/L for males aged 10 to 69 years.

At baseline, 26/36 (72%) patients in the SA group and 22/30 (73%) patients in the placebo group had ALT values < 3x ULN. The table below shows the baseline and Week 20 values for ALT.

Table 9: Baseline and Week 20 ALT Values

Efficacy Endpoint	Baseline		Week 20[a]		Normalization at Week 20 n (%)		p-value
	SA n=36	Placebo n=30	SA n=36	Placebo n=30	SA n=36	Placebo n=30	
ALT (U/L) Mean ± SD Median Range	105 ± 45 90 52, 212	99 ± 42 87 50, 237	47 ± 23 45 17, 128	92 ± 43 86 33, 232	11 (31)	2 (7)	0.03

[a]In the SA group, 2 patients had the last double-blind ALT values collected at Week 2 and Week 18.

Refer to Table 32 in the Section 9 Appendix for a table of normal laboratory values as defined by the central lab.

(Source: reviewer's table, adapted from applicant's response to IR, dated April 30, 2015)

As shown above, 11/36 (31%) patients in the SA group achieved normalization of ALT as compared to 2/30 (7%) in the placebo group. The mean ALT values over time are shown below in Figure 3.

Figure 3: Mean (± SE) ALT Values over Time, by Treatment Group (FAS, Double-Blind Treatment Period) (EAS, Open-Label Period)
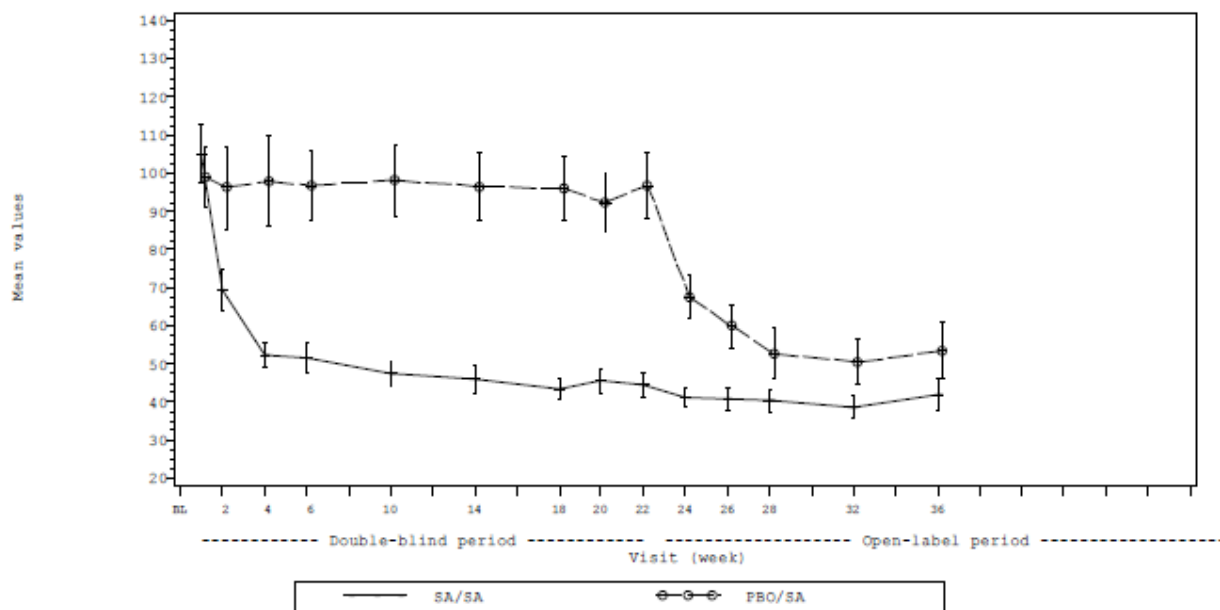
Treatment sequence: SA/SA: Sebelipase Alfa/Sebelipase Alfa, PBO/SA: Placebo/Sebelipase Alfa;
Baseline (BL): Last measurement prior to first study drug infusion of sebelipase alfa. In case of multiple pre-treatment measurements, the average of the last (up to 3) measurements within 45 days;
Visits for a treatment sequence are presented as long as at least 5 subjects for that treatment sequence are available;

(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 202/354)

Week 22 was the first study visit during the open-label extension period during which patients who were initially randomized to placebo during the double-blind treatment period received treatment with SA, as indicated by "PBO/SA" above. Patients treated with SA had normalization of ALT as early as Week 2. Furthermore, the trends observed during the open-label period demonstrate that the reduction in ALT values for patients treated with SA during the double-blind treatment period are sustained over time. In addition, patients treated with placebo during the double-blind treatment period who initiated treatment with SA at Week 22 of the open-label period also experienced reductions in ALT.

As demonstrated in the natural history study conducted by the applicant (LAL-2-NH01), ALT values fluctuated and remained elevated over time, but were generally below 200 U/L. Therefore, markedly elevated ALT values were not generally observed in patients with CESD in the natural history study nor in the patient population of Study LAL-CL02 since the majority of patients had baseline ALT < 3x ULN, despite underlying liver disease related to accumulation of cholesteryl esters and triglycerides. While consistent decreases over time and sustained improvement in ALT may reflect a pharmacodynamic response to treatment with sebelipase alfa,

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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 this patient population. In addition, a relationship between ALT normalization and change in fibrosis score was not observed; however, this reviewer acknowledges that 20 weeks is likely an insufficient duration to demonstrate a meaningful change in liver fibrosis. Furthermore, normal ALT does not necessarily preclude the presence or progression of liver disease.[9,10] As stated in the consult review by Dr. Poonam Mishra, Division of Antiviral Products, dated June 1, 2105, "Although ALT is used as an indicator of hepatic inflammation, its correlation with hepatic disease progression is not well documented.[10] Previous studies in individuals with chronic hepatitis C have shown that individuals with normal ALT can have advanced disease with stage 3 or 4 fibrosis and even individuals with persistently normal ALT over 3-6 years can have fibrosis progression.[9,28]" Therefore, based on available data, normalization of ALT is not an appropriate primary endpoint to support a clinical benefit in this patient population. Additional data will be requested as a post-marketing study to demonstrate the long-term treatment benefit of sebelipase alfa on the progression of liver disease since liver disease is an important clinical manifestation of CESD.

6.1.5   Analysis of Secondary Endpoints

LDL-c (first ranked key secondary endpoint)
Hyperlipidemia is a prominent finding in patients with CESD and patients are at risk for accelerated atherosclerosis, even though atherosclerosis is likely underdiagnosed or underreported.[1,2] Based on the data collected during Study LAL-CL02, LDL-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 ≥ 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. Therefore, this assessment of efficacy will focus on change from baseline in LDL-c and normalization of LDL-c on sebelipase alfa treatment in patients with CESD. However, additional data will be requested as a post-marketing study to demonstrate the long-term treatment benefit of sebelipase alfa on cardiovascular events in patients with CESD.

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[28] Hui CK, et al. A comparison in the progression of liver fibrosis in chronic hepatitis C between persistently normal and elevated transaminase. J Hepatol 2003;38:511-517.

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Table 10: Baseline, Week 20, and Percent Change from Baseline at Week 20 for LDL-c

Efficacy Endpoint	Baseline		Week 20[a]		% Change from Baseline at Week 20		95% Confidence Interval (p-value)
	SA n=36	Placebo n=30	SA n=36	Placebo n=30	SA n=36	Placebo n=30	
LDL-c (mg/dL) Mean ± SD Median Range	190 ± 57 193 70, 280	230 ± 70 213 135, 378	139 ± 66 138 32, 348	213 ± 66 201 99, 408	-28 ± 22 -29 -60, 46	-6 ± 13 -5 -33, 16	-33, -15 (p < 0.0001)

[a]In the SA group, 1 patient had the last double-blind LDL-c value collected at Week 2. In the placebo group, 1 patient had the last double-blind LDL-c value collected at Week 14.
Refer to Table 32 in the Section 9 Appendix for a table of normal laboratory values as defined by the central lab.
(Source: reviewer's table, adapted from applicant's response to IR, dated April 30, 2015)

Of the 66 patients, 18/36 (50%) patients in the SA group and 20/30 (67%) patients in the placebo group had a baseline LDL-c ≥ 190 mg/dL, placing them at high risk for coronary heart disease. As shown above in Table 10, the change from baseline in LDL-c was a mean decrease of 28 ± 22% in the SA group and a mean decrease of 6 ± 13% in the placebo group, which represents a difference of 22% between the groups in favor of the SA group (p < 0.0001).

Figure 4 below shows the mean percent change from baseline over time for LDL-c. The baseline value is set to 0% since the figure shows the change from baseline and the Week 2 value reflects the LDL-c after patients had received one SA infusion. There is a notable mean increase in LDL-c of 18% from baseline at Week 2 followed by consistent reductions in LDL-c over time. This initial increase in LDL-c was also observed during Study LAL-CL01 (phase 1, single-arm, open-label, dose escalation 4-week trial) after initiation of treatment with SA. The short-term increase is likely reflective of mobilization of accumulated lysosomal lipids and was not associated with other clinical symptoms.

Figure 4: Mean Percent Change from Baseline LDL-c Over the 20-Week[a] Double-Blind
Treatment Period (FAS, Double-blind Treatment Period)
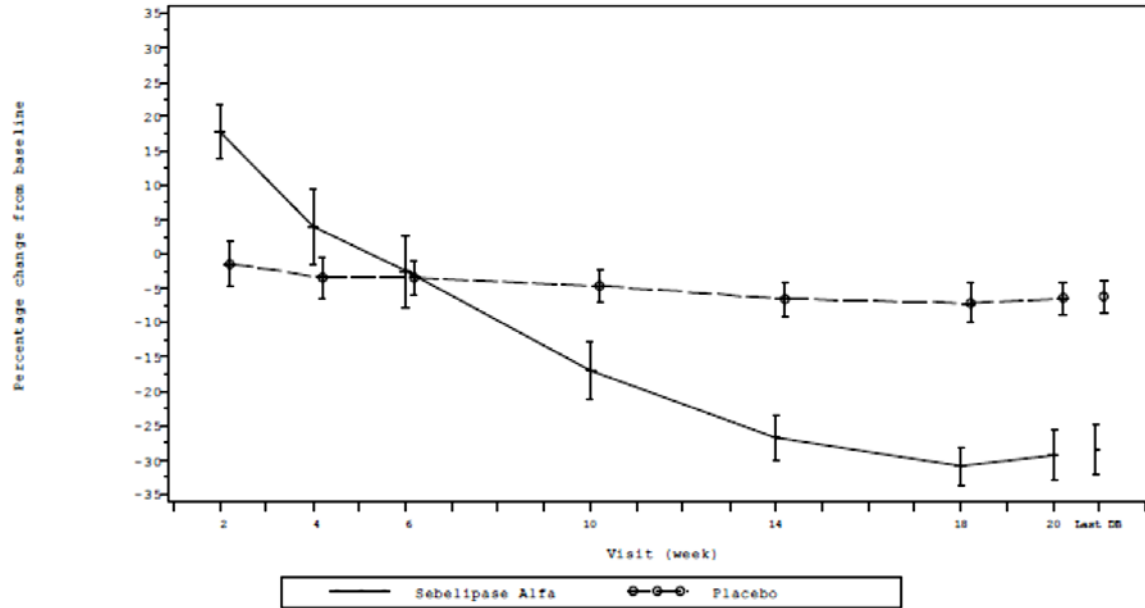
Last DB: Last measurement of the double-blind treatment period;
Note: Last DB and Week 20 will differ if some subjects had their last DB measurement on a week other than Week 20;
[a]In the SA group, 1 patient had the last double-blind LDL-c value collected at Week 2. In the placebo group, 1
patient had the last double-blind LDL-c value collected at Week 14.
(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 213/354)

The figure above shows very small changes from baseline in the placebo group, whereas the SA
group initially experiences an increase in LDL-c but after Week 6, decreases to below baseline
values are observed.

In addition to evaluating mean changes from baseline for the overall patient population, the
change from baseline to the last assessment in the double-blind treatment period by patient is
shown below in Figure 5.

Figure 5: LDL-c Change from Baseline to Week 20[a] in the Double-blind Treatment Period by Patient
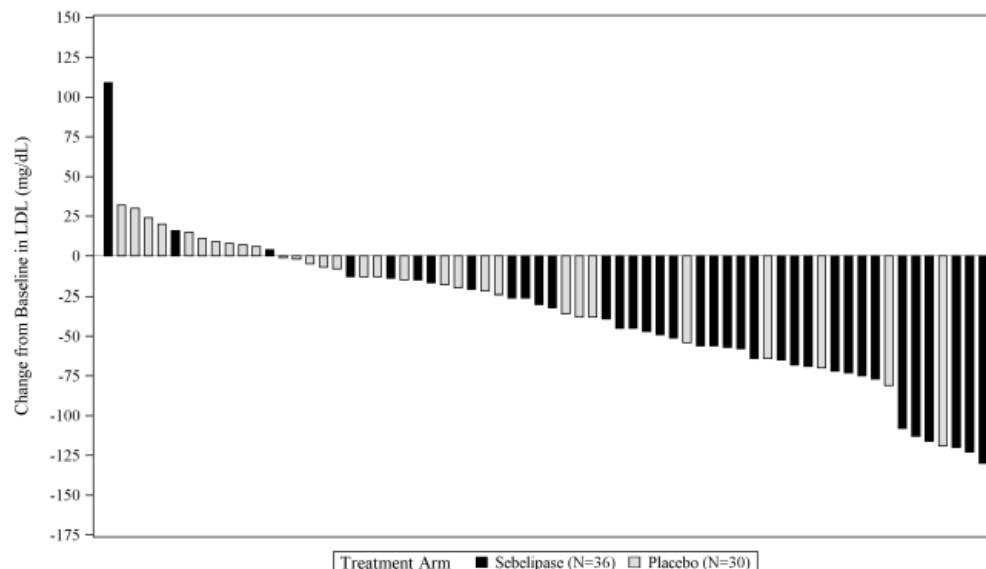
[a]In the SA group, 1 patient had the last double-blind LDL-c value collected at Week 2. In the placebo group, 1 patient had the last double-blind LDL-c value collected at Week 14.
(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 186/354)

As seen above, 3 patients in the SA group, all of whom were not receiving LLM, demonstrated an increase from baseline to the last time point in the double-blind period in LDL-c.

- Subject ____(b)(6): Baseline LDL-c value was 239 mg/dL and a 46% increase (absolute increase of 109 mg/dL) was observed at the last double-blind assessment. This patient demonstrated the largest percent increase from baseline in LDL-c at the last time point in the double-blind period but showed improvement from baseline in LDL-c of 19% at Week 10, 9% at Week 14, and 14% at Week 18. Furthermore, by the first time point in the open-label period (Week 22), this patient again demonstrated a 9% decrease (absolute change 21 mg/dL) from baseline in LDL-c, with a 25% decrease at Week 24 (absolute change 60 mg/dL), the last time point assessed as of the data cut-off. Therefore, the marked increase at Week 20 is inconsistent with the prior and subsequent values and appears to be an isolated finding.

- Subjec ____(b)(6): Baseline LDL-c value was 138 mg/dL and a 12% increase (absolute increase of 16 mg/dL) was observed at the last double-blind assessment. This patient experienced improvements from baseline in LDL-c during the open-label period. At Week 26, a decrease from baseline of 9% (absolute change -13 mg/dL) and at Week 28, a decrease of 8% (absolute change 11 mg/dL) was reported. However, at the last time point assessed for this patient, Week 32, a slight increase from baseline of 4% (absolute

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change 5 mg/dL) was seen.

- Subject _____ (b) (6): Baseline LDL-c value was 203 mg/dL and a 2% increase (absolute increase of 4 mg/dL) was observed at the last time double-blind assessment. It is important to note that the last time point assessed for this patient was Week 2 since this patient only received 2 study drug infusions during the double-blind period before discontinuing from the trial.

During the open-label period, a continued improvement in LDL-c was observed in the SA group with a maximum mean decrease from baseline of 44% at Week 36. The patients initially randomized to placebo during the double-blind period, who were then treated with SA during the open-label period (shown by PBO/SA in the figure below), demonstrated an initial increase in LDL-c followed by a maximum mean reduction of 25% in LDL-c at Week 14 of the open-label period; a similar response to the outcomes observed in the SA group during the double-blind treatment period. The response to SA for LDL-c during the open-label period is shown below.

Figure 6: LDL-c Mean Percent Change from Baseline Over Time (Double-blind period through the Open-Label Period)

(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 215/354)

There was a transient 16% increase from baseline in LDL-c at Week 24 of the open-label period (Week 2 of SA treatment for the patients originally randomized to placebo during the double-blind treatment period), which is consistent with the 18% transient increase from baseline in LDL-c that was observed during the double-blind period. The short-term increase is likely reflective of mobilization of accumulated lysosomal lipids.

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As previously discussed in this document, patients with CESD are often treated with statin therapy or other lipid-lowering medications (LLM). While cholesterol parameters may improve in some patients with LLM, many patients continue to have elevated lipid levels. Furthermore, the liver disease continues to progress despite treatment with LLM.[2] Patients were required to be on a stable dose of LLM for at least 6 weeks prior to the trial and dose adjustments in the LLM were not permitted during the double-blind treatment period. Since baseline use of LLM may have an impact on the lipid-related efficacy endpoint, a subgroup analysis was conducted to evaluate the change in LDL-c between patients receiving LLM and those were not treated with LLM.

Subgroup Analyses: Lipid-Lowering Medication (LLM) Use
The dose of LLM remained unchanged during the double-blind period, allowing for interpretable results based on the effects of SA. At baseline, 26/66 (39%) patients were receiving LLM and 40/66 (61%) patients were not. The mean and median age of patients receiving LLM were 21 years and16 years, respectively, and ranged from 8 to 58 years of age. The mean and median ages of patients not receiving LLM were 13 years and 12 years, respectively, and ranged 4 to 31 years. The mean baseline LDL-c value was abnormal despite treatment with LLM; the baseline mean LDL-c was 174 mg/dL in patients receiving LLM and 230 mg/dL in patients not receiving LLM. The percent change from baseline in LDL-c by baseline use of LLM is shown below.

Table 11: Mean Percent Change from Baseline in LDL-c by Treatment Group and Baseline Use of Lipid Lowering Medications (LLM)

% 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	

*95% CI and Total/Combined were calculated by the FDA statistical reviewer.
(Source: reviewer's table, adapted from applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 245/354)

Both groups experienced reductions in LDL-c from baseline; however, the combination of LLM with SA appears to have a numerically greater reduction in LDL-c compared to SA alone. In addition to the overall mean decreases from baseline, a subset of patients achieved LDL-c values < 130 mg/dL, thereby lowering the LDL-c into a range that reduces the risk of developing coronary heart disease.[29] Of note, there were only 4 patients, all in the SA group, had baseline LDL-c < 130 mg/dL; all 4 patients were receiving LLM. For patients with abnormal baseline LDL-c (> 130 mg/dL), 13/32 (41%) patients in the SA group achieved an LDL-c of < 130 mg/dL as compared to only 2/30 (7%) patients in the placebo group.

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[29] 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(19):2486-2497.

The relationship of LLM use and attaining LDL-c < 130 mg/dL was reviewed to determine whether lowering LDL-c into this desirable range was enhanced by concomitant therapy with LLM. Of the 13 patients in the SA group with LDL-c levels < 130 mg/dL at the end of the double-blind period, 7/13 patients were receiving LLM, but 6/13 patients were not receiving LLM and still achieved a LDL-c < 130 mg/dL. In contrast, LDL-c > 190 mg/dL, a high risk LDL-c value, at the end of the double blind period was seen in 7 patients in the SA group and 6/7 patients were not receiving concomitant LLM. In the placebo group, 13/17 patients with LDL-c levels > 190 mg/dL at the end of the double-blind period and all 13 were not receiving LLM.

Based on data from the natural history study conducted by the applicant (LAL-2-NH01), LDL-c was consistently elevated > 100 mg/dL in 24/29 (83%) patients who had at least 4 LDL-c values reported. Only 5 patients had ≥ 3 LDL-c values ≤ 100 mg/dL after treatment with LLM. Therefore, while LLM may improve LDL-c in some patients, most patients continue to have elevated LDL-c. While these findings are based on a small number of patients, treatment with sebelipase alfa appears to have the ability to lower LDL-c in addition to what is achieved with LLM therapy. However, since the effect of LLM on reductions in LDL-c in patients treated with SA was not a pre-specified endpoint, additional studies that are designed to evaluate this outcome would be needed to determine the relationship between LLM and SA on lowering LDL-c.

Additional Subgroup Analyses: Baseline LDL-c Levels
Subgroup analyses were performed for the primary and secondary endpoints with respect to baseline LDL-c using 190 mg/dL as a cut-off (i.e., < 190 mg/dL and ≥ 190 mg/dL).

Table 12: Change from Baseline in Primary and Secondary Endpoints by Baseline LDL-c (< 190 mg/dL and ≥ 190 mg/dL)

	< 190 mg/dL		≥ 190 mg/dL	
	SA (N=18)	Placebo (N=10)	SA (N =18)	Placebo (N=20)
ALT normalization n (%)	6 (33%)	1 (10%)	5 (28%)	1 (5%)
Difference	23%		23%	
LDL-c mean percent change from baseline ± SD	-33 ± 19	-6 ± 13	-24 ± 25	-6 ± 14
Difference	-27		-18	
non-HDL-c mean percent change from baseline ± SD	-32 ± 15	-5 ± 10	-24 ± 21	-8 ± 12
Difference	-27		-16	
AST normalization n (%)	9 (50%)	1 (10%)	6 (33%)	0
Difference	40%		33%	
Triglyceride mean percent change from baseline ± SD	-32 ± 24	5 ± 28	-19 ± 34	-19 ± 27

Difference	-36		-0.4	
HDL-c mean percent change from baseline ± SD	17 ± 14	2 ± 10	22 ± 20	-1 ± 13
Difference	15		24	
Liver fat content mean percent change from baseline ± SD	n=16 -26 ± 33	n=8 -13 ± 18	n=16 -39 ± 18	n=17 -0.3 ± 13
Difference	-13		-38	
Liver volume (MN) mean percent change from baseline ± SD	n=17 -13 ± 11	n=9 -2 ± 9	n=16 -7 ± 9	n=18 -3 ± 11
Difference	-11		-4	

(Source: Reviewer's table, adapted from applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, page 241/354)

As shown above, in patients with baseline LDL-c ≥ 190 mg/dL, there appears to be a greater numerical reduction from baseline to the last double-blind assessment in HDL-c and liver fat content. In contrast, patients with baseline LDL-c < 190 mg/dL experienced greater numerical reductions from baseline in non-HDL-c, TG, and liver volume. The results of this subgroup analysis do not reveal a clear pattern of response to treatment based on baseline LDL-c using 190 mg/dL as a cut-off value. There appears to be a response to treatment regardless of the degree of baseline elevation in LDL-c.

While there are limited data on CESD patients with cardiovascular disease (CVD), many patients are diagnosed at a young age and may not have developed CVD. Of the five cases of CVD reported in the literature, the patients were mostly asymptomatic and the diagnosis was made at a later age.[2,30] The 2001 National Cholesterol Education Program Adult Treatment Panel III (ATP III) recommends that LDL-c be the primary target of lipid-lowering therapy in patients with elevated cholesterol.[31] Additionally, the American College of Cardiology/American Heart Association Task Force on Practice Guidelines 2013 Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Risk in Adults identified groups of individuals most likely to benefit from statin therapy. The guidelines state that based on results from randomized clinical trials evaluating statin therapy, there is extensive evidence to support the treatment of individuals with elevations in LDL-c ≥ 190 mg/dL to reduce events of arteriosclerotic cardiovascular disease (ASCVD).[32] Over half (58%) of the patients enrolled in LAL-CL02 had baseline LDL-c ≥ 190, thereby placing them at high risk for cardiovascular disease. Elevated LDL-c is a well-

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[30] Fouchier, S., Defesche, J., Lysosomal acid lipase A and the hypercholesterolaemic phenotype. Curr Opin Lipidol 2013, 24:332–338.

[31] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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) final report. Circulation. 2002 Dec 17;106(25):3143-421.

[32] Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;00:000–000.

established risk factor for the development of CVD;[33] therefore, reducing LDL-c in patients with CESD is also likely to be associated with reduction in cardiovascular risks, and CESD patients who do not have evidence of severe liver disease or liver failure may remain asymptomatic until a cardiovascular event occurs.[2] Furthermore, in pediatric patients, elevated serum lipids are also considered as a risk factor for cardiovascular disease.[34]

Given that elevated LDL-c is a known risk factor for the development of coronary heart disease, reduction of LDL-c in patients with CESD who are treated with SA, alone or in combination with statin therapy, represents a clinical benefit of therapy with SA. Furthermore, SA is an enzyme replacement therapy that targets the underlying cause of LAL deficiency, and has demonstrated efficacy in infants with Wolman disease (i.e., survival) in the most severely affected phenotype of LAL deficiency.

Additional Secondary Endpoints
As shown above in Table 8, other secondary endpoints included non-HDL-c reduction from baseline, AST normalization, TG reduction from baseline, HDL-c reduction from baseline, liver fat content reduction from baseline, liver histology improvement from baseline, and liver volume reduction from baseline.

AST
At baseline, all but 1 patient in the placebo group had abnormal AST values.

Table 13: Baseline and Week 20 AST Values

Efficacy Endpoint	Baseline		Week 20[a]		Normalization at Week 20 n (%)		p-value
	SA n=36	Placebo n=30	SA n=36	Placebo n=30	SA n=36	Placebo n=30	
AST (U/L) Mean ± SD Median Range	87 ± 33 75 41, 173	78 ± 35 71 39, 220	45 ± 17 41 19, 98	72 ± 42 62 34, 261	15 (42)	1 (3)	0.0003

[a]In the SA group, 3 patients had the last double-blind AST values collected at Week 2 (1 patient) and Week 18 (2 patients).
(Source: reviewer's table, adapted from applicant's response to IR, dated April 30, 2015)

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[33] Graham, I., et al. Dyslipidemias in the Prevention of Cardiovascular Disease: Risk and Causality. Curr Cardiol Rep (2012) 14:709- 720.
[34] Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011 Dec;128 Suppl 5:S213-56.

For AST, the central laboratory specified the ULN for females 4 to 7 years of age as 48 U/L, females 7 to 18 years of age as 40 U/L, females 18 to 59 years of age as 34 U/L. For males 4 to 7 years of age, the ULN was 59 U/L, males 7 to 18 years of age as 40 U/L, and males 18 to 59 years of age as 36 U/L.

Most patients had AST values < 3x ULN: 29/36 (81%) patients in the SA group and 28/30 (93%) patients in the placebo group. Seven out of 36 patients (19%) and 2/30 (7%) patients had AST values ≥ 3x ULN at baseline. AST normalization was seen in 15/36 (42%) patients in the SA group and 1/29 (3%) patients in the placebo group (p < 0.0003). Of the 36 patients in the SA group, only 7 (19%) patients achieved normalization of both ALT and AST during the double-blind treatment period. No patients in the placebo group achieved normalization of both ALT and AST. Similar to ALT, AST 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 this patient population. Additional long-term data are needed to evaluate the relationship between improvements in liver disease related to CESD and treatment with sebelipase alfa.

Non-HDL-c

Non-high-density lipoprotein cholesterol (non-HDL-c) is the difference between the total cholesterol and the HDL cholesterol, which estimates cholesterol concentrations of lipid particles (e.g., VLDL and LDL).[35] The non-HDL-c values at baseline, Week 20, and the percent change from baseline are shown below.

Table 14: Baseline, Week 20, and Percent Change from Baseline at Week 20 for non-HDL-c

Efficacy Endpoint	Baseline		Week 20[a]		% Change from Baseline at Week 20		95% Confidence Interval (p-value)
	SA n=36	Placebo n=30	SA n=36	Placebo n=30	SA n=36	Placebo n=30	
non-HDL-c (mg/dL) Mean ± SD	221 ± 61	264 ± 75	162 ± 69	243 ± 67	-28 ± 19	-7 ± 11	-30, -15
Median	224	242	158	229	-26	-6	(p < 0.0001)
Range	93, 332	155, 408	55, 378	127, 424	-53, 35	-31, 7	

[a]In the SA group, 1 patient had the last double-blind non-HDL-c value collected at Week 2. In the placebo group, 1 patient had the last double-blind non-HDL-c value collected at Week 14.
(Source: reviewer's table, adapted from applicant's response to IR, dated April 30, 2015)

The central lab in this trial did not have a specified normal range for non-HDL-c; therefore, the normal range for non-HDL-c (65-165 mg/dL) was based on the definition obtained from another central lab.

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At the end of the double-blind treatment period, a mean reduction from baseline of 28 ± 19% was observed in the SA group as compared to a mean percent reduction of 7 ± 11% in the placebo group, indicating a difference between the groups of 21% in favor of SA (p < 0.0001). During the open-label period, continued improvement in non-HDL-c was observed. Reductions in non-HDL-c are further supportive of the cholesterol lowering properties of SA and the protective benefit against the development of cardiovascular disease. The 2001 National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines support evaluating non-HDL-c in patients with triglycerides greater than 200 mg/dL.[35] However, as shown below in the next section, hypertriglyceridemia, defined as TG levels ≥ 200 mg/dL, was seen at baseline in only 6/36 (17%) patients in the SA group and 8/30 (27%) in the placebo groups. Therefore, non-HDL-c may be less meaningful since the majority of patients enrolled in LAL-CL02 did not have baseline TG levels > 200 mg/dL.

Triglyceride (TG)
Overall, the majority of patients did not have elevated baseline TG of > 200 mg/dL. Hypertriglyceridemia, defined as TG levels ≥ 200 mg/dL, at baseline was seen in 6/36 (17%) patients in the SA group and 8/30 (27%) in the placebo groups. The baseline, Week 20, and % change from baseline for TG are shown below.

Table 15: Baseline, Week 20, and Percent Change from Baseline at Week 20 for Triglycerides

Efficacy Endpoint	Baseline		Week 20[a]		% Change from Baseline at Week 20		95% Confidence Interval (p-value)
	SA n=36	Placebo n=30	SA n=36	Placebo n=30	SA n=36	Placebo n=30	
Triglyceride (mg/dL) Mean ± SD Median Range	153 ± 54 138 65, 307	174 ± 66 170 66, 361	114 ± 56 114 35, 245	148 ± 59 139 60, 301	-25 ± 30 -33 -67, 59	-11 ± 29 -15 -51, 56	-28, -1 (p=0.04)

[a]In the SA group, 1 patient had the last double-blind TG value collected at Week 2.
(Source: reviewer's table, adapted from applicant's response to IR, dated April 30, 2015)

In the SA group, there was a mean decrease of 25 ± 30% from baseline to Week 20. A reduction from baseline was also seen in the placebo treated patients; a mean percent reduction of 11 ± 29% from baseline was seen in the placebo group. Similar to the transient increase in LDL-c, prior to TG levels improving, a transient mean increase of 5% was seen at Week 4 in the SA-treated patients and was not associated with clinical symptoms. The short-term increase is likely reflective of mobilization of accumulated lysosomal TGs.

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[35] Saenger, A.. Cardiovascular Risk Assessment Beyond LDL Cholesterol: Non-HDL Cholesterol, LDL Particle Number, and Apolipoprotein B. Communique. Available at :
http://www.mayomedicallaboratories.com/articles/communique/2011/11.html.

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While improvements in TG levels were observed in SA-treated patients, baseline TG levels ≥ 200 mg/dL were seen in small number of patients. Persistently elevated TG does not appear to occur as frequently in patients with CESD based on the findings from the natural history study (LAL-2-NH01), which revealed that elevated triglycerides were seen in 27% of patients and 323/411 (79%) TG values collected were ≤ 200 mg/dL. In contrast, LDL-c was elevated in 64% of patients, total cholesterol was elevated in 63% patients, and low HDL was seen in 44% patients. Of those lipid abnormalities, only LDL-c remained consistently elevated in the majority of patients (53% to 73%) over time. Therefore, these findings suggest persistently elevated TG values do not occur as frequently as other lipid abnormalities, and since baseline elevations > 200 mg/dL were seen in a small number of patients, it is difficult to draw conclusions on the ability of SA to reduce TG based on these data.

HDL-c
HDL-c < 40 is also considered to be a risk factor for coronary heart disease, according to the APT III criteria.[31,36] In the SA group, 31/36 (86%) patients had a baseline HDL-c ≤ 40 mg/dL and in the placebo group, 24/30 (80%) patients had baseline HDL-c ≤ 40 mg/dL. In the natural history study (LAL-2-NH01), 20/46 (43%) patients had HDL-c values < 40 mg/dL at baseline. Since patients with CESD may have HDL-c values in the low or low to normal range,[2] the pattern of HDL values seen in Study LAL-CL02 is generally consistent with what is reported in the literature.

The baseline, Week 20, and percent change at Week 20 HDL-c values are shown below.

Table 16: Baseline, Week 20, and Percent Change from Baseline at Week 20 for HDL-c

Efficacy Endpoint	Baseline		Week 20[a]		% Change from Baseline at Week 20		95% Confidence Interval (p-value)
	SA n=36	Placebo n=30	SA n=36	Placebo n=30	SA n=36	Placebo n=30	
HDL-c (mg/dL) Mean ± SD Median Range	32 ± 7 32 18, 48	33 ± 7 34 16, 47	38 ± 10 36 22, 72	33 ± 9 35 19, 49	19 ± 16 18 -23, 64	-1 ± 12 0 -27, 19	12, 26 (p < 0.0001)

[a]In the SA group, 1 patient had the last double-blind non-HDL-c value collected at Week 2. In the placebo group, 1 patient had the last double-blind non-HDL-c value collected at Week 14.
(Source: reviewer's table, adapted from applicant's response to IR, dated April 30, 2015)

Overall, a mean increase from baseline of 19 ± 16% was demonstrated in the SA group and mean decrease from baseline of 1 ± 12% was seen in the placebo group. The difference between the

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[36] http://www.nhlbi.nih.gov/health-pro/guidelines/current/cholesterol-guidelines/quick-desk-reference-html

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groups was 20% in favor of the SA group (p = < 0.0001). Therefore, the SA-treated patients achieved greater increases in HDL-c as compared to placebo-treated patients, who achieved little to no improvement in HDL-c levels. Figure 7 below shows the change from baseline in HDL-c (mg/dL) per patient.

Figure 7: HDL-c Change from Baseline to Week 20[a] by Patient for the Double-blind Treatment Period
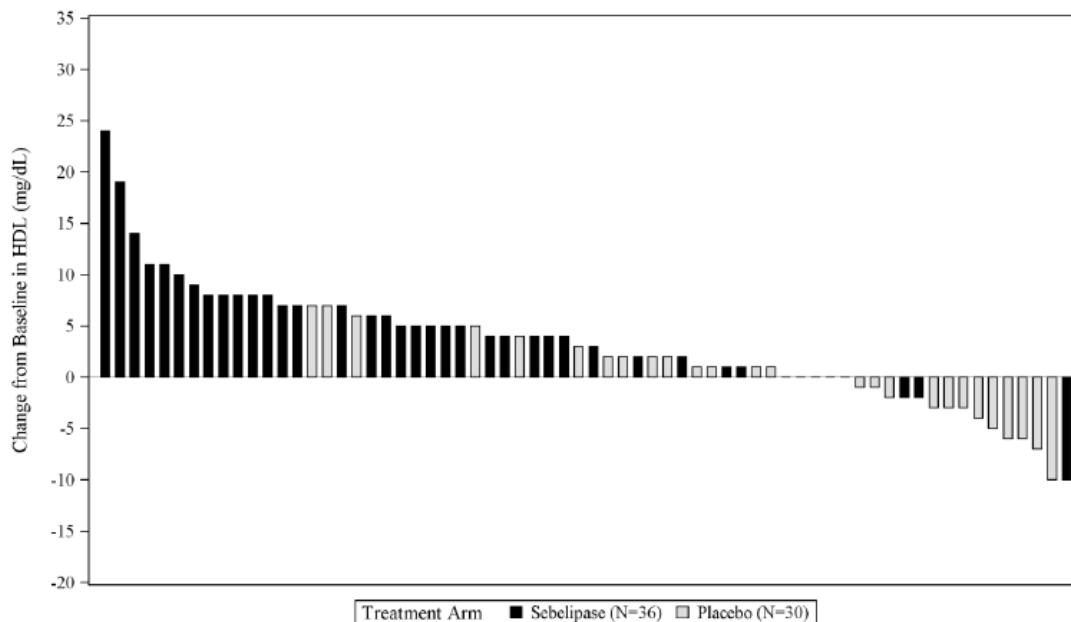
[a]In the SA group, 1 patient had the last double-blind non-HDL-c value collected at Week 2. In the placebo group, 1 patient had the last double-blind non-HDL-c value collected at Week 14.
(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, page 191/354)

In the SA group, 31/36 patients had a baseline HDL-c ≤ 40 mg/dL and of those, 7/31 (23%) achieved a HDL-c > 40 mg/dL at the last double-blind assessment. In the placebo group, 24/30 patients had baseline HDL-c ≤ 40 mg/dL and of those, 3/24 (13%) achieved a HDL-c > 40 at the last double-blind assessment. While only a small number of SA-treated patients achieved HDL-c values > 40 mg/dL, SA-treated patients experienced an improvement in HDL-c as compared to placebo-treated patients in whom little to no improvement in HDL-c was seen.

Liver Fat Content
Liver fat content was assessed by multi-echo gradient echo (MEGE) MRI. MEGE-MRI has been used to quantify hepatic lipid content in patients with NAFLD and NASH.[23,24,37] However, important differences exist between the type of lipid accumulation between patients with NALFD and patients with CESD; patients with NALFD tend to have cytosolic accumulation of hepatic fat and macrovesicular steatosis, whereas patients with CESD are observed to have

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[37] Reeder, S. B. (2013), Emerging quantitative magnetic resonance imaging biomarkers of hepatic steatosis. Hepatology, 58: 1877–1880.

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lysosomal accumulation of cholesteryl esters and triglycerides and microvesicular steatosis. Furthermore, the ability of MEGE-MRI to distinguish between cholesteryl esters, triglycerides, and other types of hepatic lipid accumulation (e.g., macrovesicular steatosis seen in NAFLD) is not known. The ability of MEGE-MRI to accurately measure the specific type and location of lipid accumulation in patients with CESD needs to be explored further. Outside of the sebelipase drug development program, MEGE-MRI has not been evaluated in patients with CESD. Therefore, the results of the liver fat content analysis in this trial will be considered as a pharmacodynamic measure rather than a clinical outcome.

Baseline MEGE MRI assessment of fat content was available in 35 patients in the SA group and 26 patients in the placebo group. Of the 5 patients without MEGE results, 2 patients in the placebo group did not have MRI performed due to procedural-related anxiety in one patient (Subject (b) (6)), and due to a contraindication to the procedure (the presence of internal metal device previously placed to correct a clavicular fracture) in another patient (Subject (b) (6)). The remaining 3 patients had MEGE performed, but the results were not interpretable for one patient (Subject (b) (6)) in the SA group and for 2 patients (Subject (b) (6) and Subject (b) (6)) in the placebo group. Of note, one additional patient in the SA group was excluded from this analysis since the Week 20 MRI was conducted 2 days after the Week 22 infusion. The baseline, Week 20, and percent change from baseline at Week 20 values are shown below.

Table 17: Baseline, Week 20, and Percent Change from Baseline at Week 20 for Liver Fat Content, as measured by MRI

Efficacy Endpoint	Baseline		Week 20[a]		% Change from Baseline at Week 20		95% Confidence Interval (p-value)
Liver Fat Content (%)	SA n=35	Placebo n=26	SA n=32	Placebo n=26	SA n=32	Placebo n=25	
Mean ± SD Median Range	9 ± 4 8 3, 25	8 ± 3 8 2, 13	5 ± 2 5 2, 9	8 ± 3 8 2, 13	-32 ± 27 -35 -75, 52	-4 ± 16 -4 -37, 25	-41, 19 (p <0.0001)

(Source: reviewer's table, adapted from applicant's response to IR, dated April 30, 2015)

As shown above, the baseline mean liver fat content was $9 \pm 4\%$ in the SA group and $8 \pm 3\%$ in the placebo group. In the SA group, the mean change from baseline was a decrease of $32 \pm 27\%$, as compared a mean decrease from baseline of $4 \pm 16\%$ in the placebo group. While both groups experienced an overall mean reduction in liver fat content, as measured by MEGE MRI, the decrease was greater in the sebelipase-treated patients with a difference between the groups of 28% in favor of SA (p < 0.0001). While decrease in liver fat content assessed by MRI may reflect a pharmacodynamic effect of sebelipase alfa, it does not represent a clinically meaningful outcome. Based on the 20-week duration of Study LAL-CL02, there are no data available data at

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this time to demonstrate that a reduction in liver fat correlates with improved long-term outcomes of liver disease in patients with CESD. Additional data will be requested in the form of a post-marketing study to further evaluate the long-term outcomes related to liver and cardiovascular disease in patients with CESD who are treated with sebelipase alfa.

Since liver fat content was measured by both MEGE MRI and morphometric analysis of steatosis on liver biopsy, an exploratory analysis was performed to evaluate the relationship between liver fat as measured by MRI and by biopsy.

Figure 8: Change from Baseline to Last Double-Blind Assessment in Liver Fat Content as Measured by MRI vs. Liver Fat Content as Measured by Liver Biopsy

(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, page 227/354)

The figure above shows that 9/16 (56%) patients in the SA group and 2/7 (29%) patients in the placebo group had a reduction in liver fat content as measured by both MRI and liver biopsy (lower left quadrant). As seen in the figure above, there is some variability and because of the small numbers, it is difficult to make definitive conclusions. Additional studies are needed to determine whether there is a correlation between liver fat content, as measured by MRI, and liver fat content, as measured by biopsy, in patients with CESD. The changes in liver histology over the 20-week double-blind treatment period are discussed below.

Liver Histology
Hepatic steatosis score, as assessed by morphometry (H&E stained fat [%])
Improvement in liver histopathology was defined as a decrease of ≥ 5% in hepatic steatosis score, as assessed by morphometry of H&E stained sections (H&E stained fat [%]), from baseline to the last time point in the double-blind treatment period. A cut-point of 5% decrease from baseline was selected by the applicant based on the calculated false positive rate described in the SAP. Computer morphometry quantifies liver fat using computer software to measure fat

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on digitally scanned H&E stained slides.[38] The ability to quantify fibrosis and steatosis has been described in liver diseases including alcoholic liver disease, NASH, and hepatitis C, and appears to have the ability to measure the diameter of fat globules to distinguish between microvesicular and macrovesicular steatosis.[38,39]

In the patients enrolled in Study LAL-CL02 who underwent baseline liver biopsy, at baseline, all patients except one patient in the placebo group had evidence of microvesicular steatosis, and fat vacuoles were seen in all or nearly all of the hepatocytes in 18/19 (95%) patients in the SA group and 10/13 (77%) patients in the placebo group. In contrast, macrovesicular steatosis was not seen in 16/19 (84%) patients in the SA group and 11/13 (85%) patients in the placebo group. Because of the baseline characteristics of the patient population, the morphometric score of H&E stained fat may reflect mainly microvesicular steatosis in this patient population; however, based on the data submitted, it is unclear whether the fat globule diameter was measured. Therefore, the morphometric hepatic steatosis score is limited in that it may reflect both microvesicular and macrovesicular steatosis. Furthermore, based on this reviewer's own analysis performed using the applicant's data (Analysis Liver Biopsy Data "adxp.xpt" dataset), the baseline morphometry steatosis scores (H&E stain fat [%]) do not correlate with the microscopic steatosis score (percentage of hepatocyte area replaced by fat vacuoles), as determined by the pathologist. However, the lack of correlation between pathologist assessment and computer estimation of hepatic steatosis has also been described in the literature.[40] Liver biopsy samples to quantify hepatic steatosis are also limited in that liver biopsies may be subject to sampling error since an adequate biopsy only represents 1/50,000 – 1/65,000 of the liver,[41,42,43] and tissue fixatives and staining may interfere with the ability to accurately measure lipid droplets.[40,44,45]

Liver pathology data were assessed by a blinded central reader in an unpaired fashion for 27 patients. However, one patient (Subject ___ (b) (6)) in the SA group was excluded from this analysis as the biopsy was performed after entry into the open-label period (i.e., 1 day after the Week 22 infusion); therefore resulting in a total of 26 patients in the analysis. Of note, she was found to have a reduction from baseline in liver steatosis.

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[38] Li, M., et al. Comparing morphometric, biochemical, and visual measurements of macrovesicular steatosis of liver. Human Pathology (2011); 42: 356-360.

[39] Zaitoun, AM., et al. Quantitative assessment of fibrosis and steatosis in liver biopsies from patients with chronic hepatitis C. Journal of Clinical Pathology (2001); 54(6):461-465.

[40] El-Badry, AM., et al. Assessment of Hepatic Steatosis by Expert Pathologists: the end of a gold standard. Ann Surg 2009;250: 691–697).

[41] Brunt, E., and Tiniakos, D.. Histopathology of nonalcoholic fatty liver disease. World J Gastroenterol. 2010 Nov 14; 16(42): 5286–5296.

[42] Regev A, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol. 2002 Oct; 97(10):2614-8.

[43] Vuppalanchi, R., et al. Increased Diagnostic Yield from Liver Biopsy in Suspected Nonalcoholic Fatty Liver Disease (NAFLD) Using Multiple Cores and Multiple Readings. Clin Gastroenterol Hepatol. 2009 Apr; 7(4): 481–486.

[44] DiDonato D, Brasaemle DL. Fixation methods for the study of lipid droplets by immunofluorescence microscopy. J Histochem Cytochem. 2003;51:773–780.

[45] Fukumoto S, Fujimoto T. Deformation of lipid droplets in fixed samples. Histochem Cell Biol. 2002;118:423–428.

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A baseline liver biopsy was performed in 32 patients, 19 in the SA group and 13 in the placebo group. Six patients did not have a Week 20 liver biopsy performed. Five patients (Subjects (b)(6)) did not provide consent for a Week 20 liver biopsy and one patient (Subject (b)(6)) did not undergo a Week 20 biopsy since the site IRB did not approve Week 20 liver biopsies in pediatric patients. Of the 26 patients with available Week 20 liver biopsy results, 16 were in the SA group and 10 were in the placebo group. At baseline, the mean hepatic steatosis score, as assessed by morphometry of H&E stained sections (H&E stained fat [%]), in the SA group was 30 ± 20%, median 25%, and range 6 – 80%. In the placebo group, the mean hepatic steatosis score was 34 ± 25%, median 25%, range 5 – 81%. At baseline, hepatic steatosis scores > 50% were seen in 2/16 (13%) patients in the SA as compared to 3/10 (30%) patients in the placebo group. At Week 20, 10/16 (63%) patients in the SA group met the pre-specified criteria for improvement in liver histopathology as compared with 4/10 (40%) patients in the placebo group. The difference between the groups was 23% which was not statistically significant (p = 0.42). While there appears to be an improvement in a larger proportion of patients in the SA group, the sample size is too small to make meaningful conclusions based on biopsy data alone. Figure 9 below summarizes the change from baseline for patients with available liver biopsy data.

Figure 9: Liver Histology Steatosis Score Change from Baseline to Last Double-Blind Assessment (FAS with Liver Biopsy Data)

Result at Last Visit in the Double-blind Treatment Period	Sebelipase Alfa (N=19) n (%)	Placebo (N=13) n (%)	Difference (%)	P-value
N	16	10		
Endpoint improved from baseline[1]	10 (63)	4 (40)	23	0.4216
Endpoint unchanged from baseline[1]	5 (31)	1 (10)	21	0.3524
Endpoint worsened from baseline[1]	1 (6)	5 (50)	-44	0.0184
Overall distribution of results[2]		0.0454		

N: Number of subjects in specified treatment group where liver biopsy obtained; n: Number of subjects with data available; %: Percentage based on N; p-value: Fisher's exact test for treatment differences; Difference: Difference between the percentage of Sebelipase Alfa – Placebo.

[1] P-value for this row compares proportion of subjects with this result vs any other result.

[2] P-value for this row compares distribution of 3 possible results across treatment groups.

(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, page 193/354)

Of the patients in the SA group, 15/16 (94%) patients were found to have either no change from baseline or an improvement from baseline in liver steatosis, as measured on liver biopsy. A lower proportion of patients in the placebo group, 5/10 (50%) patients, experienced either no change or an improvement from baseline. This difference was not statistically significant between the groups, but it should be noted that only 1/16 (6%) patients in the SA group showed worsening from baseline in liver steatosis as compared to 5/10 (50%) in the placebo group. While some of these findings could be due to sampling error associated with liver biopsy,[41,42,43] overall, the SA-treated patients showed no change or an improvement from baseline. The change from baseline per patient in shown below.

Figure 10: Liver Morphometry Scores (Percent Steatosis) Change from Baseline to Last Double-Blind Assessment by Patient
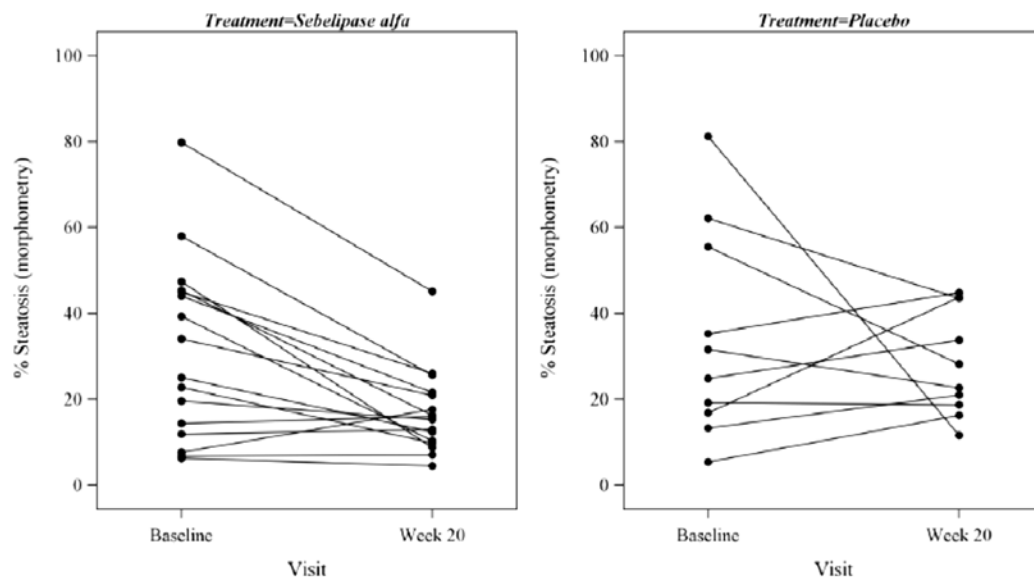
(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, page 194/354)

There is one clear outlier in the placebo group (Subject ____(b) (6)) with a high baseline score who had a decrease of 70% from baseline. A post-hoc, unblinded evaluation revealed that the morphometry results for microvesicular steatosis may have been a result of a reduction in the H&E staining intensity of the baseline biopsy as compared to the staining of the Week 20 biopsy. Since morphometry analysis is dependent on the intensity of the cytoplasmic eosin staining, the difference in staining intensity may have confounded the interpretation of the results in this patient. Additional methods of controlling the staining consistency of the biopsy results are needed to produce more interpretable biopsy results.

Ishak Fibrosis Score
Changes in fibrosis were evaluated since improvement in fibrosis may represent a more meaningful clinical benefit than steatosis scores. At baseline, all 32 (100%) patients with baseline biopsy data had evidence of fibrosis. Fifteen of the 19 (80%) patients in the SA group and 10/13 (77%) patients in the placebo group had Ishak scores of > 2 (fibrous expansion of more than 50% portal tracts). Five of the 19 (25%) patients in the SA group and 5/13 (38%) patients in the placebo group were found to have Ishak scores of 5 (indicating early or incomplete cirrhosis) or a score of 6 (indicating probable or definite cirrhosis). Refer to the Appendix, Table 33, for a description of the Ishak score.

Of the 26 patients with liver biopsy data at Week 20, most patients either had no change or a one point change in Ishak fibrosis score from baseline to Week 20. Ten out of 16 patients in the SA group and 7/10 patients in the placebo group showed no change in Ishak fibrosis scores. Five patients showed an improvement by only one point on the Ishak score, 4/16 patients in the SA

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group, including the one patient who had the biopsy performed after the Week 22 infusion, and 1/10 in the placebo group. One patient in the SA group and one patient in the placebo group worsened by one point. One patient (Subject ____(b) (6)____) in the placebo group showed a change from cirrhosis (score 6) at baseline to no fibrosis (score 0) at Week 20; however, the pathologist for Study LAL-CL02, who confirmed that this patient had cirrhosis at baseline, determined that given the fragmented nature of the biopsies, the change in score was likely an artifact due to loss of surrounding fibrotic tissue during the biopsy procedure, as previously discussed. The Ishak scores at baseline and Week 20 are shown below for patients with paired liver biopsies.

Table 18: Changes in Ishak Fibrosis Score from Baseline to Week 20

Sebelipase alfa (SA)			Placebo		
Age (sex) at Baseline Liver Biopsy (years), Performed during Screening	Ishak Score on Baseline Biopsy	Ishak Score on Liver Biopsy Performed at Week 20	Age (sex) at Baseline Liver Biopsy (years), Performed during Screening	Ishak Score on Baseline Biopsy	Ishak Score on Liver Biopsy Performed at Week 20
Score- 6: Cirrhosis, probable or definite					
19 (F)	6	6	17 (M)	6	6
12 (F)	6	6	14 (F)	6	6
14 (F)	6	6	9 (F)	6	6
5 (F)	6	6	22 (F)	6	0**
Score 5: Early or incomplete cirrhosis					
7 (M)	5	4	No placebo patient in this category		
Score 4: Bridging fibrosis involving > 50% of portal and/or central areas					
22 (F)	4	5	13 (F)	4	4
Score 3: Bridging fibrosis involving < 50% of portal and/or central areas					
24 (M)	3	6	33 (M)	3	3
18 (M)	3	2	21 (M)	3	3
21 (F)	3	2			
22 (M)	3	3			
28 (M)	3	3			
55 (M)	3	3			
19 (M)	3	3			
Score 2: Fibrous expansion of > 50% of portal tracts, with or without short fibrous septa					
55 (F)	2	2	31 (M)	2	3
21 (F)	2	2	20 (M)	2	1
42 (F)#	2	1#			
Score 1: Fibrous expansion of < 50% of portal tracts, with or without short fibrous septa					
12 (F)	1	3	59 (F)	1	1

** Score of 0 due to staining artifact.
# Liver biopsy performed 1 day after Week 22 infusion during OL period.
 (source: reviewer's table created using information provided in the applicant's response to IR, received 3/25/15, and applicant's dataset, "ADXP", module 5.3.5.1, BLA 125561, Study LAL-CL02)

Patients either demonstrated no or minimal change in the Ishak scores at Week 20. Twenty weeks may not be a sufficient duration of time to observe a meaningful change in histology; therefore, assessment of liver biopsies after a longer duration and in a larger number of patients may provide more meaningful information. Additional data will be requested as a post-marketing study to further evaluate the effect of sebelipase alfa on the long-term outcomes of liver disease in patients with CESD.

Refer to consult review by Dr. Prakash Jha for further details of the liver histopathology results. As per the SAP, formal hypothesis testing was stopped at this endpoint; however, the change in liver volume is discussed below.

Liver Volume

While the SAP did not allow for further formal hypothesis testing of this endpoint, reduction in liver volume from baseline will be reviewed in this document. Liver volume, as measured by MRI, was reported in multiples of normal (MN).[46] As per conversations with patients with LAL-deficiency during the patient listening call, held February 27, 2015, hepatomegaly is one of the few noticeable symptoms to patients while many of the other disease manifestations (e.g., elevated serum transaminase levels, hyperlipidemia) are not noticeable to patients. Additionally, hepatomegaly was the most common hepatic condition reported in the medical history of 38/66 (58%) patients enrolled in LAL-CL02. Furthermore, the review of 135 patients by Bernstein, et al.,[2] states that hepatomegaly was present in 134/135 (99.3%) patients. The baseline, Week 20, and percent change from baseline at Week 20 for liver volume, as measured by MRI is shown below.

Table 19: Baseline, Week 20, and Percent Change from Baseline at Week 20 for Liver Volume (multiples of normal [MN]), as measured by MRI

Efficacy Endpoint	Baseline		Week 20[a]		% Change from Baseline at Week 20		95% Confidence Interval (p-value)
	SA n=36	Placebo n=28	SA n=33	Placebo n=28	SA n=33	Placebo n=27	
Liver Volume (MN)							
Mean ± SD	1.4 ± 0.4	1.5 ±0.3	1.3 ± 0.3	1.4 ± 0.3	-10.3 ± 10.5	-2.7 ± 10.1	-12.3, -2.6 (p=0.007)
Median	1.4	1.4	1.3	1.4	-11.7	-4.6	
Range	1, 3	1 , 2	1, 2	1, 2	-35.6, 12.4	-22.4, 18.7	

(Source: reviewer's table, adapted from applicant's response to IR, response dated April 30, 2015)

As shown above, the baseline mean liver volume, measured in multiples of normal (MN), in the SA group was 1.4 ± 0.4 MN, and 1.5 ± 0.3 MN in the placebo group. Of the patients with baseline liver volume ≥ 1.58 MN, 11/26 (31%) patients were in the SA group and 11/30 (39%)

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[46] Liver volume (MN) = subjects organ volume/(body weight [kg]*0.025)

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patients were in the placebo group. As previously mentioned, one patient (Subject _____ (b) (6)) in the SA group was excluded from the analysis since the Week 20 MRI was performed after the Week 22 infusion during the open-label (OL) extension period.

There were 33/36 (92%) patients in the SA group and 27/30 (90%) patients in the placebo group who had liver volume, as assessed by MRI, at both baseline and the last double-blind assessment, Week 20. As shown above in Table 19, the change in liver volume from baseline in the SA group was a mean decrease of $10 \pm 11\%$, as compared to a mean decrease from baseline of $3 \pm 10\%$ in the placebo group; a difference between the groups of 8% in favor of SA (p = 0.007). While each treatment group demonstrated very small mean absolute changes from baseline, the mean percent change from baseline for SA appears much larger than that of placebo due to the mean absolute change from baseline being numerically much greater relatively for SA as compared to placebo. Furthermore, it should be noted that as per the SAP, formal hypothesis testing was stopped at the previous endpoint (liver biopsy); therefore, liver volume is considered as not significant based on the order of the statistical testing. As noted previously in this document, the clinical review team considers liver volume to be a pharmacodynamic measure of effect, rather than a clinical efficacy outcome.

6.1.6   Other Endpoints

The other endpoints discussed in this section were not ranked in the formal hypothesis testing for primary and secondary efficacy endpoints.

GGT
Of the 25 patients with GGT > ULN at baseline, 8/13 (62%) in the SA group and 1/12 (8%) patients in the placebo group achieved a GGT value ≤ ULN after the last double-blind assessment. At Week 14 of open-label treatment with sebelipase alfa, 3/7 (43%) patients originally in the placebo group achieved GGT < ULN after transitioning to sebelipase alfa during the open-label period. In the open-label period, the reductions in GGT were sustained through Week 36 for patients initially randomized to the SA group.

Alkaline Phosphatase
At baseline, the mean alkaline phosphatase (ALP) was 256 ± 140 U/L in the SA group and 269 ± 129 U/L in the placebo group. The lowest mean value in the SA group was 214 ± 120 U/L at Week 14 and the lowest mean value in the placebo group was 252 ± 122 U/L at Week 6; a mean decrease from baseline of $16 \pm 13\%$ at Week 14 in the SA group and $5 \pm 13\%$ at Week 6 in the placebo group. The ALP values fluctuated during the trial and the mean change from baseline to the last double-blind assessment was numerically similar between the two groups.

Albumin
No patient had baseline albumin below the lower limit of normal (LLN). Small, non-clinically relevant changes were seen in albumin during the double-blind treatment period. The mean change from baseline in albumin in the SA group was -0.2 ± 2 g/L, median 0, range -4 to 5 g/L.

The mean change from baseline in albumin in the placebo group was -1 ± 2 g/L, median -1 g/L, range -6 to 3 g/L.

Bilirubin

Three of the 5 patients in the SA group with baseline indirect bilirubin > ULN showed a reduction from baseline as compared to 0/5 patients in the placebo group. At Week 20, the mean indirect bilirubin in the SA group was 12 ± 10 umol/L and mean in the placebo group was 16 ± 15umol/L. At Week 20, the mean change from baseline was 20 ± 29% in the SA group and 9 ± 24% in the placebo group. Since only 10 patients had indirect bilirubin > ULN at baseline, it is difficult to make generalizable conclusion on the relationship between bilirubin levels and treatment with sebelipase alfa.

Two of the 4 patients in the SA group with baseline direct bilirubin > ULN showed a reduction from baseline and 1 patient in the placebo group with a direct bilirubin > ULN at baseline showed an 11% increase from baseline. However, of the 66 patients enrolled, only 1 patient in the SA group had a direct bilirubin of > 1.5x ULN. Overall, mean direct bilirubin levels were numerically similar between the SA and placebo groups at baseline (3 ± 2 umol/L vs. 3 ± 2 umol/L) and at all post-baseline assessments, with the exception of Week 18. At Week 18, in the SA group demonstrated a mean decrease from of 7 ± 17% and an increase of 2 ± 13% was seen in the placebo group. Since baseline abnormalities in bilirubin were present only in a few patients, conclusions based on small numbers of patients are not generalizable to the broader patient population.

Coagulation Studies

At baseline, coagulopathy was not common overall. Of the 11 patients with 2 or more abnormal coagulation studies at baseline, there were no clinically meaningful changes observed during the double-blind treatment period in either the SA or placebo group, overall. However, one patient (Subject _____ (b) (6)) in the SA group had a marked improvement in both PT and INR. This patient had the highest INR of 2.15 and a baseline ALT of 57 mg/dL, no documentation of cirrhosis, and baseline Ishak score of 2 (fibrous expansion of > 50% of portal tracts, with or without short fibrous septa).

Apolipoproteins and Lipid Particles

Additional biochemical assessments were performed, including apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and lipoprotein particle analysis by nuclear magnetic resonance (NMR) at baseline and at the last double-blind assessment. In addition to the standard lipid parameters, ApoB and lipid particles are thought to also have atherogenic potential.[35] These analyses are considered as exploratory but the results will be discussed briefly in the following sections.

ApoA1

The lower limit of normal (LLN) for ApoA1 in this trial was 100 mg/dL. Baseline mean ApoA1 concentration was at the low end of normal. The baseline mean ApoA1 concentration was 103 ± 18 mg/dL in the SA group and 102 ± 18 mg/dL in the placebo group. While the baseline values

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were at the low end of the normal range, the Week 20 mean concentration in the SA group demonstrated a slight increase as compared to a small decrease in the placebo group (111 ± 21 mg/dL vs. 100 ± 18 mg/dL). At the time of the data cut-off for the open-label period, there were < 5 patients in each treatment group with recorded ApoA1 values in the open-label period; therefore, the results are not discussed.

ApoB
The upper limit of normal (ULN) for ApoB concentration was defined as ≤ 120 mg/dL. The baseline mean ApoB concentration was elevated at 148 ± 36 mg/dL in the SA group and 169 ± 32 mg/dL in the placebo group. At Week 20, ApoB levels in the SA group demonstrated a greater decrease from baseline as compared to the placebo group (110 ± 38 mg/dL vs. 160 ± 32 mg/dL). At the time of the data cut-off for the open-label period, there were < 5 patients in each treatment group with recorded values in the open-label period; therefore, the results are not discussed.

Lipid Particles
NMR-based lipoprotein analysis was used to determine the total number of particles and particle size for HDL and LDL. These assessments may provide insight into the impact of disease on lipid metabolism.

HDL-Particle
The mean total HDL particle (HDL-P) number at baseline was less than the 10th centile, defined as 25 μmol/L for males and 27 μmol/L for females. The baseline mean HDL-P number was 18 ± 5 umol/L in the SA group and 18 ± 6 umol/L in the placebo group. At Week 20, the mean in the SA group and placebo groups were similar (24 ± 6 umol/L vs. 20 ± 7 umol/L).

IDL-Particle
The mean total intermediate-density lipoprotein-particle (IDL-P) number at baseline was > 90th centile, defined as 183 nmol/L for males and 187 nmol/L for females. The baseline IDL-P number in the SA and placebo groups was similar (227 ± 145 nmol/L and 223 ± 137 nmol/L). At Week 20, the mean value in the SA was lower than in the placebo group (154 ± 158 nmol/L vs. 189 ± 140 nmol/L).

LDL-Particle
The mean total LDL-particle (LDL-P) number at baseline was at the upper end of the normal range, where the 90th centile was defined as 2100 nmol/L for males and 2158 nmol/L for females. At baseline, the total LDL-P number was smaller in the SA as compared to the placebo group (1942 ± 577 nmol/L vs. 2414 ± 684 nmol/L). At Week 20, the SA group demonstrated a numerically larger reduction from baseline in the mean LDL-P value as compared to the placebo group (1465 ± 570 nmol/L and 2342 ± 620 nmol/L).

Lipoprotein Insulin Resistance Score
Lipoprotein insulin resistance score is determined on a scale of 0 to 100 and is a combination of large VLDL-P, small LDL-P, and large HDL-P levels and VLDL, LDL, and HDL size. Higher

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scores suggest a higher degree of insulin resistance.[47] At baseline, mean lipoprotein insulin resistance scores were similar between the SA and placebo groups (47 ± 17 and 49 ± 17). At Week 20, the mean scores remained similar between the SA and placebo groups (45 ± 16 and 45 ± 17).

Spleen Volume (MN) and Spleen Fat (%), as measured by MRI
Spleen volume, as measured by MRI, was reported in multiples of normal (MN).[48] MRI results at Week 20 were available for 33 patients in the SA group and 27 patients in the placebo group. The mean absolute change from baseline to Week 20 in SA-treated patients was -0.4 ± 0.9 MN as compared to 0.2 ± 0.4 MN in the placebo group; a difference of 0.5 MN between the groups in favor of SA. As of the data cut-off for open-label period, there were < 5 patients in each treatment group with MRI assessment of spleen volume and fat content during the open-label period; therefore, the results are not discussed. The change from baseline at Week 20 was also small for spleen fat content (%), as measured by MRI. The mean absolute change from baseline to Week 20 in SA-treated patients was $-0.4 \pm 2\%$ as compared to $0.03 \pm 1\%$ in the placebo group; a difference of 0.4%.

Additional Liver Histopathology Analyses
Additional exploratory analyses of liver histopathology were conducted, including assessment of CD68+ cells (macrophage lineage). There were baseline imbalances in the morphometric scores for CD68 between the SA and placebo groups with a higher mean score in the SA group as compared to the placebo group ($9 \pm 7\%$ vs. $6 \pm 5\%$). At Week 20, a numerically greater mean reduction was observed in the SA group as compared to placebo ($-3 \pm 5\%$ vs. $-0.2 \pm 4\%$).

The baseline scores for SMA immunostaining to assess stellate cells, an indirect measure of fibrosis, was also imbalanced between the groups with a lower mean score in the SA group as compared to the placebo group ($6 \pm 6\%$ vs. $8 \pm 10\%$). At Week 20, a slightly greater reduction in mean SMA score was observed in the placebo group as compared with the SA group ($-1 \pm 8\%$ vs. $-0.02 \pm 5\%$).

The baseline morphometric scores for collagen, assessed by Sirius red staining, were lower in the SA group as compared to the placebo group ($9 \pm 5\%$ vs. $18 \pm 20\%$). These values are substantially higher than the levels expected in normal liver (typically approximately 1%, based on the applicant's communication with Z. Goodman, the applicant's consultant pathologist). Large variation in scores was observed in both the SA and placebo groups, with no evidence of an interpretable treatment effect.

Refer to consult review by Dr. Prakash Jha for further details of the liver histopathology results.

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[47] Shalaurova, I., et al. Lipoprotein Insulin Resistance Index: A lipoprotein particle-derived measure of insulin resistance. Metab Syndr Relat Disord. 2014 Oct 1; 12(8): 422–429.
[48] Spleen volume (MN) = subjects organ volume / (body weight [kg]*0.002)

Anthropometric/Growth Measurements

Patients in both the SA and placebo groups experienced small increases in weight and height during the 20-week double-blind treatment period. In the SA group, the baseline mean ± SD weight (kg) was 49 ± 20 kg and increased slightly to 50 ± 20 kg at Week 20. In the placebo group, the baseline mean ± SD weight (kg) was 47 ± 20 kg and increased slightly to 49 ± 20 kg at Week 20. Similarly, small increases from baseline to Week 20 in height were seen in both the SA and placebo groups. Height was assessed at both baseline and Week 20 for only those patients who were< 18 year of age. In the SA group, the baseline mean height was 141 ± 19 cm and increased to 143 ± 18 cm at Week 20. In the placebo group, the baseline height was 148 ± 22 cm and increased to 150 ± 21 cm at Week 20. The data are difficult to interpret since data on z-scores were not reported and the mean values for weight and height include both males and females, across a wide range of ages. Furthermore, it is difficult to draw conclusions on the clinical benefit on SA on weight and/or height in this patient population over a short duration (i.e., 20 weeks) of treatment.

6.1.7 Subpopulations

Age at Randomization

The percent change from baseline in LDL-c was analyzed by age at randomization (< 12 years of age, ≥ 12 years to < 18 years, and ≥ 18 years of age). Overall, a numerically greater improvement was observed in patients ≥ 12 years of age as compared to those < 12 years of age for LDL-C. Table 20 below shows the percent change from baseline in LDL-c by age at randomization and Table 21 show the proportion of patients with abnormal LDL-c (≥ 130 mg/dL) at baseline who achieved LDL-c (<130 mg/dL) at Week 20, by age group at randomization.

Table 20: Change from Baseline in LDL Cholesterol by Age at Randomization

Age at Randomization	< 12 years		≥ 12 to < 18 years		≥ 18 years	
Treatment Group	Sebelipase alfa (n=14)	Placebo (n=10)	Sebelipase alfa (n=9)	Placebo (n=14)	Sebelipase alfa (n=13)	Placebo (n=6)
LDL-c % Change from Baseline						
Mean (SD)	-17 (25)	-1 (11)	-32 (17)	-9 (13)	-38 (18)	-9 (16)
Median	-24	2	-41	-8	-42	-6
Range	-54, 46	-21, 16	-50, 2	-33, 10	-59, -9	-30, 7

(Source: reviewer's table adapted from applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, Table 14.2.2.1, pages 125-133/11252)

There appears to be a numerically greater improvement in LDL-c in patients ≥ 12 years of age as compared to patients < 12 years of age; however, when normalization of LDL-c, defined as LDL < 130 mg/dL, was evaluated in patients with baseline abnormal LDL-c, patients across all age groups achieved LDL-c < 130 mg/dL after 20 weeks of SA treatment.

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Table 21: Proportion of Patients with LDL-c $\geq$ 130 mg/dL at Baseline who Achieved LDL-c <130 mg/dL at Week 20 by Age at Randomization

Age at Randomization	< 12 years		$\geq$ 12 to < 18 years		$\geq$ 18 years	
Treatment Group	Sebelipase alfa (n=14)	Placebo (n=10)	Sebelipase alfa (n=7)	Placebo (n=14)	Sebelipase alfa (n=11)	Placebo (n=6)
Patients who Achieved LDL-c < 130 mg/dL at Week 20 n (%)	5 (36)	0	3 (43)	1 (7)	5 (46)	1 (17)
95% CI	11, 61		-3, 75		-13, 71	

(Source: reviewer's table adapted from applicant's response to IR for Drug Trials Snapshot, received May 27, 2015, BLA 125561)

While the number of patients in each age group with LDL-c < 130 mg/dL at Week 20 is small, the total number of each age subgroup is also small, but there is a numerically larger difference when SA-treated patients are compared to placebo. Overall, the small numbers of patients in each age category make it difficult to draw definitive conclusions.

Sex
Analyses of the percent change from baseline in LDL-c by sex did not reveal a meaningful difference between males and females with respect to outcome, as shown below.

Table 22: Percent Change from Baseline in LDL Cholesterol by Sex

Sex	Male		Female	
Treatment Group	Sebelipase alfa (n=18)	Placebo (n=15)	Sebelipase alfa (n=18)	Placebo (n=15)
LDL-c % Change from Baseline Mean (SD) Median Range	-26 (27) -29 -59, 46	-6 (13) -1 -30, 8	-31 (17) -29 -54, 12	-7 (14) -9 -33, 16

(Source: reviewer's table adapted from applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, Table 14.2.2.2, pages 138 and 142/11252)

Race and Ethnicity
Analyses of percent change in LDL-c from baseline by race and ethnicity was conducted. Note that the number of white patients was greater than the non-white patients, and the number of non-Hispanic/Latino patients was greater than the Hispanic/Latino patients. Two analyses were conducted to evaluate whether there were differences between race (white vs other) and ethnicity (Hispanic or Latino vs. not Hispanic or Latino), shown below; the shading represents the latter analysis.

Table 23: Percent Change from Baseline in LDL Cholesterol by Race and Ethnicity

Race/Ethnicity	White		Other		Hispanic or Latino		Not Hispanic or Latino	
Treatment Group	Sebelipase alfa (n=27)	Placebo (n=28)	Sebelipase alfa (n=9)	Placebo (n=2)	Sebelipase alfa (n=6)	Placebo (n=4)	Sebelipase alfa (n=30)	Placebo (n=26)
LDL-c % Change from Baseline Mean (SD) Median Range	-29 (19) -32 -59, 12	-6 (12) -5 -30, 16	-25 (31) -26 -12, -46	-12 (29) -12 -33, 9	-25 (16) -24 -54, -9	-8 (19) -4 -33, 8	-29 (24) -34 -59, 46	-6 (12) -5 -30, 16

(Source: reviewer's table adapted from applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, Table 14.2.2.3, pages 147,151,156,160/11252)

As shown above, the results are numerically similar across groups of patients treated with SA. There do not appear to be significant differences in the percent change in LDL cholesterol from baseline with respect to race or ethnicity.

6.1.8   Analysis of Clinical Information Relevant to Dosing Recommendations

Proposed dosing and administration: The recommended dosage of sebelipase alfa is 1 mg/kg IV infusion every other week. During Study LAL-CL02, all patients received a dose of 1 mg/kg IV every other week; therefore, there are no data to support alternative dosing regimens in patients with CESD. Refer to the clinical pharmacology review by Dr. Jing Fang for further details.

6.1.9   Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and tolerance effects could be affected by immunogenicity to enzyme replacement products. Only 5 patients in Study LAL-CL02 developed anti-drug antibodies (ADA); however, efficacy did not appear to be impacted in patients who were ADA positive. In fact, by the end of the 20-week double-blind treatment period, all 5 patients were ADA negative. Therefore, there appears to be a tolerizing effect over time. Refer to Section 7.4.2 Laboratory Findings for details on anti-drug IgG antibody formation.

6.1.10   Additional Efficacy Issues/Analysis

Classification of Genotype
Currently, a clear genotype/phenotype correlation has not been described for CESD. The most common genotype is a donor-splice site mutation (i.e., c.894 G>A or former nomenclature E8SJM$^{-1G>A}$), and patients with this mutation in one or both alleles are found across a spectrum of age of onset, disease severity, disease progression, and clinical manifestations.[2] Overall, 85% of patients enrolled in this trial had at least one copy of the c.849G>A common exon 8 splice junction mutation (32% homozygotes and 53% compound heterozygotes), resulting in the

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common exon 8 splice junction mutation allele frequency of 60% in this trial, which is consistent with the reported literature.[49] The following three groups were evaluated:

- Group 1: Homozygous for the c.849G>A common exon 8 splice junction mutation (n=21)
- Group 2: Confirmed or presumed compound heterozygous for c.849G>A common exon 8 splice junction mutation (n=35)
- Group 3: Other mutations (n=10)

Due to the small sample size, it is not possible to draw a conclusion regarding the relationship between genotype and the impact on clinical outcome at this time.

Additional supportive endpoints included serum chitotriosidase and ferritin, macrophage activation markers, and quality of life-related surveys (FACIT-Fatigue, CLDQ and PedsQL™).

Macrophage Activation Markers
In CESD, serum chitotriosidase levels have been reported to be elevated; however, this marker is not specific to CESD. At baseline, mean serum chitotriosidase levels were similar between the SA and placebo groups, 8 U/mL and 7 U/mL, respectively. At the last double-blind assessment, the mean value decreased by 2 U/mL in the SA group and increased by 0.3 U/mL in the placebo group. However, the placebo group initially decreased until Week 10, after which there was a small increase. In addition, the mean values for the SA and placebo groups overlap somewhat during the 20-week treatment period.

Ferritin is an acute phase reactant and elevated in patients with macrophage activation. However, in this clinical trial, the baseline mean serum ferritin values were not above the ULN. At baseline, the mean ferritin in the SA group was 72 µg/L and in the placebo group was 79 µg/L. Since the central lab used in this trial did not have pre-specified normal ranges for ferritin, another central lab's normal range was used as reference (ULN for females was 291 µg/L and 322 µg/L for males). Both the SA and placebo groups demonstrated a decrease from baseline over the 20-week double-blind treatment period; however, since the baseline values were not abnormal, this change is not clinically meaningful.

FACIT-Fatigue
Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale is a 13-item scale, developed to measure levels of fatigue in people living with a chronic disease. The total score ranges from 0-52. A score of < 30 indicates severe fatigue. The 20 enrolled patients ≥ 17 years of age completed this survey. At baseline, there was considerable between-patient variability with the baseline scores ranging from 17 to 52. At baseline, 6/20 (30%) patients reported a score of < 40 and 2/20 (10%) reported a score of < 30, indicating severe fatigue. However, there was no clear treatment effect at Week 20.

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[49] Scott, SA., et al. Frequency of the cholesteryl ester storage disease common LIPA E8SJM mutation (c.894G>A) in various racial and ethnic groups. Hepatology. 2013 Sep;58(3):958-65.

CLDQ Questionnaire

The Chronic Liver Disease Questionnaire (CLDQ) is a disease-specific instrument designed to assess health-related quality of life in patients with chronic liver disease. The CLDQ includes 29 items related to fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry. Each response is scaled using seven points (1=all of the time, 7=none of the time). Higher values indicate better quality of life. The 20 enrolled patients $\geq$ 17 years of age completed this survey. At baseline, scores ranged from 3 to 6.9. Four of the 20 (20%) patients had a total baseline score of < 5. There was no clear treatment effect at Week 20.

PedsQL™ Questionnaire

The Pediatric Quality of Life Inventory (PedsQL™) Generic Core Scales 4.0 is a 23-item scale designed to measure core dimensions of health, as delineated by the World Health Organization (WHO). The scale includes 4 multidimensional scales of physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items). In addition to the total scale score (all 23 items), 2 summary scores, the Physical Health Summary (8 items) and Psychosocial Health Summary (15 items). There were 48 patients between 5 and $\leq$ 18 years of age who completed this survey. The baseline scores ranged from 37 to 100 with 16/48 (33%) patients had a baseline score of < 80 and 8/48 (17%) had a baseline score of < 70. There was no clear treatment effect at Week 20.

Alcohol Use Disorders Identification Test (AUDIT) Questionnaire

For patients $\geq$ 18 years of age, a history of alcohol consumption was obtained at screening and during the trial duration via the AUDIT questionnaire. The total score ranges from 0 to 40 with higher scores indicating a greater likelihood of harmful drinking habits. The highest total score was 18 in this patient population at baseline for one patient in the placebo group; this patient had a score of 0 at Week 20. Only 4 patients had an AUDIT score > 10 at baseline (3 patients in the placebo and 1 in the SA group). It is unlikely that changes in drinking habits, as measured by improvement in AUDIT score, influenced the overall results of this trial since the majority of the adult patients scored low and the overall majority of the patient population was < 18 years of age.

7   Review of Safety

Overall, the safety profile reported from Study LAL-CL02 is similar to the safety profile of other enzyme replacement therapies. Of the 66 patients enrolled into Study LAL-CL02, 65/66 (98%) patients completed the 20-week double-blind treatment phase and continued into the ongoing open-label extension.

There were no deaths during Study LAL-CL02. Three of the 66 (5%) patients experienced at least one serious adverse event (SAE): 2/36 (6%) patients in the SA group and 1/30 (3%) patient in the placebo group. No same SAE was reported in more than 1 patient. The SAEs included a hypersensitivity reaction and gastritis in the SA group and a motor vehicle accident in the

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placebo group. Only one of the SAEs was considered treatment-related; Subject _____ (b) (6) in the SA group experienced a Grade 3 hypersensitivity reaction after 2 study drug infusions and withdrew from the double-blind treatment period. No other patients withdrew from the double-blind treatment period. As of the data cutoff date for the ongoing open-label period for this submission (May 30, 2014), 65 patients entered the open-label period to continue in the trial and no additional study-drug related SAEs or TEAEs have resulted in drug discontinuation.

Overall, 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.

During the double-blind treatment period, 2/36 (6%) patients in the SA group experienced hypersensitivity reactions. Subjec _____ (b) (6) experienced onset of a rash approximately 7.5 hours after the first SA infusion; therefore, (b) (6) was pre-medicated with prednisone and cetirizine hydrochloride prior to the second infusion. Approximately 8.5 hours after the second infusion, the patient was found to have a generalized rash on the chest, abdomen, and legs, in addition to acid-reflux-like symptoms in the throat and chest. The patient had difficulty breathing and speaking, accompanied by anxiety. The patient's mother administered a single dose of diphenhydramine and Mylanta and within 30 minutes, the rash was resolving and patient began to improve. This reaction was assessed as a serious, Grade 3 hypersensitivity reaction and the patient did not resume double-blind treatment after study Week 2. Another patient, Subject _____ (b) (6), experienced mild edema at the infusion site on the 7th SA infusion at Week 12. The infusion was held for 1 hour 40 minutes and the edema resolved. No additional supportive treatment for the reaction was administered and the patient received the next 4 study drug infusions (Weeks 14, 16, 18, 20) without pre-medication and no recurrence of edema.

During the open-label period, two patients experienced hypersensitivity reactions, both of whom were initially randomized to placebo during the double-blind treatment period. Subject _____ (b) (6) experienced a mild papular rash and pruritus with 12 minutes remaining of the infusion during the first infusion of SA during the open-label period. The patient was administered an antihistamine and the symptoms resolved 45 minutes later. The patient received the next infusion without pre-medication and without recurrence of symptoms. The second patient, Subject _____ (b) (6), experienced mild urticaria approximately 36 minutes after the start of the second SA infusion during the open-label period. The infusion rate was decreased from 100 ml/hr to 50 ml/hr and the infusion was completed. The urticaria resolved without medication approximately 7 hours after the onset. For subsequent infusions, the patient was administered pre-medication with an antihistamine (cetirizine hydrochloride) and was able to complete the study drug infusions at a rate of 100 ml/hr without recurrence of symptoms.

There were a small number of patients who routinely received pre-medication with the study drug infusion. Four patients total, 2 patients (Subjects ▓▓ (b)(6) and ▓▓ (b)(6)) in the SA group and 2 patients (Subjects ▓▓ (b)(6) and ▓▓ (b)(6)) in the placebo group, regularly received prophylactic pre-medication with acetaminophen/paracetamol and/or an anti-histamine. One patient (Subject ▓▓ (b)(6)) experienced urticaria on Study Day 15 despite having received pre-medication. One additional patient in the SA group (Subject ▓▓ (b)(6)), who has been discussed previously in this document, received the first study drug infusion without pre-medication but received pre-medication prior to the second infusion; however, this patient experienced a Grade 3 hypersensitivity reaction after the second infusion and was withdrawn from the double-blind treatment period.

Of these 35 patients in the SA group who continued treatment beyond Week 2, 5 patients (Subjects ▓▓▓▓▓▓▓▓ (b)(6)) tested positive for anti-drug antibodies (ADA) and no patient was found to have neutralizing antibodies during the double-blind treatment period. Positive ADA results were observed as early as Week 4 with the highest titers of 1:448 (Subject ▓▓ (b)(6)) and 1:816 (Subject ▓▓ (b)(6)) at that time. Three patients tested positive for ADA at only one time point and 2 patients (Subjects ▓▓ (b)(6) and ▓▓ (b)(6)) tested ADA positive at more than 1 time point during the double-blind treatment period. Only one patient was ADA positive at Week 20 with a titer of 1:39. Titers decreased over time during the double-blind period. None of the 5 patients remained ADA positive at the last time point prior to the data cut-off. Only one patient (Subject ▓▓ (b)(6)) with ADA experienced a hypersensitivity reaction. This patient is a 13 year old ▓▓ (b)(6) reported to have mild edema at the infusion site during the Week 12 infusion (7th study drug infusion). At the time, the ADA titer was low at 1:42. The infusion was stopped, no additional treatment was administered, and the patient was able to receive subsequent study drug infusions with no pre-medication and no recurrence of edema. No other ADA positive patient experienced a hypersensitivity reaction. As of the data-cut off for the ongoing open-label extension period, no patient initially randomized to the placebo group was found to be ADA-positive after switching to SA treatment during the open-label period.

Overall, 59/66 (89%) patients experienced a treatment-emergency adverse event (TEAE) during the double-blind treatment period. Thirty-one out of the 36 (86%) SA-treated patients and 28/30 (93%) patients in the placebo group reported at least 1 TEAE. TEAEs reported in ≥ 5% of SA-treated patients (≥ 2 patients) where the frequency was higher in the SA group than in the placebo group included headache (10/36 [28%]); body temperature increased/pyrexia (9/36 [25%]); oropharyngeal pain (6/36 [17%]); nasopharyngitis (4/36 [11%]); constipation, nausea, and asthenia (3/36 [8%] each); and anxiety, arthralgia, chest pain, gastritis, rhinorrhea, sinusitis, and syncope (2/36 [6%] each). In addition, other common TEAEs included diarrhea, upper respiratory tract infection, epistaxis, and nasopharyngitis; however, these TEAEs occurred at equal or lesser frequency in the SA-treated patients as compared to placebo.

There were 11 severe TEAE that occurred in 4 patients during the double-blind treatment period. Of note, 8/10 severe TEAEs occurred in one patient (Subject ▓▓ (b)(6)) in the SA group who

withdrew from the trial after study Week 2 because of a Grade 3 hypersensitivity reaction, described above. The severe TEAEs in the SA group included anxiety, fever, chest pain, dyspnea, laryngeal edema, nausea, post-procedural (biopsy) pain, rash, sinusitis. A severe TEAE motor vehicle accident occurred in the placebo group. Of these severe TEAEs, the motor vehicle accident, sinusitis, and post-procedural pain were considered as unrelated to SA. The remaining listed reactions occurred in one patient (Subject   (b) (6) in the SA group and were considered to be signs and symptoms consistent with a hypersensitivity reaction.

Additionally, patients with egg allergies were excluded from Study LAL-CL02; however, since SA is produced in the whites of transgenic chicken eggs, the risks and benefits of treatment should be considered for patients with known systemic hypersensitivity to egg proteins.

In conclusion, the adverse reactions reported from Study LAL-CL02 were similar to the adverse reactions known to be associated with enzyme replacement therapies. Since hypersensitivity reactions are the most concerning adverse reactions associated with Kanuma (sebelipase alfa), it is important to monitor patients for signs and symptoms that are consistent with hypersensitivity reactions, including anaphylaxis. Therefore, the risk of hypersensitivity reactions, a description of the associated signs and symptoms, and mitigating strategies will be communicated through the labeling. There are no other available therapies for patients with LAL deficiency and the risks and mitigation strategies will be communicated through the label; therefore, SA offers substantial clinical benefits compared to the risks that are associated with the product.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Refer to Section 5 above for an overview of the clinical trials conducted to evaluate the safety of sebelipase alfa in patients with LAL deficiency. This document will review the safety data collected from Study LAL-CL02. Refer to the clinical review by Dr. Lauren Weintraub for details on safety data collected from Study LAL-CL03.

7.1.2 Categorization of Adverse Events

This clinical reviewer compared verbatim terms with the applicant's coded/preferred term to ensure consistency in coding and revised as needed. Overall, this clinical reviewer's analysis was similar to the applicant's analysis, but the following adjustments were made by the clinical reviewer prior to re-analysis of the safety data.

Table 24: Recoded Terms

Applicant's AE Code (number of events recoded)	Reviewer's Recoded Term
Abdominal discomfort (1)	Abdominal pain
Abdominal pain lower (2)	Abdominal pain
Abdominal pain upper (7)	Abdominal pain

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Abdominal tenderness (1)	Abdominal pain
Chest discomfort (1)	Chest pain
Iron deficiency anemia (1)	Iron deficiency
Productive cough (1)	Cough
Respiratory tract infection viral (2)	Respiratory tract infection
Viral upper respiratory tract infection (1)	Upper respiratory tract infection
Body temperature increased (3)	Fever
Pyrexia (13)	Fever
Infusion-related reaction (1)	Hypersensitivity reaction

7.1.3   Pooled Safety Data from Clinical Trials to Compare Incidence

The applicant included data from four completed or ongoing clinical trials in the integrated summary of safety (Studies LAL-CL01, LAL-CL04, LAL-CL02, and LAL-CL03).   However, the limitations of pooled safety data should be noted since there are differences in the rate of disease progression and severity between infants with Wolman disease, enrolled into Study LAL-CL03, and children and adults with CESD, enrolled into Study LAL-CL02. In addition, the interpretation of pooled safety data is further limited by the small number of patients (n=9) enrolled into Study LAL-CL03 and the open-label trial design. Cross-study comparisons are of limited value since the disease severity and dosing varied across the trials, and small numbers of patients were enrolled into LAL-CL01/04 and LAL-CL03. Overall, generalizable conclusions cannot be made based on the interpretation of the pooled data due to the differences in disease severity of the patients and variations in the doses and dosing regimens administered across the trials. Therefore, this safety review will focus on data obtained from Study LAL-CL02.

7.2   Adequacy of Safety Assessments

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

The majority of the patients completed all 11 study drug infusions during the 20-week double-blind treatment period. Of the patients randomized to sebelipase alfa (SA) during the double-blind treatment period, 35/36 patients continued into the open-label extension period. Of the 30 patients randomized to the placebo group during the double-blind treatment period, all 30 continued into the open-label extension. As of the data cut-off for the ongoing open-label extension, 35 patients had received at least 12 study drug infusions and 8 patients had received at least 20 study drug infusions. The 20-week double-blind treatment period combined with the ongoing open-label extension represents appears adequate to assess safety in this patient population.

As described previously in this review, one patient (Subject ⬛⬛⬛ (b) (6)) received 2/11 infusions because this patient withdrew from the double-blind treatment period on Day 15 after a Grade 3 hypersensitivity reaction. Another patient in the placebo group (Subject ⬛⬛⬛ (b) (6)) missed the

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Week 8 infusion because she had chickenpox and completed 10/11 infusions. Table 25 below shows the exposure to SA and placebo during the double-blind treatment period.

Table 25: Exposure during the Double-blind Treatment Period (FAS)

Parameter / Statistic	Sebelipase Alfa (N=36)	Placebo (N=30)
Number of study drug infusions [n (%)]		
2	1 (3)	0
10	0	1 (3)
11	35 (97)	29 (97)
Number of completed study drug infusions [n (%)]		
2	1 (3)	0
10	3 (8)	1 (3)
11	32 (89)	29 (97)
Number of incomplete study drug infusions [n (%)]		
0	33 (92)	30 (100)
1	3 (8)	0

(Source: applicant's submission, BLA 125561, Study LAL-CL02, clinical study report, page 263/354)

Three out of 66 (5%) patients in the SA group (subjects   (b) (6)) did not complete one of the scheduled infusions for the following reasons:

- Subject (b) (6) received 88 ml out of 100 ml at Week 6 because the infusion bottle broke and the remaining 12 ml could not be administered.
- Subject (b) (6) received 92 ml out of 100 ml at Week 0 because technical difficulties were encountered with the infusion line.
- Subject (b) (6) received the complete drug infusion at Week 12 but the normal saline flush after the infusion was not administered due to technical difficulties with the infusion line.

Since the three patients described above received the majority of the infusion and an incomplete infusion was only reported once during the 20-week double-blind treatment period, this reviewer concludes that the three incomplete infusions were unlikely to have an impact on the efficacy and safety outcomes in this trial.

All patients received a dose of 1 mg/kg during the double-blind treatment period without changes in the dose. Between Week 0 to Week 22, study drug infusions were administered over 2 hours at a rate of 50 ml/hr to 150 ml/hr, depending on the patient weight. During the open-label extension starting at Week 24, infusions were administered over 1 hour but the duration could be adjusted if the shorter infusion duration was not well tolerated. During the open-label period, Subject (b) (6), randomized to placebo during the double-blind treatment period, received the first open-label SA infusion at a rate of 100 ml/hr; however, she required the infusion rate to be lowered to 50 ml/hr in response to the onset of mild urticaria. The SA infusion with premedication was continued at the lower rate. Over the following 4 open-label infusions, the patient did experience an adverse reaction and has tolerated a rate of 100 ml/hr. Of note, the second infusion during the open-label extension was administered at 100 ml/hr and lowered to 50 ml/hr for 5 additional patients (Subjects   (b) (6), and (b) (6)) at the same study center as Subject (b) (6). The change was made in error rather than in

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response to an adverse reaction. All 5 patients received the subsequent SA infusions during the open-label period at 100 ml/hr over approximately 1 hour. As of the data-cut off for the open-label extension for this submission, all other patients have tolerated the increased rate of 100 ml/hr.

7.2.2 Explorations for Dose Response

During the double-blind treatment period of LAL-CL02, patients remained on a dose of 1 mg/kg. As of the data cut-off for the ongoing open-label period for this submission, no patients in the open-label period met the criteria for dose escalation; therefore, all patients in the open-label period were also treated with 1 mg/kg.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Patients were evaluated with physical examination, vital signs, and laboratory testing before and during the trial as outlined in Section 9.4 Appendix. The routine clinical testing and safety monitoring appear to be adequate to ensure the safety of the patients enrolled in LAL-CL02.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to clinical pharmacology review by Dr. Jing Fang for details. A summary is provided above in Section 4.4 Clinical Pharmacology.

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

Hypersensitivity reactions, including anaphylaxis, are known adverse reactions associated with the class of enzyme replacement therapies. No new or unexpected adverse reactions were identified from the data provided in this submission.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during Study LAL-CL02.

7.3.2 Nonfatal Serious Adverse Events

Three of the 66 (5%) patients experienced at least one serious adverse event (SAE); 2/36 (6%) patients in the SA group and 1/30 (3%) patient in the placebo group reported a SAE during Study LAL-CL02. No SAE was reported in more than 1 patient. Only one of the SAEs was considered

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to be treatment-related; Subject 2106-044 experienced a Grade 3 hypersensitivity reaction after 2 study drug infusion and withdrew from the double-blind treatment period (discussed below Section 7.3.3).

Table 26: Nonfatal Serious Adverse Events (FAS, Double-blind treatment period)

Event	SA N = 36 n (%)	Placebo N= 30 n (%)
Hypersensitivity reaction	1 (3%)	0
Gastritis	1 (3%)	0
Motor vehicle accident	0	1 (3%)

(source: reviewer's analysis using applicant's data, BLA 125561, Study LAL-CL02 dataset, module 5.3.5.1)

Of note, during the open-label extension, only one additional patient experienced a serious adverse event; patient ____ (b) (6) reported to have gastroenteritis, which was not considered to be related to treatment with sebelipase alfa.

7.3.3 Dropouts/Discontinuations

Sixty-five out of the 66 patients (98%) completed the double-blind period and continued in the open-label period. One patient in the SA group (Subject ____ (b) (6)) withdrew from the double-blind period after Week 2. This patient, a 13-year-old ____ (b) (6), who experienced onset of a rash approximately 7.5 hours after the first infusion of the study drug; therefore, (b)(6) was pre-medicated with prednisone and cetirizine hydrochloride prior to the second infusion. Approximately 8.5 hours after the second infusion, the patient was found to have a generalized rash on the chest, abdomen, and legs, in addition to acid-reflux-like symptoms in the throat and chest. The patient had difficulty breathing and speaking, accompanied by anxiety. The patient's mother administered a single dose of diphenhydramine and Mylanta and within 30 minutes, the rash was resolving and patient began to improve. This reaction was assessed as a serious, Grade 3 hypersensitivity reaction and the patient did not resume double-blind treatment after study Week 2. Of note, this patient has a history of allergies including morphine that causes a rash, environmental allergies, and plan allergies (birch, dogwood). The patient has no known food allergies and eats and tolerates eggs. After the patient withdrew from the trial, (b)(6) was evaluated by the Allergy-Immunology and Gastroenterology departments at the study center where endoscopy findings were consistent with either eosinophilic esophagitis, severe reflux esophagitis, or a drug reaction. Despite possible comorbid conditions, this reviewer agrees with the applicant that this patient experienced a Grade 3 hypersensitivity reaction that resulted in withdraw from the trial.

As of the data cutoff date for the ongoing open-label period for this submission (May 30, 2014), 65 patients had entered the open-label period to continue in the trial and no study-drug related SAEs or TEAEs have resulted in drug discontinuation.

7.3.4   Significant Adverse Events

There were 11 severe treatment-emergent adverse events (TEAE) that occurred in 4 patients during the double-blind treatment period. Of note, 8/10 severe TEAEs occurred in one patient (Subject _____ (b) (6)) in the SA group, described above in the previous section.

Table 27: Severe Treatment-Emergent Adverse Events (FAS, Double-blind treatment period)

Event	SA N = 36 n (%)	Placebo N= 30 n (%)
At least 1 Severe TEAE	3 (8%)	1 (3%)
Anxiety	1 (3%)	0
Fever	1 (3%)	0
Chest pain	1 (3%)	0
Dyspnea	1 (3%)	0
Hypersensitivity reaction	1 (3%)	0
Laryngeal edema	1 (3%)	0
Nausea	1 (3%)	0
Procedural pain (post-biopsy)	1 (3%)	0
Rash	1 (3%)	0
Sinusitis	1 (3%)	0
Motor vehicle accident	0	1 (3%)

 (source: reviewer's analysis using applicant's data, BLA 125561, Study LAL-CL02 dataset, module 5.3.5.1)

Of the severe TEAEs described in the table above, only traffic accident, sinusitis, and post-biopsy pain were considered as unrelated to the study drug. All other reactions occurred in one patient (Subject _____ (b) (6)) and were considered to be signs and symptoms associated with a hypersensitivity reaction related to SA (previously described in Section 7.3.3).

7.3.5   Submission Specific Primary Safety Concerns

Anaphylaxis and Hypersensitivity Reactions
Of note, the Agency is moving away from using the term "infusion reaction" and is currently recommending that the term "infusion reaction" be replaced with "hypersensitivity reaction" or "anaphylaxis," as appropriate. Although the term "infusion reaction" implies a temporal relationship, infusion reactions are not well defined and may encompass a wide range of clinical events, including anaphylaxis.

Anaphylaxis and hypersensitivity reactions are known adverse reactions associated with enzyme replacement therapies. In this review, the terms "infusion-associated reaction" or "infusion-related reaction" will be replaced with "hypersensitivity reaction," and the signs and symptoms associated with those reactions will be described. Signs and symptoms that are consistent with

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clinical criteria[50] and likely to be related to treatment will be considered as a hypersensitivity reaction or anaphylaxis.

Overall, 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 one patient in the SA group. Of the patients treated with SA during the double-blind and open-label extension periods, 4 patients experienced a hypersensitivity reaction: 2 patients during the double-blind period and 2 patients during the open-label period. The reaction was serious in only one patient (Subject   (b) (6)   ), who discontinued SA treatment after 2 study drug infusions.

During the 20-week double-blind treatment period, no patients met the clinical criteria for anaphylaxis, 2/36 (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 (described as infusion associated reactions (IAR) by the applicant). While the signs and symptoms were temporally related to the infusion, it is unlikely that the signs and symptoms were reflective of a hypersensitivity reaction related to SA since these patients were receiving placebo.

In the SA group, Subject   (b) (6)   experienced a Grade 3 hypersensitivity reaction approximately 8.5 hours after the second study drug infusion, as described previously in this review. Another patient (Subject   (b) (6)   ) experienced mild edema at the infusion site on the 7th study drug infusion at Week 12. The infusion was held for 1 hour 40 minutes and the edema resolved. No additional supportive treatment for the reaction was administered and the patient received the next 4 study drug infusions (Weeks 14, 16, 18, 20) without pre-medication and no recurrence of edema. Of note, a third patient (Subject   (b) (6)   ) reported mild pruritus 2 days after the first SA infusion without additional reports of reactions with subsequent infusions; therefore, this reviewer considers the reactions as unlikely related to SA based on the timing of onset and lack of repeated reactions with SA infusions.

In the placebo group, 4 patients experienced signs and symptoms that could be considered as hypersensitivity reactions, including arthralgia and fatigue (Subject   (b) (6)   ), pyrexia (Subject   (b) (6)   ), body temperature increased (Subject   (b) (6)   ), and dyspnea (Subject   (b) (6)   ). These reactions were considered to be mild, non-serious, and no infusion was withheld due to the reaction.

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[50] Sampson HA, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.

Table 28: Hypersensitivity Reactions (FAS, Double-blind treatment period)

Event	SA N = 36 n (%)	Placebo N= 30 n (%)
At least 1 hypersensitivity reaction	2 (6%)	4 (13)
Anxiety	1 (3)*	0
Fever	1 (3)*	2 (7)
Chest pain	1 (3)*	0
Dyspnea	1 (3)*	0
Laryngeal edema	1 (3)*	0
Nausea	1 (3)*	0
Edema at infusion site	1 (3)	0
Rash	1 (3)*	0
Arthralgia	0	1 (3)
Fatigue	0	1 (3)

*All reactions experienced by one patient in the SA group, Subject 2106-044.
(source: reviewer's analysis using applicant's data, BLA 125561, Study LAL-CL02 dataset, module 5.3.5.1)

During the open-label period, two patients experienced hypersensitivity reactions, both were initially randomized to placebo during the double-blind treatment period. Subject ⬛⬛ (b) (6) experienced a mild papular rash and pruritus with 12 minutes remaining of the infusion during the first infusion of SA during the open-label period. The patient was administered an antihistamine and the symptoms resolved 45 minutes later. The patient received the next infusion without pre-medication and without recurrence of symptoms. The second patient, Subject ⬛⬛ (b) (6), experienced mild urticaria approximately 36 minutes after the start of the second SA infusion during the open-label period. The infusion rate was decreased from 100 ml/hr to 50 ml/hr and the infusion was completed. The urticaria resolved without medication approximately 7 hours after the onset. For subsequent infusions, the patient was administered pre-medication with an antihistamine (cetirizine hydrochloride) and was able to complete the study drug infusions at a rate of 100 ml/hr without recurrence of symptoms.

There were a small number of patients who routinely received pre-medication with the study drug infusion. Four patients total, 2 patients (Subjects ⬛⬛ (b) (6) and ⬛⬛ (b) (6)) in the SA group and 2 patients (Subjects ⬛⬛ (b) (6) and ⬛⬛ (b) (6)) in the placebo group, regularly received prophylactic pre-medication with acetaminophen/paracetamol and/or an anti-histamine. One patient (Subject ⬛⬛ (b) (6)) experienced urticaria on Study Day 15 despite having received pre-medication. One additional patient in the SA group (Subject ⬛⬛ (b) (6), who has been discussed previously in this document, received the first study drug infusion without pre-medication but received pre-medication prior to the second infusion; however, this patient experienced a Grade 3 hypersensitivity reaction after the second infusion and was withdrawn from the double-blind treatment period.

Egg Allergy
Patients with egg allergies were excluded from Study LAL-CL02; however, since

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SA is produced in the whites of transgenic chicken eggs, the risks and benefits of treatment should be considered for patients with known systemic hypersensitivity to egg proteins. This will be addressed through labeling.

7.4   Supportive Safety Results

7.4.1   Common Adverse Events

Overall, 59/66 (89%) patients experienced a TEAE during the double-blind treatment period. Thirty-one out of the 36 (86%) SA-treated patients and 28/30 (93%) patients in the placebo group reported at least 1 TEAE.

Table 29: Overall Adverse Events Reported in ≥ 5% of SA-Treated Patients (≥ 2 patients) with a Higher Incidence than Placebo (FAS, Double-blind Treatment Period)

Event	SA N = 36 n (%)	Placebo N= 30 n (%)
Headache	10 (28)	6 (20)
Fever	9 (25)	7 (23)
Oropharyngeal pain	6 (17)	1 (3)
Nasopharyngitis	4 (11)	3 (10)
Constipation	3 (8)	1 (3)
Nausea	3 (8)	2 (7)
Asthenia	3 (8)	1 (3)
Anxiety	2 (6)	0
Arthralgia	2 (6)	1 (3)
Chest pain	2 (6)	0
Gastritis	2 (6)	0
Rhinorrhea	2 (6)	1 (3)
Sinusitis	2 (6)	0
Syncope	2 (6)	0

 (source: reviewer's analysis using applicant's data, BLA 125561, Study LAL-CL02 dataset, module 5.3.5.1)

In addition to the common TEAEs shown above, other common TEAEs with ≥ 10% incidence included diarrhea, upper respiratory tract infection, and epistaxis. However, these TEAEs occurred at equal or lesser frequency in the SA-treated patients as compared to placebo.

7.4.2   Laboratory Findings

In general, there are no expected or known associations with laboratory abnormalities and enzyme replacement therapies. Laboratory parameters that are disease-related are discussed above in Section 6. An overview of other laboratory evaluations performed during Study LAL-CL02 is summarized below.

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Hematology Parameters

All mean values for hematology parameters were within the normal range during the 20-week double-blind treatment period. The only exception was the mean value for monocytes, which was low at baseline in both the SA and placebo groups and remained low during the double-blind treatment period. There were no clinically meaningful changes over time in any hematologic lab values. There were shifts in individual patient values during the treatment period; however, no trend was identified between the SA and placebo groups.

Serum Chemistry Parameters

Serum transaminases and lipids are reviewed previously in this document in Section 6. No other clinically meaningful trends were identified between the SA and placebo groups in serum chemistry lab values. The mean hemoglobin A1c (HbA1c) values were normal at baseline and Week 20 and no significant change from baseline was observed in either the SA or placebo group.

Immunogenicity

There were 35 patients in the SA group who continued treatment beyond Week 2. Of these 35 patients, 5 patients (Subjects   (b) (6)) tested positive for anti-drug antibodies (ADA) and no patient was found to have neutralizing antibodies during the double-blind treatment period. Positive ADA results were observed as early as Week 4 with the highest titers of 1:448 (Subject   (b) (6)) and 1:816 (Subject   (b) (6)) at that time. Three patients tested positive for ADA at only one time point and 2 patients (Subjects   (b) (6)   ) tested ADA positive at more than 1 time points during the double-blind treatment period. Only one patient was ADA positive at Week 20 with a titer of 1:39. Titers decreased over time during the double-blind period. None of the 5 patients remained ADA positive at the last time point prior to the data cut-off. As of the data-cut off, no patient initially randomized to the placebo group was found to be ADA-positive after switching to SA treatment during the open-label period.

While only 5 patients with ADA positive tests are available for an analysis of the impact of antibody development on efficacy, the patients who were ADA positive did not appear to experience decreased efficacy. All 5 patients experienced a decrease from baseline in ALT, AST, LDL-c, non-HDL-c. However, since the number of patients with ADA is small, the titers were low, and no patient developed neutralizing antibodies during the double-blind treatment period, it is difficult to make generalizable conclusions on the impact of ADA on efficacy.

Only one patient (Subject   (b) (6)) with ADA experienced a hypersensitivity reaction. This patient is a 13 year old female who reported to have mild edema at the infusion site during the Week 12 infusion (7th study drug infusion). At the time, the ADA titer was low at 1:42. The infusion was stopped, no additional treatment was administered, and the patient was able to receive subsequent study drug infusions with no pre-medication and no recurrence of edema. No other ADA positive patient experienced a hypersensitivity reaction.

See immunogenicity review by Dr. Joao Pedras-Vasconcelos for additional details.

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7.4.3   Vital Signs

Vital signs were assessed during LAL-CL02. Overall, pyrexia/increased body temperature was the most common vital sign abnormality reported as a TEAE in 9/36 (25%) patients in the SA group and 7/30 (23%) in the placebo group. Pyrexia/increased body temperature was considered as related to SA in 1/36 (3%) patient in the SA group and was associated with a hypersensitivity reaction (Subject   (b) (6)). Other vital sign abnormalities included hypertension in Subject   (b) (6) in the SA group and bradycardia in Subject   (b) (6) in the placebo group; however, Subject   (b) (6) was noted to have bradycardia at baseline.

7.4.4   Electrocardiograms (ECGs)

ECGs were performed during Study LAL-CL02. The mean change from baseline in QTc interval was greater in the SA group than in the placebo group but remained within the normal range of 420.5 msec. Two patients in the SA group had prolonged QTc intervals at baseline and QTc intervals > 450 msec at Week 20 (listed below).

- Subject   (b) (6) is a 14 year old   (b) (6) with a baseline QTc interval of 494 msec and QTc interval of 511 msec at Week 20.
- Subject   (b) (6) is an 11 year old   (b) (6) with a baseline QTc of 457 msec and QTc interval of 464 msec at Week 20.

One patient, Subject   (b) (6) , had a prolonged QTc interval of 474 msec at baseline with a decrease in QTc interval to 442 msec at Week 20. No patient had an ECG abnormality that was reported as a TEAE during the double-blind treatment period.

7.4.5   Special Safety Studies/Clinical Trials

None.

7.5   Other Safety Explorations

7.5.1   Dose Dependency for Adverse Events

There were no dose dependent adverse events seen in LAL-CL02 since all patients remained on the same dose of sebelipase 1 mg/kg.

7.5.2   Time Dependency for Adverse Events

In addition to acute reactions that occur within minutes to hours of the infusion, enzyme replacement therapies also have the potential for delayed hypersensitivity and immune mediated responses secondary to immune complex formation.[51] The most commonly reported adverse

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[51] Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products (2014). Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf

events that occurred ≤ 24 hours after the end of the infusion included headache in 5/36 (14%) patients in the SA group and 1/20 (3%) patients in the placebo group, and pyrexia in 3/36 (8%) patients in the SA group and 2/30 (7%) patients in the placebo group. As described previously, there were 4 patients treated with SA during the double-blind and open-label extension periods who experienced a hypersensitivity reaction; 2 patients during the double-blind period and 2 patients during the open-label period. The reaction was serious in only one of these patients (Subject ___(b) (6)___), who discontinued SA treatment after 2 study drug infusions. The serious hypersensitivity reaction in Subject ___(b) (6)___ occurred approximately 8 hours after completion of the second study drug infusion, thereby suggesting that this patient may have experienced a delayed-onset hypersensitivity reaction. The other 3 patients experienced onset of symptoms during the infusion. Therefore, patients receiving treatment with sebelipase alfa should be monitored closely for both acute and delayed-onset type hypersensitivity reactions.

7.5.3 Drug-Demographic Interactions

There were no unusual distribution of safety signals based on sex, age, or race overall; however, comparisons are difficult because of the small number of patients. There were 78 adverse events that occurred in females and 64 adverse events that occurred in males. There were 61 adverse events that occurred in patients < 12 years of age, 66 adverse events that occurred in patients ≥ 12 - < 18 years of age, and 30 adverse events that occurred in patients ≥18 years of age. While it appears that fewer adverse events occurred in patients ≥18 years of age, only 19/66 (26%) patients enrolled in Study LAL-CL02 were ≥18 years of age. When adverse events by race were evaluated, there were 91 adverse events in white patients, 9 adverse events in black/African American patients, 7 adverse events in Asian patients, and 30 adverse events in "other" patients. Importantly, the majority of patients enrolled in Study LAL-CL02 were white (55/66 [83%] vs. 7/66 [11%] "other", 1/66 [2%] black/African American, and 3/66 [5%] Asian).

As described previously in this review, only three patients experienced serious, treatment-emergent adverse events (TEAE): gastroenteritis, gastritis, and a hypersensitivity reaction in one patient each. The only serious TEAE considered as related to treatment with SA was the hypersensitivity reaction that occurred in a 13-year-old ___(b) (6)___ The other two events occurred in a 20-year-old ___(b) (6)___ (gastroenteritis) and 21-year-old ___(b) (6)___ (gastritis).

7.5.4 Drug-Disease Interactions

Drug- disease interactions were not assessed in this submission.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not assessed in this submission.

7.6   Additional Safety Evaluations

7.6.1   Human Carcinogenicity

Human carcinogenicity was not assessed in this submission.

7.6.2   Human Reproduction and Pregnancy Data

No pregnancies occurred during Study LAL-CL02.

7.6.3   Pediatrics and Assessment of Effects on Growth

Refer to Section 6.1.6 above for details of the effects on growth. Patients in both the SA and placebo groups experienced small increases in weight and height during the 20-week double-blind treatment period. Since both groups experienced increases in weight and height, no safety signals were identified based on the data provided for the effects of SA on growth in the pediatric population.

7.6.4   Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no concerns for overdose or drug abuse potential. No studies were conducted to investigate the effect of withdrawal and rebound.

7.7   Additional Submissions/Safety Issues

120-Day Safety Update Report
As agreed upon with the applicant, the 120-day safety update report was submitted on May 8, 2015. The safety update includes pooled safety data from May 30, 2014 to June 27, 2014. Safety data reported in statistical outputs in the 120-day safety update report are based on the clinical data cut-off date of January 26, 2015. In addition to data from the four trials included in the original BLA submission (LAL-CL01/04, LAL-CL03, and LAL-CL02), two recently initiated trials (LAL-CL06 and LAL-CL08) are included as late-breaking information with a safety data cut-off of September 8, 2014. Across these six trials, 106 patients have been treated with sebelipase alfa (SA): 14 infants, 57 children, and 33 adults. In addition, 2 patients have received treatment under a compassionate use protocol.

Study LAL-CL01/04
No new safety signals were identified in the submission of the 120-day safety update report. The most frequent TEAEs occurring in > 3 patients included abdominal pain, diarrhea, nasopharyngitis, nausea, and musculoskeletal pain. There were no deaths and no TEAEs leading to discontinuation of sebelipase alfa treatment or withdrawal from the study.

Study LAL-CL02
No new safety signals were identified as part of the 120-day safety update report. During the late-breaking information period from January 26, 2015 through April 8, 2015, no deaths were reported and 2 additional patients experienced serious adverse reactions. During the open-label period, one patient experienced anaphylaxis, including signs and symptoms included chest discomfort, eyelid edema, dyspnea, urticaria, hyperemia, and pruritus; the patient recovered after treatment with an antihistamine and hydrocortisone; treatment with sebelipase alfa has been held pending further evaluation. Another patient experienced appendicitis and peritonitis, unlikely to be related to treatment with sebelipase alfa.

Overall, 6/66 (9%) patients treated with sebelipase alfa were ADA-positive: 4 patients were positive only during the double-blind phase, 1 patients was positive during both the double-blind and open-label phase, and 1 patient was positive only during the open-label phase. Of the 6 patients who were ADA-positive, the titers decreased to undetectable in 4 patients, 1 patient was found to have undetectable titers after becoming ADA positive at Week 4 but then tested positive again during the open-label period at Week 52, and 1 patient initially randomized to placebo was ADA positive at Week 20 of the open-label treatment phase. The two patients (Subjects (b) (6) and (b) (6)) who tested positive during the open-label phase at Week 20 and Week 52 of open-label treatment also developed neutralizing antibodies to cellular uptake but not to enzyme activity. Subject (b) (6) reported onset of a rash ≥ 48 hours after the infusion at Week 58; therefore, it is less likely reflective of a hypersensitivity reaction due to the onset being ≥ 48 hours after the infusion.

Study LAL-CL03
Refer to clinical review by Dr. Lauren Weintraub for the 120-day update of Study LAL-CL03.

Study LAL-CL06 and LAL-CL08
While data from Study LAL-CL06 and LAL-CL08 were not submitted as part of the BLA 125561 submission, important safety findings from the 120-day safety update will be summarized below.

Study LAL-CL06
Study LAL-CL06 is an ongoing phase 2, single-arm, open-label trial of sebelipase alfa in pediatric patients > 8 months and adults with LAL deficiency who were not eligible for other trials due to age, disease complications, previous treatment with hematopoietic stem cell or liver transplant, or less common disease manifestations. As of January 26, 2015, 17 patients have been enrolled. Four patients reported at least 1 TEAE but no same TEAE occurred in more than 1 patient. The TEAEs included diarrhea, upper abdominal pain, hematochezia, malaise, anaphylaxis, nasopharyngitis, rhinitis, gastroenteritis, abscess, headache, and hypotension. The event of anaphylaxis was considered as severe and serious; the infusion was interrupted and the one patient who experienced anaphylaxis recovered. Three patients experienced hypersensitivity reactions. In addition to anaphylaxis, other hypersensitivity reactions included hypertension, hypothermia, and abdominal pain. No deaths were reported and no TEAEs led to discontinuation of sebelipase treatment or withdrawal from the study.

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Study LAL-CL08
Study LAL-CL08 is a phase 2, single-arm, open-label trial to evaluate sebelipase alfa administered at a dose of 1 mg/kg weekly in infants < 8 months of age with rapidly progressive LAL deficiency. As of January 26, 2015, 5 patients have been treated in this trial. Frequent TEAEs occurring in ≥ 3 patients include tachycardia, pyrexia, and urticaria. All 5 patients enrolled in this trial have experienced serious TEAEs including tachycardia, pyrexia, and sepsis. One patient experienced urticaria, tachycardia, and respiratory distress, which are reactions that could characterize anaphylaxis; the infusion was interrupted and the patient recovered. One patient tested ADA-positive at 3 time points through Week 20; this patient also tested positive for neutralizing antibodies to enzyme activity and cellular uptake. One patient experienced a pericardial effusion, leading to death. The post mortem report listed the primary cause of death as pericardial effusion following transmural necrosis of the left atrium associated with the presence of and leakage from an indwelling IV line, and the secondary cause of death as Wolman's disease.

Deaths
No new deaths were reported beyond the 6 patient deaths that were previously submitted in the original BLA Summary of Clinical Safety; 3 deaths were reported as late-breaking information (Subjects   (b) (6)). All deaths occurred in infants ≤ 2 years of age with rapidly progressive disease; 4 patients in Study LAL-CL03, 1 patient in LAL-CL08, and 1 patient under a compassionate use protocol.

Dose-related TEAEs
Evaluation of the pooled safety set of patients for the 120-day safety update revealed that patients who received sebelipase alfa at a dose of 3 mg/kg had a higher incidence of serious TEAEs, hypersensitivity reactions, and treatment-related TEAEs as compared to patients who received doses of either 0.35 mg/kg or 1 mg/kg. The onset of TEAEs within 4 to 24 hours of the end of the infusion occurred at a higher incidence in patients who received the 3 mg/kg dose; however, it is important to note that most patients receiving the high dose were infants with more severe disease.

Treatment-related Adverse Events (TEAEs)
Overall, the most frequent treatment-related TEAEs occurring in ≥ 3 patients were similar to those reported in the BLA 125561 submission: urticaria (6 patients), diarrhea (5 patients), tachycardia, pyrexia, vomiting, nausea, and abdominal pain (4 patients each), and fatigue (3 patients). Frequent TEAEs occurring in ≥ 3 patients in children and adults enrolled in Study LAL-CL01/04, LAL-CL02, and LAL-CL06 reported included abdominal pain, diarrhea, and nausea (4 patients each), and fatigue (3 patients). Frequent TEAEs reported in ≥ 3 infants enrolled in Study LAL-CL03 and LAL-CL08 included tachycardia (4 patients), urticaria (4 patients), vomiting (3 patients), and pyrexia (3 patients); all occurring with greater incidence as compared to the children and adults. No new TEAEs were identified in the 120-day safety update report.

8   Post-market Experience

There is no post-marketing experience because this drug has not yet been approved.

9   Appendices

9.1   Literature Review/References

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9.2   Labeling Recommendations

The labeling negotiations were ongoing at the time of this review. For final labeling agreements, see the approved label for Kanuma. This reviewer recommends the following revisions to the proposed label.
-   The indications statement should be revised to state that Kanuma is a   (b) (4)

-   Consider including a statement to describe that the effect of Kanuma on hepatic and cardiovascular morbidity and mortality has not been established.

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- Section 6 should include only drug-related adverse reactions and the incidence,   (b) (6)

         .
- Section 6 and 14 should be revised   (b) (6)

           However, it is appropriate to include the adverse reactions that occurred in this study that were considered to be a hypersensitivity reaction or anaphylaxis in Section 5.
- Section 14.2 should be revised to focus on improvement in LDL-c during Study 2 (LAL-CL02) during the 20-week double-blind treatment period.   (b) (6)

9.3   Advisory Committee Meeting

None.

9.4 Supplementary Tables

Table 30: Patients with Medically Important Chronic Liver Disease at Baseline

Subject Number	Age[1]	Gender	Ishak Score on Baseline Biopsy	Histological Evidence of Cirrhosis on Baseline Biopsy[2]	Medical History of Cirrhosis	Medical History of Portal Hypertension	Coagulopathy[3]
SA Group							
(b) (6)	18	(b) (6)	6	Y	-	-	-
	12		ND	-	-	-	Y
	15		ND	-	-	Y	Y
	20		3	-	Y	-	Y
	12		ND	-	-	-	Y
	21		2	-	-	-	Y
	11		ND	-	-	-	Y
	11		6	Y	-	-	Y
	14		6	Y	-	Y	Y
	6		5	Y	-	-	-
	15		ND	-	-	-	Y
	4		6	Y	-	Y	Y
	24		3	-	Y	-	-
	16		ND	-	-	-	Y
	41		2	-	-	-	Y
	22		3		-	-	Y
Placebo Group							
(b) (6)	15		ND	-	-	-	Y
	11		ND	-	-	-	Y
	17		6	Y	-	-	-
	13		6	Y	-	-	-
	21		6	Y	Y	-	-
	12		ND	-	-	-	Y
	11		ND	-	-	-	Y
	4		ND	-	-	-	Y
	12		ND	-	-	-	Y
	9		ND	-	-	-	Y
	6		ND	-	-	-	Y
	9		6	Y	Y	Y	Y
	9		5	Y	-	-	-

Source: Listing 16.2.4.1, Listing 16.2.4.6, Listing 16.2.6.5.4, and Listing 16.2.8.5.
F=female; Hx=history; M=Male; ND=Not done.
1   Age at randomisation
2   Histological evidence of cirrhosis on baseline biopsy.
3   History of coagulopathy or coagulopathy, as evidenced by at least 1 abnormal clotting test (PT, PTT, or INR), at baseline.

(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 162-163/354)

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Figure 11: Study Schedule of Events: Double-Blind Treatment Period

Assessments	Screening Day -45 to Day -7	Wk 0	Wk 2 ±5 days	Wk 4 ±5 days	Wk 6 ±5 days	Wk 8 ±5 days	Wk 10 ±5 days	Wk 12 ±5 days	Wk 14 ±5 days	Wk 16 ±5 days	Wk 18 ±5 days	Wk 20 −2/+7 days
Informed Consent/Assent	X											
Inclusion/Exclusion Criteria	X	X										
Randomisation		X										
Medical History	X											
12-lead ECG	X											X
Physical Examination[1]	X	X			X				X			X
Height (subjects <18 years)	X	X			X				X			X
Height (subjects ≥18 years)	X											
Weight	X	X			X				X			X
AUDIT Questionnaire (subjects ≥18 years)	X											X
Abdominal MRI	X											X
Liver Biopsy[2]	X											X
HRQOL (subjects ≥5 years)[3]	X						X					X
Clinical Laboratory Assessments												
DNA Blood Sample[4]	X											
LAL Enzyme Activity	X											
Liver Panel[5]	X[11]	X[p]	X[p]	X[p]	X[p]		X[p]		X[p]		X[p]	X[p, 12]
Lipid Panel[5]	X	X[p]	X[p]	X[p]	X[p]		X[p]		X[p]		X[p]	X[p, 12]
Haematology[5], Electrolytes[5], Glucose, Creatinine	X				X[p]				X[p]			X[p]
Macrophage Activation Markers[5]	X						X[p]					X[p]
HbA1c	X											X[p]
Coagulation Panel[5]	X						X[p]					X[p]

Assessments	Screening Day -45 to Day -7	Wk 0	Wk 2 ±5 days	Wk 4 ±5 days	Wk 6 ±5 days	Wk 8 ±5 days	Wk 10 ±5 days	Wk 12 ±5 days	Wk 14 ±5 days	Wk 16 ±5 days	Wk 18 ±5 days	Wk 20 −2/+7 days
Urinalysis[5]	X						X[p]					X[p]
Pregnancy Test[6]	X	X[p]		X[p]		X[p]		X[p]		X[p]		X[p]
Viral Hepatitis Screen	X											
Anti-Drug Antibody		X[p]		X[p]		X[p]		X[p]				X[p]
CDT (subjects ≥18 years)	X	X										X
Urine Exploratory Biomarkers	X											X
Blood Exploratory Biomarkers	X						X[p]					X[p]
Pharmacokinetic Profile[7]		X										
Vital Signs[8]		X	X	X	X	X	X	X	X	X	X	X
Study Drug Infusion[9]		X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	Continuous											
Concomitant Meds/Treatment[10]	Continuous											

*Note: All study visits were scheduled relative to Week 0; consecutive infusions were administered at least 7 days apart. Assessments to be performed for subjects of a certain age were based on the subject's age on the date that informed consent was obtained.
[p] = Pre-infusion.

1 All physical examinations included assessment of liver and spleen size, lymphadenopathy, arterial disease, and skin manifestations of hepatic disease or dyslipidaemia (see Section 8.5.2.1).
2 Liver biopsies were obtained in subjects ≥ 18 years of age unless medically contraindicated, and may have been obtained on an optional basis in subjects < 18 years of age with consent from a parent or legal guardian (and assent from the subject, if applicable) and where permitted by local regulations and each centre's IRB/IEC (see Section 8.5.1.2.3). A historical biopsy obtained within 26 weeks prior to randomisation and adequate for histological examination may have been used in lieu of a screening biopsy. In subjects < 18 years of age, a Week 20 biopsy was obtained only if a screening biopsy had been collected. If the liver biopsy was obtained via the transjugular method, the hepatic venous pressure gradient also was measured, whenever feasible.
3 Age-appropriate health-related quality of life questionnaires were completed prior to any other study procedures.
4 A sample was obtained at screening, or as soon as practically possible thereafter.
5 Refer to Section 8.5.2.4 for a list of analytes in each laboratory panel. Subjects fasted for at least 9 hours prior to collection of samples for the lipid panel and fasting serum glucose, and abstained from alcohol for at least 24 hours prior to the liver and lipid panels.
6 For female subjects of childbearing potential only, a serum pregnancy test was performed at screening and urine pregnancy tests at all designated visits thereafter.
7 Refer to Section 8.5.3.1 for PK sampling time points.
8 Vital signs were measured pre-dose, every 30 (±10) minutes during the infusion, and every 30 (±10) minutes from 0 to 2 hours post-infusion (see Section 8.5.2.2).
9 Infusions were administered over approximately 2 hours, if the infusion was not well tolerated, the infusion rate may have been decreased (see Section 8.4.5.1).
10 Subjects were queried about any changes in LLM or lipid-lowering diets, UDCA, metformin, glitazones, or vitamin E (see Section 8.4.7).
11 Two liver panels were obtained at screening, at least a week apart.
12 Samples collected at Week 20 for liver and lipid panels were obtained within 12-21 days of the previous infusion at Week 18.

(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 69-71/354)

Figure 12: Study Schedule of Events: Open-Label Period (Week 22- Week 52)

Assessments	Open-label Period*															
	Wk 22 ±5 days	Wk 24 ±5 days	Wk 26 ±5 days	Wk 28 ±5 days	Wk 30 ±5 days	Wk 32 ±5 days	Wk 34 ±5 days	Wk 36 ±5 days	Wk 38 ±5 days	Wk 40 ±5 days	Wk 42 ±5 days	Wk 44 ±5 days	Wk 46 ±5 days	Wk 48 ±5 days	Wk 50 ±5 days	Wk 52 ±5 days
12-lead ECG											X					X
Physical Examination[1]				X				X			X					X
Height (subjects <18 years)				X				X			X					X
Weight				X				X			X					X
AUDIT Questionnaire (subjects ≥18 years)											X					X
Abdominal MRI											X					X
Liver Biopsy[2]																X
HRQOL (subjects ≥5 years)[3]						X					X					X
Clinical Laboratory Assessments																
Liver Panel[4]	Xᴾ	Xᴾ	Xᴾ	Xᴾ		Xᴾ		Xᴾ		Xᴾ	Xᴾ		Xᴾ		Xᴾ	
Lipid Panel[4]	Xᴾ	Xᴾ	Xᴾ	Xᴾ		Xᴾ		Xᴾ		Xᴾ	Xᴾ		Xᴾ		Xᴾ	
Haematology[4], Electrolytes[4], Glucose, Creatinine				Xᴾ				Xᴾ			Xᴾ					Xᴾ
Macrophage Activation Markers[4]						Xᴾ					Xᴾ					Xᴾ
HbA1c											Xᴾ					
Coagulation Panel[4]						Xᴾ					Xᴾ		If abnormal at the preceding assessment, or if clinically indicated based on emerging evidence of hepatic dysfunction			
Urinalysis[4]						Xᴾ					Xᴾ					Xᴾ
Urine Pregnancy Test[5]	Xᴾ	Xᴾ		Xᴾ		Xᴾ		Xᴾ		Xᴾ		Xᴾ		Xᴾ		Xᴾ
Anti-Drug Antibody	Xᴾ			Xᴾ		Xᴾ		Xᴾ			Xᴾ					Xᴾ

Assessments	Open-label Period*															
	Wk 22 ±5 days	Wk 24 ±5 days	Wk 26 ±5 days	Wk 28 ±5 days	Wk 30 ±5 days	Wk 32 ±5 days	Wk 34 ±5 days	Wk 36 ±5 days	Wk 38 ±5 days	Wk 40 ±5 days	Wk 42 ±5 days	Wk 44 ±5 days	Wk 46 ±5 days	Wk 48 ±5 days	Wk 50 ±5 days	Wk 52 ±5 days
CDT (subjects ≥18 years)											Xᴾ					Xᴾ
Urine Exploratory Biomarkers											Xᴾ					
Blood Exploratory Biomarkers				Xᴾ							Xᴾ					Xᴾ
Pharmacokinetic Profile[6]	X															
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sebelipase alfa Infusion[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	Continuous															
Concomitant Meds/Treatment[9]	Continuous															

*Note: All study visits were scheduled relative to Week 22; consecutive infusions were administered at least 7 days apart. Assessments to be performed for subjects of a certain age were based on the subject's age on the date that informed consent was obtained.

ᴾ = Pre-infusion

1 All physical examinations included assessment of liver and spleen size, lymphadenopathy, arterial disease, and skin manifestations of hepatic disease or dyslipidaemia (see Section 8.5.2.1).

2 Liver biopsies at Week 52 were optional for all subjects. Week 52 biopsies were obtained in subjects < 18 years of age only if a screening biopsy was collected, and only with consent from a parent or legal guardian (and assent from the subject, if applicable) and where permitted by local regulations and each centre's IRB/IEC (see Section 8.5.1.2.3). If the liver biopsy was obtained via the transjugular method, the hepatic venous pressure gradient was measured, wherever feasible.

3 Age-appropriate health-related quality of life questionnaires were completed prior to any other study procedures (see Section 8.5.3.2 for details).

4 Refer to Section 8.5.2.4 for a list of analytes in each laboratory panel. Subjects fasted for at least 9 hours prior to collection of samples for the lipid panel, and fasting serum glucose, and abstained from alcohol for at least 24 hours prior to the liver and lipid panels.

5 Female subjects of childbearing potential only.

6 Refer to Section 8.5.3.1 for PK sampling time points.

7 Vital signs were measured pre-dose, every 30 (±10) minutes during the infusion, and every 30 (±10) minutes from 0 to 2 hours post-infusion. Beginning at Week 52, the post-infusion period for vital sign monitoring may have been shortened to 1 hour for subjects who completed at least 24 weeks of treatment with no occurrence of moderate or severe IARs, contingent upon approval from the Sponsor (see Section 8.4.5.3).

8 Infusions were administered over approximately 2 hours at Week 22, and over approximately 1 hour at all subsequent study visits; if the infusion was not well tolerated, the infusion rate may have been decreased (see Section 8.4.5).

9 Also queried about any changes in LLM or lipid-lowering diets, UDCA, metformin, glitazones, or vitamin E (see Section 8.4.7).

(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, pages 72-74/354)

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Table 31: Safety Alerts for Blinded Laboratory Tests

Laboratory Test	Safety Alert Range
Serum Transaminases and GGT	
ALT	> 5 × ULN[1] and at least twice the highest pre-treatment value
AST	> 5 × ULN[1] and at least twice the highest pre-treatment value
GGT	> 5 × ULN[1] and at least twice the highest pre-treatment value
Serum Lipids[2]	
Total Cholesterol	> 400 mg/dL (10.36 mmol/L) and at least 50% increase from baseline value during 2 consecutive assessments
Triglycerides	> 800 mg/dL (9.04 mmol/L) during any assessment

1 Based on the normal range of the central laboratory performing the assay.
2 A safety alert for LDL-c was not used, as total cholesterol was considered to provide the necessary clinical insights. A safety alert for HDL-c was not used, as the results were not relevant to the evaluation of subject safety in this study.

(Source: applicant's submission, BLA 125561, Study LAL-CL02 clinical study report, page 88/354)

Table 32: Table of Normal Values as Defined by the Central Lab

Lab	Age	Normal Range
ALT	Females 4 to 69 years Males 1 to 10 years	6 to 34 U/L
	Males 10 to 69 years	6 to 43 U/L
AST	Females 4 to 7 years	10 to 48 U/L
	Females 7 to 18 years Males 7 to 18 years	10 to 40 U/L
	Females 18 to 59 years	9 to 34 U/L
	Males 4 to 7 years	10 to 59 U/L
	Males 18 to 59 years	11 to 36 U/L
		Upper Limit Normal (ULN)
GGT	Females 4 to 10 years	24 U/L
	Females 10 to 18 years	33 U/L
	Females 18 to 59 years	49 U/L
	Males 4 to 10 years	24 U/L
	Males 10 to 18 years	51 U/L
	Males 18 to 59 years	61 U/L

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ALP	Females 4 to 7 years	297 U/L
	Females 7 to 10 years	325 U/L
	Females 10 to 15 years	300 U/L
	Females 15 to 18 years	110 U/L
	Females 18 to 50 years	106 U/L
	Females 50 to 58 years	123 U/L
	Males 4 to 7 years	309 U/L
	Males 7 to 10 years	315 U/L
	Males 10 to 15 years	385 U/L
	Males 15 to 18 years	250 U/L
	Males 18 to 50 years	129 U/L
	Males 50 to 58 years	131 U/L
Bilirubin	Total and Indirect Bilirubin	21 µmol/L
	Direct Bilirubin	7 µmol/L
		Lower Limit Normal (LLN)
Albumin	Females and males 4 to 16 years	< 29 g/L
	Females and males 16 to 58 years	< 33 g/L

(Source: reviewer's table, generated using the information provided in the clinical study report (CSR) for Study LAL-CL02, BLA 125561)

Table 33: Description of Ishak Score

Score	Description
0	No fibrosis
1	Fibrous expansion of <50% of portal tracts, with or without short fibrous septa
2	Fibrous expansion of >50% of portal tracts, with or without short fibrous septa
3	Bridging fibrosis involving <50% of portal and/or central areas
4	Bridging fibrosis involving >50% of portal and/or central areas
5	Early or incomplete cirrhosis
6	Cirrhosis, probable or definite

(Source: reviewer's table, generated using applicant's dataset "ADXP," BLA 125561, Study LAL-CL02)

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Figure 13: Clinical Investigator Financial Disclosure Forms

Clinical Investigator Financial Disclosure
Review Template

Application Number: BLA
Submission Date(s): January 8, 2015
Applicant: Synageva
Product: Sebelipase alfa (SBC-102)
Reviewer: Juli Tomaino
Covered Clinical Study (Name and/or Number): Study LAL-CL02

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 54 (principal investigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4 investigators who participated in LAL-CL02		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):
 	
    Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
 	
    Significant payments of other sorts: 4
 	
    Proprietary interest in the product tested held by investigator: 0
 	
    Significant equity interest held by investigator in sponsor of covered study: 0		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 10 (Studies LAL-CL03 and LAL-CL04). No investigators were listed for Study LAL-CL02.		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

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Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are applicant employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)

- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are applicant employees, or lack of disclosure despite due diligence affect the approvability of the application.

The following disclosed financial interests/arrangements do not affect the approvability of the application or raise questions about the data integrity since the majority of the funding was for education, fellowship programs, and research. Moreover, the trial was a randomized, double-blind design. This reviewer does not believe that the results were influenced by the disclosed financial interests/arrangements.

- *Dr. _____ (b) (6) (site (b) (6)): Received $25,012 for educational presentations and materials and outreach activities. This investigator also participated in trial (b) (6) (site (b) (6)).*

- *Dr. _____ (b) (6) (site (b) (6)): Received $34,000 for investigator initiated research, unrelated to (b) (6) and the support was paid to the institution for unrelated investigator initiated research, and was not paid directly to the investigator. This investigator also participated in (b) (6) (site (b) (6)).*

- *Dr. _____ (b) (6) (site (b) (6)): Received $129,732 for investigator initiated research. No patients were enrolled at this clinical site.*

- *Dr. _____ (b) (6) (site (b) (6)): Received $137, 861 for investigator initiated research. (b) (6) was a randomized, double-blind trial with objective endpoints that could not be influenced by human interpretation; therefore, support provided to this investigator is unlikely to have an impact on the outcome of the trial. This investigator also participated in (b) (6) (site (b) (6) but the one patient enrolled was only temporarily under the care of Dr. (b) (6), then transferred to another study center. In addition, the support was paid to the institution and not directly to the physican for unrelated investigator initiated research.*

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/s/

JULI A TOMAINO
06/08/2015

JESSICA J LEE
06/08/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125561   **Applicant: Synageva**   **Stamp Date: 1/8/2015**

Previous Rolling Review Submission Dates: 10/21/14, 11/21/14

Drug Name: sebelipase alfa   **NDA/BLA Type: BLA**

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

	Content Parameter	Yes	No	NA	Comment
	FORMAT/ORGANIZATION/LEGIBILITY				
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
	LABELING				
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
	SUMMARIES				
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?				
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1) BLA
	DOSE				
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: LAL-CL01 and LAL-CL04 (extension study) Study Title: An Open-label Multicenter Study to Evaluate the Safety, Tolerability and Pharmacokinetics of SBC-102 in Adult Patients with Liver Dysfunction Due to Lysosomal Acid Lipase Deficiency. Sample Size: 9 patients	X			

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Arms: 3 patients per dose arm (0.35 mg/kg, 1 mg/kg, and 3 mg/kg) Location in submission: LAL-CL01 is in module 5.3.3.2, and LAL-CL04 is in module 5.3.5.2.				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: (LAL-CL03) An Open Label, Multicenter, Dose Escalation Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of SBC-102 In Children With Growth Failure Due To Lysosomal Acid Lipase Deficiency. Indication: Lysosomal Acid Lipase Deficiency Pivotal Study #2: (LAL-CL02) A Multicenter, Randomized, Placebo-controlled Study of SBC-102 in Patients with Lysosomal Acid Lipase Deficiency (ARISE [Acid Lipase Replacement Investigating Safety and Efficacy]). Indication: Lysosomal Acid Lipase Deficiency	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.		X		Primary endpoint for LAL-CL02 is normalization of ALT, which was not agreed upon by the Division. The primary endpoint for LAL-CL03 is consistent with previous agreements.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	U.S. patient population is represented in the multi-center, multi-national trial(s)
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	Biologics are currently not known to have arrythmogenic potential
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			LAL is a rare disease; therefore, the Division considers exposure of 66 patients in study LAL-CL02 & 9 patients in study LAL-CL03 to be sufficient for this patient population.
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			While pediatric assessments were included, it should be noted that sebelipase alfa has Orphan Designation
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	U.S. patient population is represented in the multi-center, multi-national trial(s)
DATASETS					
31.	Has the applicant submitted datasets in a format to allow	X			

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

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

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	reasonable review of the patient data?				
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	No specific requests were previously made. We will request additional CRFs if necessary.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

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

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

Clinical Review Issue

As stated in the pre-BLA meeting, held on August 19, 2014, the Division remains concerned that the primary efficacy endpoint, normalization of ALT, for Study LALCL02 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 children and adults with late-onset LAL deficiency (i.e., cholesteryl ester storage disease [CESD]). Therefore, ALT normalization is unlikely to serve as the sole basis to establish efficacy in the CESD patient population. Instead, the Division will review the totality of the clinical and laboratory parameters for which there are pre- and on-treatment data.

In light of the concerns with the primary endpoint used to assess efficacy in the CESD population, it will be important to be able to link disease manifestations in infants to children and adults with LAL deficiency to facilitate extrapolation of the clinical benefit observed in infants to the broader population. You have provided an overview of clinical similarities between the two populations (i.e., infants and children/adults) with LAL

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deficiency based on published literature. However, a side-by-side comparison of your clinical trial data that demonstrate similar treatment effect on overlapping disease manifestations would provide further scientific justification to support extrapolation. Therefore, we request that you provide available data from the clinical trials (Study LALCL02 and LAL-CL03) and natural history studies (LAL-1-NH01 and LAL-2-NH01) that demonstrate (1) presence of one or more overlapping disease manifestations between infants and children and adults with LAL deficiency, and (2) similar treatment effect of sebelipase alfa on overlapping disease manifestations in the two patient populations.

Juli Tomaino, MD
Lauren Weintraub, MD

Reviewing Medical Officers	Date

Jessica Lee, MD

Clinical Team Leader	Date

Reference ID: 3707098