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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA #: BLA 125561

Drug Name: KANUMA™ (sebelipase alfa; SBC-102) 1 mg/kg as an intravenous (IV) infusion to be administered once every week or once every other week

Indication(s): (b) (4) for patients with Lysosomal Acid Lipase (LAL) Deficiency

Applicant: Synageva BioPharma Corporation

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1 EXECUTIVE SUMMARY

The applicant submitted the results from the LAL-CL03 and LAL-CL02 trials to support the efficacy of KANUMA™ (sebelipase alfa; SBC-102), (b) (4) in patients with Lysosomal Acid Lipase (LAL) deficiency (i.e., the proposed indication). For the LAL-CL03 trial, conducted in the Wolman Disease patient population, sebelipase alfa was demonstrated to be superior to an acceptable historical control group, extracted from retrospective natural history study LAL-1-NH01, with respect to survival, i.e., time to death from birth up to Month 12. For the LAL-CL02 trial, conducted in the Cholesteryl Ester Storage Disease (CESD) patient population, sebelipase alfa was demonstrated to be superior to placebo in the Week 20 change from baseline in low density lipoprotein cholesterol (LDL-c), non-high density lipoprotein cholesterol (non-HDL-c), triglycerides, and HDL-c. There is an open-label treatment period for the LAL-CL02 study currently ongoing, which suggests a sustained/durable efficacy profile with respect to the aforementioned four parameters.

For both Wolman Disease and CESD, sufficient evidence has been given to support the proposed efficacy claims for sebelipase alfa and no statistical review issues were identified for this application that would preclude product approval. For the CESD patient population, it is recommended that results from only these lipid parameters (i.e., LDL-c, non-HDL-c, triglycerides, and HDL-c) be included in the product labeling as these were the only parameters deemed clinically meaningful by the clinical review team.

Overall, the design of the LAL-CL03 study, in addition to the LAL-1-NH01 protocol for extracting comparable retrospective natural history data to be utilized as a historical control, was ultimately deemed reasonable from a statistical perspective. Although comparisons to a historical control group generally cannot provide results that are as robust or reliable as those from comparisons within a randomized controlled study, the applicant's statistical analysis plan (SAP) was adjudicated as being appropriate. Due to the scarcity of the Wolman Disease patient population, i.e., the prevailing public health circumstances related to Wolman Disease, and the fact that it is a highly progressive disease with an unmet medical need, the determination of the clinical effectiveness of sebelipase alfa will rely more on clinical judgment than on the statistical rigor usually required for larger randomized controlled studies.

The design of the LAL-CL02 study, and corresponding SAP, was also deemed adequate from a statistical perspective, and the estimated sample size was appropriate given the assumptions on the anticipated treatment effect. The only review issue pertained to the adequacy of the primary endpoint, i.e., normalization of alanine aminotransferase (ALT); this was a clinical review issue. Throughout sebelipase alfa's clinical development program, the Division of Gastroenterology and Inborn Errors Products (DGIEP) had communicated to the applicant that ALT alone would not be sufficient as a basis for approval in the CESD patient population. After much internal debate and collaboration among clinical team members during this Biologics Licensing Application (BLA) review cycle, it was adjudicated that the lipid parameters (i.e., LDL-c, non-HDL-c, triglycerides, and HDL-c) were the only clinically meaningful efficacy data captured in this CESD study, with LDL-c being chief among them.

2 INTRODUCTION

2.1 Overview

On October 21, 2014, Synageva BioPharma Corporation initiated the filing of this Original Biologics Licensing Application (BLA) for KANUMA™ (sebelipase alfa; SBC-102) in accordance with Section 351(a) of the Public Health Service Act and Title 21 of the Code of Federal Regulations (CFR), Part 601.2. The active pharmaceutical ingredient (API) of sebelipase alfa (1 mg/kg of body weight to be administered once every week [QW] or every other week [QOW] as an intravenous [IV] infusion) is recombinant human lysosomal acid lipase (rhLAL). Effective on April 2, 2010, the applicant had initiated clinical development of sebelipase alfa, under IND 108,460, as a long-term enzyme replacement therapy (ERT) in patients with Lysosomal Acid Lipase (LAL) deficiency, which is the proposed indication.

LAL deficiency is a lysosomal storage disorder that occurs when the body, specifically the lysosomes within the cells of the body, does not produce enough active LAL enzyme. This enzyme plays an important role in breaking down fatty material (i.e., cholesteryl esters and triglycerides) in the body, specifically at the cellular level. Infants, children and adults that suffer from LAL Deficiency experience a range of serious health problems. The lack of the LAL enzyme can lead to a build-up of fatty material in a number of body organs including the liver, spleen, gut, and in the wall of blood vessels and other important organs. This build-up of fatty material can be lethal if not adequately assuaged. Currently there is no available treatment for LAL deficiency. Sebelipase alfa is an ERT whose mechanism of action is to directly replace the non-existent LAL enzyme thereby, as hypothesized by the applicant, reversing the disease process by breaking down the aforementioned fatty material at the cellular level.

There are two distinct forms of this disease. One is in infants which is called Wolman Disease (i.e., “infantile onset”). The other is in children and adults which is called Cholesteryl Ester Storage Disease (CESD). Wolman Disease presents shortly after birth, is homogeneous in its phenotype, and is often highly progressive and thus fatal within the first six months of life. Sebelipase alfa is to be administered once every week in the Wolman Disease patient population. In comparison to Wolman Disease, CESD is heterogeneous in its phenotype and is less progressive. However, CESD does ultimately result in death if not treated in a timely manner. Sebelipase alfa is to be administered once every other week in the CESD patient population. Wolman Disease is estimated to occur in 1 per 528,000 births which is roughly 600 total people in the USA. The estimated prevalence of CESD ranges from 1 per 40,000 people to 1 per 300,000 people which corresponds to between roughly 1,055 and 7,925 total people in the USA. As can be readily seen, this is a rare disease in both patient populations with the infant population being much rarer than the children/adult population. Overall, LAL deficiency is a rare, serious and life-threatening condition with an unmet medical need.

The applicant obtained *Orphan Designation* from the Office of Orphan Products Development (OOPD) on July 1, 2010. Note that there was also a pending request for *Rare Pediatric Disease Designation*, which OOPD did approve during this BLA review cycle. Synageva also obtained *Fast Track Designation* from the Division of Gastroenterology and Inborn Errors Products (DGIEP) on June 14, 2011. Consequently, DGIEP has agreed to receive the BLA on a rolling

basis with the final component of the BLA having been submitted on January 8, 2015. *Breakthrough Therapy Designation* was also granted by DGIEP on May 13, 2013, (b) (4) for Wolman disease. (b) (4) A priority 8-month review cycle under the Prescription Drug User Fee Act (PDUFA) V Program has been determined for this BLA.

There were a series of communications and meetings between the applicant and DGIEP throughout sebelipase alfa's clinical development program. The relevant industry meetings are as follows: A Pre-IND meeting was held on July 29, 2010 for issues pertaining to non-clinical toxicology and manufacturing. An End of Phase 1 (EOP1) meeting was held on June 12, 2012 in order to have preliminary discussions regarding the pivotal studies for the clinical development program. These discussions were continued in a Type C advice meeting later in that calendar year on November 6, 2012. A little more than one year later on February 25, 2014, an important Post Breakthrough Therapy meeting was held to further discuss these trials along with the eventual BLA itself. These discussions further continued on April 1, 2014 at a Type C advice meeting, and, finally, the pre-BLA meeting communication was made on August 15, 2014 outlining DGIEP's expectations regarding the content and format of the BLA submission. Please see Table 21 in the Appendix for further details regarding these relevant communications and meetings held under IND 108,460.

For Wolman Disease (i.e., LAL deficiency in infants), the regulatory pathway is for full approval under 21 CFR Part 601 utilizing survival data. The lone trial used for the basis of this full approval is study LAL-CL03 which is phase 1/2, multicenter, open-label, single-arm, dose escalation study in treatment naïve Wolman Disease patients. This study compares overall survival (up to 12 months) between infants being administered sebelipase alfa and baseline matched infants from a historical control group (i.e., natural history data for 21 total patients collected retrospectively from chart reviews though natural history study LAL-1-NH01). Note that patients being administered sebelipase alfa in this trial can stay on treatment for up to 208 weeks. A total of 10 patients were targeted for enrollment in trial LAL-CL03. Ultimately nine patients were recruited in three years, and the trial is still currently ongoing during its follow-up period. The primary analysis has been completed.

For CESD (i.e., LAL deficiency in children and adults), the regulatory pathway is also for full approval under 21 CFR Part 601 utilizing an endpoint that has consensus for directly measuring clinical benefit, i.e., percentage change from baseline in LDL cholesterol. The lone trial used for the basis of this full approval is study LAL-CL02, a phase 3, multicenter, randomized, double-blind, placebo-controlled, 20 week (followed by an open-label rollover period of up to 130 weeks) trial in treatment naïve children and adults. The double-blind/placebo-controlled portion of this trial has already been locked and unblinded. The open-label rollover period is still currently ongoing. A total of 50 patients were targeted for enrollment, and 66 patients were ultimately recruited to participate in this study.

Table 1 below presents information on the relevant trials contained in this submission.

Table 1
Summary Information for Relevant Clinical Trials

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Patients	Patient Diagnosis	Duration of Treatment
Safety and Efficacy; Phase 1/2	LAL-CL03	Efficacy, Safety, Pharmacokinetics (PK)	Multicenter, Open-label, Single-arm, Dose escalation	Sebelipase Alfa; Dose escalation from 0.35 mg/kg to 1 mg/kg every week, and then up to 3-5 mg/kg every week; IV	Total: 9	LAL Deficiency (Wolman Disease)	Up to 208 weeks
Natural History	LAL-1-NH01	Chart review of infants with LAL Deficiency	Observational, Natural History, Non-interventional	N/A	Zero patients dosed; 35 total patients participated; 21 patients ultimately adjudicated as being appropriate for comparison	LAL Deficiency (Wolman Disease)	N/A
Safety and Efficacy; Phase 3	LAL-CL02	Efficacy, Safety, Pharmacokinetics (PK)	Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel group	Sebelipase Alfa; 1 mg/kg every other week; IV	Total: 66	LAL Deficiency (CESD)	20 weeks followed by an open-label period up to 130 weeks

Source: Reviewer's Table from applicant's tabular listing of all clinical studies (eCTD Module 5 2).

2.2 Data Sources

This BLA was submitted electronically in electronic Common Technical Document (eCTD) format via the FDA Electronic Submissions Gateway (ESG). The content, including the electronic data sets and labeling information, is located in the Center for Drug Evaluation and Research (CDER) electronic document room (EDR) at the location:

[\\CDSESUB1\evsprod\BLA125561](#). Sequences 0000, 0003, and 0015 contain all the contents relevant for this review.

The clinical study report (CSR), clinical datasets and analysis datasets were reviewed separately for the LAL-CL03, LAL-1-NH01, and LAL-CL02 studies. For each of these three studies, the clinical/tabulation datasets were compliant to the CDISC/SDTM v.3.1.2 implementation guide standard. The analysis datasets for study LAL-CL02 were compliant to the CDISC/ADaM v.1.0 implementation guide standard. However, the analysis datasets for the LAL-CL03 and LAL-1-NH01 studies were in legacy format and hence not compliant to CDISC/ADaM. Adequate data definition files (in define.xml and define.pdf formats), a reviewer's guide and software code (in .txt, format) were also submitted for all three studies.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

3.1.1 Study LAL-CL03/LAL-1-NH01

The LAL-CL03 study utilized an electronic case report form (eCRF) within an electronic data capture (EDC) system while the LAL-1-NH01 study utilized patient charts collected retrospectively from appropriately identified study sites. The submitted data quality for both studies appeared to be adequate. It was possible to reproduce the integrated primary analysis dataset (along with the integrated results presented within the LAL-CL03 CSR), specifically the primary endpoint values, from the original data source. The applicant submitted documentation of data quality control/assurance procedures within Section 8.6 and 8.5 of the LAL-CL03 CSR and LAL-1-NH01 CSR, respectively.

The original LAL-CL03 Statistical Analysis Plan (SAP) was finalized on September 14, 2012. One amendment to the SAP was made on March 7, 2014, which reflected minor edits to the original document. These minor edits did not change any aspect of the analysis plan critical for establishing the safety and efficacy profile of sebelipase alfa in the Wolman Disease patient population. Note that the LAL-CL03 SAP reflected the pertinent analyses that included data from the LAL-1-NH01 study. The LAL-CL03 SAP, along with its lone amendment, was submitted, and all relevant analyses were finalized within the original SAP. Database hard-lock for the currently ongoing LAL-CL03 study data was on June 10, 2014, which was also the study data cutoff date. All LAL-CL03 trial data presented in this written review reflects this study data cutoff date.

3.1.2 Study LAL-CL02

This study utilized an eCRF within an EDC system, and the submitted data quality appeared to be adequate. It was possible to reproduce the primary and secondary analysis datasets (along with the results presented within the CSR), specifically the primary and key secondary endpoint values, from the original data source. It was also possible to verify the randomized treatment assignments, and the applicant submitted documentation of data quality control/assurance procedures within Section 8.6 of the CSR.

The original SAP was finalized on December 18, 2012. Two amendments to the SAP were made on August 28, 2013 and April 30, 2014. These amendments introduced auxiliary analyses for exploratory lab parameters not critical for establishing the safety and efficacy profile of sebelipase alfa in the CESD patient population. These amendments also provided clarifying information for analyses that were pre-specified within the original protocol and the original SAP. The SAP, along with the amendments, was submitted, and all relevant analyses were finalized within the original SAP, which was well in advance of double-blind treatment period (see below in Section 3.2.2.1) completion on May 30, 2014. Database hard-lock for the double-blind treatment period data along with all concurrently ongoing open-label treatment data (also through May 30, 2014), was on June 13, 2014, and the study was officially unblinded on June 20, 2014. All LAL-CL02 trial data presented in this written review reflects a study data cutoff date of May 30, 2014.

3.2 Evaluation of Efficacy

3.2.1 Study LAL-CL03/LAL-1-NH01

3.2.1.1 Background, Study Objective, Design and Endpoints

Background

At the Pre-IND meeting on July 29, 2010, initial advice was conveyed from DGIEP regarding the need for a natural history study to better characterize Wolman Disease. Consequently, the applicant planned multinational, multicenter natural history study LAL-1-NH01, “A Retrospective Natural History Study of Patients with Lysosomal Acid Lipase Deficiency/Wolman Phenotype.” This retrospective natural history study was initiated on September 30, 2010 with the last patient abstracted on March 11, 2013, with at least one patient coming from 18 different sites located in six different countries. The sites selected for this study were those in which the investigator was a physician with experience in the care and treatment of Wolman Disease.

At the aforementioned Pre-IND meeting, at the EOP1 meeting on June 12, 2012, and at the Type C advice meeting on November 6, 2012, advice was conveyed from DGIEP regarding the study design, duration and endpoints for the LAL-CL03 trial, “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.” Given the extreme rarity of the Wolman Disease population, it was understood that the LAL-CL03 study (along with data extracted from the LAL-1-NH01 study) would ultimately

provide the key evidence for establishing sebelipase alfa's efficacy profile within this patient population. This study was designed as a multinational (with a total of nine participating countries), multicenter (with a total of 12 participating study sites), open-label, single-arm, repeat-dose, intra-patient dose escalation trial to evaluate the efficacy and safety of sebelipase alfa in patients with Wolman Disease considered to have rapidly progressive disease based primarily on the presence of growth failure within the first six months of life.

The original LAL-CL03 trial protocol was finalized after the Pre-IND meeting on January 11, 2011, and the trial was subsequently started on May 4, 2011. Ten additional amendments were made to the original protocol with the final amendment being made on January 24, 2014. Each amendment, save one, was clinical, country-specific or administrative in nature without changing key features of the original protocol. The sixth protocol amendment, however, was significant in that it changed the primary objective of the study from evaluating safety and tolerability to that which evaluates survival at 12 months of age compared to baseline matched natural history patient data from the LAL-1-NH01 study. This amendment was made on April 5, 2012. It should be noted that the original LAL-CL03 SAP (finalized on September 14, 2012 as previously stated in Section 3.1.1 above) corresponds to this protocol amendment. This written review reflects the sixth amendment version of the protocol.

Study Objective, Design and Endpoints

The primary objective of LAL-CL03 study was to evaluate the effect of sebelipase alfa therapy on survival at 12 months of age in children with Wolman Disease, considered to have rapidly progressive disease based primarily on the presence of growth failure within the first six months of life, who were less than or equal to eight months of age prior to their first sebelipase alfa infusion. This was done by comparing the survival of enrolled patients with baseline matched patients (i.e., a valid historical control group) found from the LAL-1-NH01 natural historical study. The secondary objective of the study was to assess the safety and tolerability of sebelipase alfa.

This phase 1/2 study consisted of a screening period of up to three weeks, a treatment period of up to four years, and a follow-up visit at least 30 days after the last dose of sebelipase alfa. After confirmation of study eligibility based on screening assessments, patients initiated weekly IV infusions with sebelipase alfa. All patients who initiated treatment under the LAL-CL03 protocol received a starting dose of 0.35 mg/kg QW, and were escalated to a dose of 1 mg/kg QW once acceptable safety and tolerability had been demonstrated during at least two infusions at the 0.35 mg/kg QW dose. The duration of each patient's treatment in the study was expected to be at least 78 weeks, and patients were allowed to continue receiving treatment in the study for up to 208 weeks. Efficacy and safety assessments were performed at regular intervals throughout the study, and a central laboratory was utilized to aid in these assessments. The study is currently ongoing. As previously stated in Section 3.1.1 above, all LAL-CL03 trial data presented in this written review (see Section 3.2.1.4 below) reflects a study data cutoff date of June 10, 2014.

The following primary endpoint was specified within the sixth protocol amendment by the applicant:

Primary Endpoint: Time to Death from Birth up to Month 12

The planned enrollment was approximately for 10 patients, including at least eight patients who were less than or equal to eight months of age on the date of their first infusion of sebelipase alfa. As can be seen in Section 3.2.1.3 below, ultimately nine patients, all of whom were less than or equal to eight months of age on the date of their first infusion, were enrolled, treated, and analyzed.

Throughout the execution of this protocol, an Independent Data Monitoring Committee (IDMC) operated according to a DMC Charter. It provided an ongoing, independent, and expert review of the safety data in order to provide risk management during the conduct of the study. IDMC approval was required prior to all dose escalations. Note that there were no formally planned interim analyses for this study.

For the LAL-1-NH01 study, specified demographic and clinical data from eligible patients were extracted through retrospective clinical chart reviews. For any patient alive as of the last chart record reviewed, their physician was contacted to determine the patient's survival status. All patients were diagnosed after January 1, 1985. The planned enrollment was approximately 40 patients.

Statistical Reviewer Comments:

Overall, the design of the LAL-CL03 study, in addition to the LAL-1-NH01 protocol for extracting comparable retrospective natural history data to be utilized as a historical control, was ultimately deemed reasonable from a statistical perspective. In general, utilization of a historical control can be valid if the course of the untreated disease within a patient population is well understood to be uniform with outcomes that can be predicted reliably. In addition a valid historical control from a natural history study must have the same eligibility requirements, medical workup, and clinical evaluations as the clinical trial, i.e., patients from the natural history study must be adequately matched to patients from the clinical trial in terms of inclusion/exclusion criteria (and thus closely resembling the trial group in all known relevant baseline and observational variables) while also having comparable clinical evaluations in each group. Using a historical control is most likely to be persuasive when the study endpoint is objective and when the outcome on treatment is markedly different from that of the historical control (including a high level of statistical significance in the treatment vs. historical control comparison). Given that Wolman Disease is homogeneous in its phenotype and expectedly fatal within the first six months of life, the acceptable similarity between both patient cohorts in terms of baseline characteristics (see Section 3.2.1.3 below), the fact that the primary study endpoint pertains to survival (which DGIEP had recommended during sebelipase alfa's clinical development program), and the significant difference in survival between the non-concurrent groups (see Section 3.2.1.4 below), it was deemed by both the clinical and statistical review teams that the historical control group from the LAL-1-NH01 study was reasonable for comparison to the LAL-CL03 study cohort.

It should be noted, however, that comparisons to a historical control group are not considered to provide results that are as robust or reliable as those from comparisons within a randomized controlled study. Even when there is an observed balance between the non-concurrent groups in

regards to identified baseline characteristics/covariates, there may be confounding due to baseline imbalances in latent variables, which can influence outcome to therapy. This potential introduction of bias results from not having a randomization mechanism. In addition, the retrospective nature of the LAL-1-NH01 study introduces the potential for selection bias, i.e., patients ultimately chosen for the historical control group may be those that result in an overly optimistic estimate of efficacy when comparisons are made to the treated patients. Both of these issues can be further magnified when operating with very small sample sizes, which is the case for Wolman Disease. Nevertheless, it was adjudicated that the applicant's due diligence in acquiring all available, and properly comparable, data was sufficient thereby mitigating the aforementioned potential issues.

3.2.1.2 Statistical Methodologies

3.2.1.2.1 Analysis Sets

For the LAL-CL03 study, the primary analysis set used for the efficacy analyses was the Primary Efficacy Analysis Set (PES). This analysis set included all enrolled Wolman Disease patients, considered to have rapidly progressive disease based primarily on the presence of growth failure within the first six months of life, who received any amount of sebelipase alfa, with their first treatment infusion being on or prior to their 8th month of age. For sensitivity analysis purposes, all efficacy analyses were repeated utilizing a Per-Protocol Set (PPS). This analysis set was comprised of patients in the PES who received at least four complete infusions of sebelipase alfa.

For the LAL-1-NH01 study, the analysis set of choice was not named by the applicant. It consisted of all extracted, and untreated, Wolman Disease patients considered to have rapidly progressive disease based primarily on the presence of growth failure within the first six months of life. This set of patients was ultimately adjudicated as being appropriate for comparison to the LAL-CL03 trial cohort.

3.2.1.2.2 Multiplicity Adjustment

There was no multiplicity adjustment pre-specified by the applicant. Formal hypothesis testing is conducted only for the primary endpoint.

3.2.1.2.3 Primary Endpoint Analysis

The primary endpoint, i.e., time to death from birth up to Month 12, was assessed for patients within the trial and historical control groups. The survival rates at Month 12 (i.e., the percentage of patients who were still alive at Month 12) were assessed for both groups separately, and a 95% Confidence Interval (CI), using the Clopper-Pearson method, for each group's survival rate was calculated by the statistical reviewer. The applicant's pre-specified analysis was to compare median time to death from birth up to Month 12 between the patient groups through a standard Kaplan-Meier approach with formal hypothesis testing utilizing the log-rank test. In addition, a hazard ratio along with a corresponding 95% CI was presented. The proportional hazards assumption was checked by graphically observing log(-log(estimated survival probability)) versus log(time in days) for each group. An additional sensitivity analysis was conducted by the statistical reviewer utilizing the Nelson-Aalen approach. All of the aforementioned analyses

were repeated by the statistical reviewer, for sensitivity analysis purposes, for the time to death from birth up to point of last contact.

3.2.1.2.4 Secondary Endpoints Analysis

There were no formal secondary endpoints. Safety and tolerability were assessed as exploratory endpoints.

3.2.1.2.5 Handling of Dropouts/Missing Data

To further assess the sensitivity of the results to censored data, the statistical reviewer espoused a worst-case imputation strategy for the primary analysis by designating censored patients as “failures”, i.e., having experienced death.

3.2.1.2.6 Other Analysis Considerations

There were no other analysis considerations.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition information for all relevant patients is displayed in Table 2 below. Note that 35 total patients were extracted in the LAL-1-NH01 study with 21 patients ultimately adjudicated as being appropriate for comparison to the LAL-CL03 trial cohort.

Table 2
Disposition – LAL-CL03/LAL-1-NH01
(PES)

	Sebelipase Alfa (N = 9)	Historical Control (N = 21)	Total (N = 30)
Primary Efficacy Analysis Set (PES)	9 (100%)	21 (100%)	30 (100%)
Per-Protocol Set (PPS)	7 (77.8%)	21 (100%)	28 (93.3%)

Source: Reviewer’s Table generated from LAL-CL03 ADSL dataset and LAL-1-NH01 ADSL dataset.

Note: Denominators for percentages are N. A total of 11 patients were screened for the LAL-CL03 study. Two patients died during screening due to severe liver failure.

The relevant demographics and baseline characteristics for all pertinent patients are presented in Table 3 below.

Table 3
Demographic and Baseline Characteristics – LAL-CL03/LAL-1-NH01
(PES)

	Sebelipase Alfa (N = 9)	Historical Control (N = 21)	Total (N = 30)
Age at Symptom Onset (months)			
n	9	21	30
Mean (SD)	1.5 (1.63)	1.4 (1.07)	1.5 (1.45)
Median	1.5	1.2	1.5
Min, Max	0, 5	0, 3	0, 5
Gender – n (%)			
Female	4 (44.4%)	11 (52.4%)	15 (50.0%)
Male	5 (55.6%)	10 (47.6%)	15 (50.0%)
Race – n (%)			
Asian	1 (11.1%)	8 (38.1%)	9 (30.0%)
Black or African American	1 (11.1%)	0	1 (3.3%)
Other	0	4 (19.0%)	4 (13.3%)
White	4 (44.4%)	6 (28.6%)	10 (33.3%)
Unknown	3 (33.3%)	3 (14.3%)	6 (20.0%)
Geographical Region – n (%)			
Europe	7 (77.8%)	14 (66.7%)	15 (50.0%)
North America	1 (11.1%)	6 (28.6%)	7 (23.3%)
Other	1 (11.1%)	1 (4.8%)	8 (26.7%)

Source: Reviewer's Table generated from LAL-CL03 ADSL dataset and LAL-1-NH01 ADSL dataset.

Note: Denominators for percentages are N. Race was not reported by the site for the three LAL-CL03 patients treated in France, in compliance with local regulations.

It can be seen from the presented demographic and baseline characteristics that there was an imbalance between the non-concurrent groups regarding race and, to a lesser degree, geographic region. However, these variables were not considered as critical as the other variables in influencing outcome to therapy.

3.2.1.4 Results and Conclusions

All results presented in this section were generated by the statistical reviewer.

Table 4
Time to Death from Birth Up to Month 12 – LAL-CL03/LAL-1-NH01 (PES)

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

Source: Reviewer's Table generated from LAL-CL03 ADSL dataset and LAL-1-NH01 ADSL dataset.

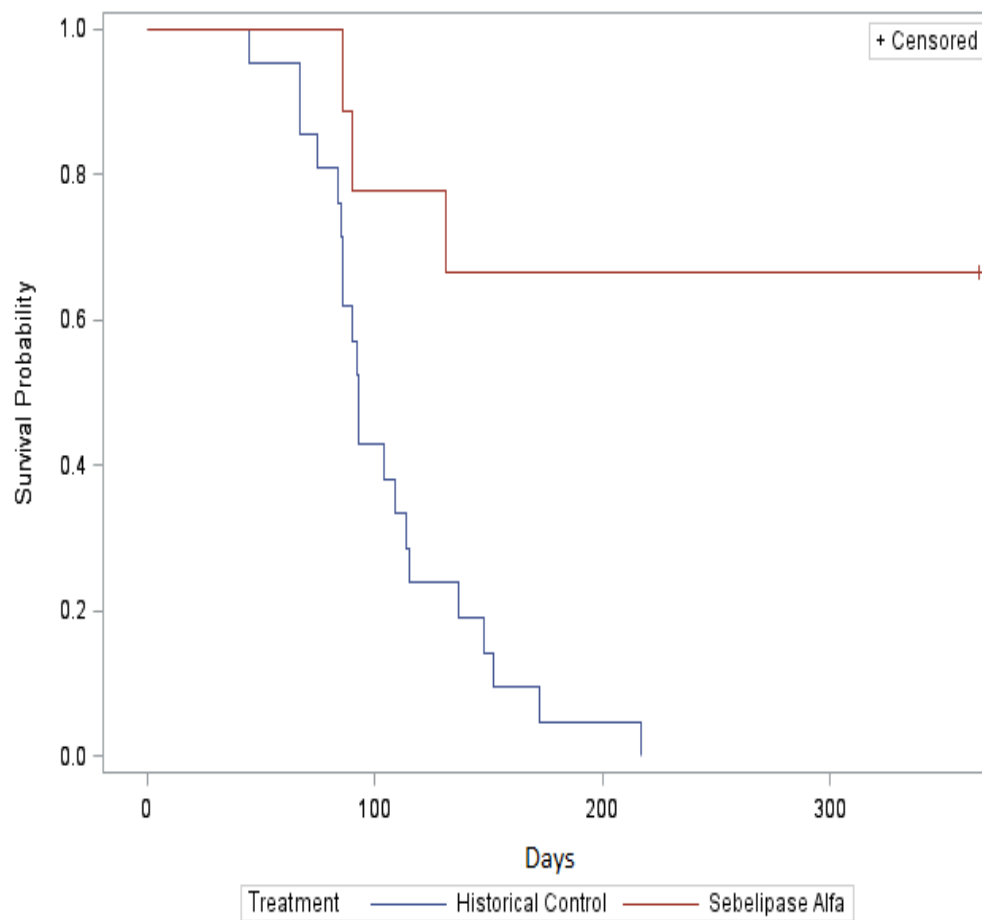
Note: Denominators for percentages are N. * denotes censoring.

[1]: Using the Clopper-Pearson method.

[2]: The applicant's pre-specified analysis.

It can be observed from Table 4 above that sebelipase alfa showed superiority in the time to death from birth up to Month 12 when compared to the historical control group. This analysis was repeated utilizing the PPS, and the conclusions were consistent. The worse-case imputation strategy did not impact the study conclusions. It should be noted that the proportional hazards assumption was deemed appropriate by graphically observing that the log(-log(estimated survival probability)) versus log(days) for each group were reasonably parallel to one another. The additional sensitivity analysis conducted by the statistical reviewer utilizing the Nelson-Aalen approach also did not impact the study conclusions. The Kaplan-Meier figure plotting the aforementioned data is presented below in Figure 1. These analyses repeated for the time to death from birth up to point of last contact follow immediately thereafter.

Figure 1
Time to Death from Birth Up to Month 12 – LAL-CL03/LAL-1-NH01
(PES)



Source: Reviewer's Figure using SAS generated from LAL-CL03 ADSL dataset and LAL-1-NH01 ADSL dataset.

Table 5
Time to Death from Birth Up to Point of Last Contact – LAL-CL03/LAL-1-NH01
(PES)

	Sebelipase Alfa (N = 9)	Historical Control (N = 21)	Treatment Difference (Sebelipase Alfa / Historical Control)
Alive at Month 12 – n (%)	6 (66.7%)	0 (0.0%)	
Corresponding 95% CI [1]	(29.9%, 92.5%)	(0.0%, 16.1%)	
Time to Death from Birth (in Days)			
n	9	21	
Mean (SD)	478.1 (386.00)	106.2 (39.95)	
Median	478.0	93.0	
Min, Max	86, 1286*	45, 217	
Hazard Ratio [2]			0.141
Corresponding 95% CI [2]			(0.040, 0.496)
Log-Rank test p-value [2]			0.0006

Source: Reviewer's Table generated from LAL-CL03 ADSL dataset and LAL-1-NH01 ADSL dataset.

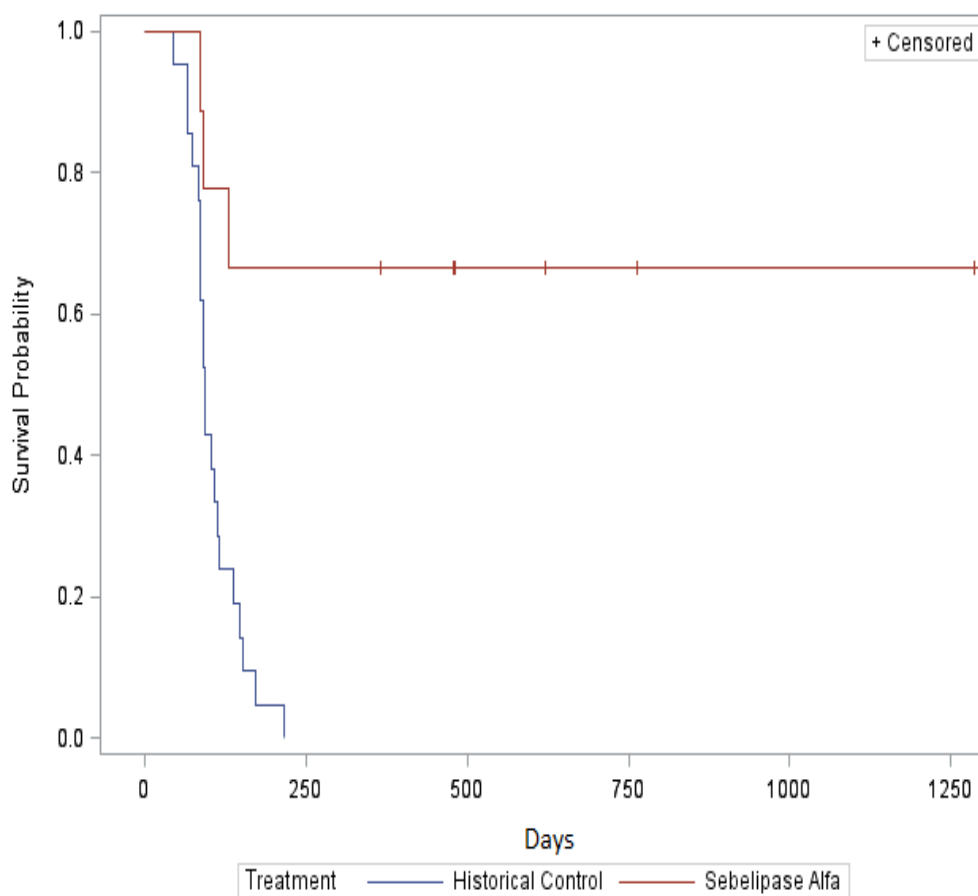
Note: Denominators for percentages are N. * denotes censoring.

[1]: Using the Clopper-Pearson method.

[2]: The applicant's pre-specified analysis.

It can be observed from Table 5 above that sebelipase alfa showed superiority in the time to death from birth up to point of last contact when compared to the historical control group. This analysis was repeated utilizing the PPS, and the conclusions were consistent. The worse-case imputation strategy did not impact the study conclusions. It should be noted that the proportional hazards assumption was deemed appropriate by graphically observing that the log(-log(estimated survival probability) versus log(days) for each group were reasonably parallel to one another. The additional sensitivity analysis conducted by the statistical reviewer utilizing the Nelson-Aalen approach also did not impact the study conclusions. The Kaplan-Meier figure plotting the aforementioned data is presented below in Figure 2.

Figure 2
Time to Death from Birth Up to Point of Last Contact – LAL-CL03/LAL-1-NH01 (PES)



Source: Reviewer's Figure using SAS generated from LAL-CL03 ADSL dataset and LAL-1-NH01 ADSL dataset.

3.2.2 Study LAL-CL02

3.2.2.1 Background, Study Objective, Design and Endpoints

Background

At the EOP1 meeting on June 12, 2012, initial advice was conveyed from DGIEP regarding the study design, duration and endpoints for the LAL-CL02 trial, “A Multicenter, Randomized, Placebo-Controlled Study of SBC-102 in Patients with Lysosomal Acid Lipase Deficiency (ARISE [Acid Lipase Replacement Investigating Safety and Efficacy]).” Given the paucity of the CESD population, it was understood that the LAL-CL02 study would ultimately provide the key evidence for establishing sebelipase alfa’s efficacy profile within this patient population. This study was designed as a multinational (with a total of 17 participating countries), multicenter (with a total of 55 participating study sites), randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of sebelipase alfa in patients with CESD. The original LAL-CL02 trial protocol was finalized after the aforementioned EOP1 meeting on July 20, 2012, and the trial was subsequently started on January 22, 2013. The original protocol incorporated all important suggestions and comments made by DGIEP at the EOP1 meeting. Three country-specific amendments were made to the original protocol. Each amendment was administrative in nature without changing key pre-specified features of the original protocol, and was only applicable to study sites within the specified country: March 5, 2013 amendment for study sites in Japan; April 10, 2013 amendment for study sites in the Czech Republic; April 18, 2013 amendment for study sites in Germany. This written review reflects the original version of the protocol.

Study Objective, Design and Endpoints

The primary objective of this study was to demonstrate the efficacy of sebelipase alfa, relative to placebo, based on the normalization of alanine aminotransferase (ALT) in patients with CESD. The secondary objectives were (1) to demonstrate the efficacy of sebelipase alfa, relative to placebo, based on the following parameters: 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, increase in HDL-c, and, in the subset of patients for whom the assessments were performed, decrease in liver fat content, improvement in hepatic histology, and decrease in liver volume; (2) to evaluate the safety, tolerability, and immunogenicity of sebelipase alfa therapy; and (3) to further characterize the PK of sebelipase alfa. The key exploratory objective was to assess the durability of the clinical response to 1 mg/kg of QOW sebelipase alfa in an open-label extension period.

This phase 3 study included a screening period of up to 6 weeks, a 20-week double-blind treatment period, an open-label extension period of up to 130 weeks, and a follow-up phone call at least 4 weeks after the last dose of study drug. After the patient (and/or their parent/legal guardian) provided informed consent each patient underwent screening assessments to determine study eligibility. If all eligibility criteria were met, the patient was stratified into one of three groups:

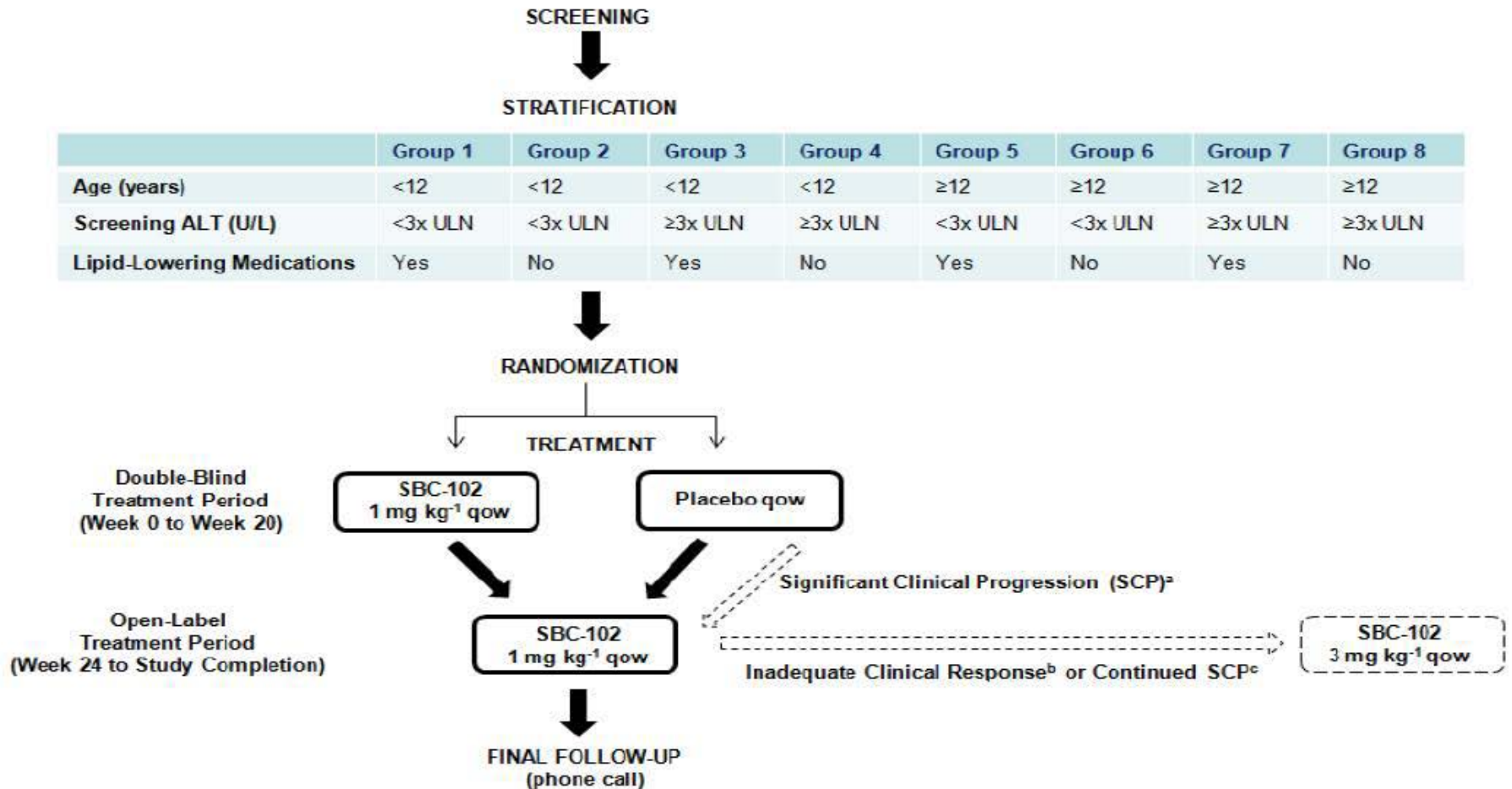
- age post-screening/pre-randomization (<12 years, ≥12 years)

- average screening ALT level ($<3 \times$ upper limit of normal [ULN], $\geq 3 \times$ ULN)
- use of lipid lowering medications (LLM) (yes, no)

The patients in each of the eight possible strata were then randomized via Interactive Voice-Response System/Interactive Web-Response System (IVRS/IWRS) in a 1:1 ratio to receive IV QOW infusions of 1 mg/kg sebelipase alfa or matching IV QOW placebo during the 20-week double-blind treatment period. After completing the 20-week double-blind treatment period, each patient, regardless of their original randomized treatment assignment, was offered to continue on open-label sebelipase alfa treatment at a dose of 1 mg/kg during an open-label treatment period beginning at Week 24. The duration of each patient's treatment in the study was expected to be at least 78 weeks, and patients were allowed to continue receiving treatment in the study for up to 150 weeks. Efficacy and safety assessments were performed at regular intervals throughout the study, and a central laboratory was utilized to aid in these assessments. No dose modifications were permitted during the double-blind treatment period.

The double-blind treatment period ended on May 30, 2014, and the open-label treatment period is currently ongoing. As previously stated in Section 3.1.2 above, all LAL-CL02 trial data presented in this written review (see Section 3.2.2.4 below) reflects a study data cutoff date of May 30, 2014. The overall study scheme is shown in Figure 3 below.

Figure 3
Study Diagram LAL-CL02



- 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.

Source: LAL-CL02 July 20, 2012 Protocol - Figure 1 on pg. 31 of 113

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

The following primary and secondary endpoints were pre-specified in the order below within the original protocol (with the order unchanged) by the applicant:

Primary Endpoint: Normalization of ALT at Week 20

Secondary Endpoints:

- Percentage change from baseline in LDL-c at Week 20
- Percentage change from baseline in non-HDL-c at Week 20
- Normalization of AST at Week 20
- Percentage change from baseline in Triglycerides at Week 20
- Percentage change from baseline in HDL-c at Week 20
- Percentage change from baseline in Liver Fat Content (as a percentage) at Week 20 (in the subset of patients for whom this assessment was performed)
- Improvement in Liver Histopathology at Week 20 (in the subset of patients for whom this assessment was performed)
- Percentage change from baseline in Liver Volume (in Multiples of Normal [MN]) at Week 20 (in the subset of patients for whom this assessment was performed).

Assuming that 71% of patients randomized to sebelipase alfa and 17% of patients randomized to placebo achieve the primary efficacy endpoint, a sample size of 50 randomized patients (approximately 25 patients per treatment group) would provide 97% power to detect a statistically significant difference between sebelipase alfa and placebo, using Fisher's exact test at two-sided $\alpha=0.05$.

Throughout the execution of this protocol, an IDMC operated according to a DMC Charter. It provided an ongoing, independent, and expert review of the safety data in order to provide risk management during the conduct of the study. Note that there were no formally planned interim analyses for this study. Liver volumes were obtained by Magnetic Resonance Imaging (MRI), and the image evaluation plan utilized a central imaging vendor. Two medically trained readers that were blinded to treatment, and time point of the image, served in this blinded and centralized imaging review.

Statistical Reviewer Comments:

Overall, the design of the LAL-CL02 study was deemed adequate from a statistical perspective, and the estimated sample size was appropriate given the assumptions on the anticipated treatment effect. The only review issue pertained to the adequacy of the primary endpoint, i.e., normalization of ALT; this was a clinical review issue. Throughout sebelipase alfa's clinical development program, DGIEP had communicated to the applicant that ALT alone would not be sufficient as a basis for approval in the CESD patient population. These communications were made on multiple occasions, i.e., the EOP1 meeting on June 12, 2012, the Type C meeting on November 6, 2012, and the Type C meeting on April 1, 2014. Please see Table 21 in the Appendix for further details. After much internal debate and collaboration among clinical team members (in addition to senior leadership from DGIEP and the Office of Drug Evaluation III [ODE III]) during this BLA review cycle, it was adjudicated that the lipid parameters (i.e., LDL-

c, non-HDL-c, triglycerides, and HDL-c) were the only clinically meaningful efficacy data captured in this CESD study, with LDL-c being chief among them. Please see the clinical review for full details. Due to the applicant's pre-specified step-down/closed sequential testing procedure (see Section 3.2.2.2 below) in tandem with successful hypothesis testing for the pre-specified primary endpoint of ALT normalization at Week 20 (see Section 3.2.2.4 below), formal hypothesis testing of these lipid parameters was ensured for labeling purposes.

3.2.2.2 Statistical Methodologies

3.2.2.2.1 Analysis Sets

The primary analysis set used for all efficacy analyses was the Full Analysis Set (FAS). This analysis set included all randomized patients who received at least one dose of blinded study drug. When utilizing this analysis set, patients were analyzed according to the treatment group that they were randomized to receive regardless of the actual treatment received. As can be seen in Section 3.2.2.3 below, all randomized patients did receive at least one dose of blinded study drug.

For sensitivity analysis purposes, all efficacy analyses were repeated utilizing a Per-Protocol Set (PPS). This analysis set was comprised of patients in the FAS who, in addition:

- Received at least nine complete infusions of study drug during the double-blind treatment period;
- Had measurements of ALT at both baseline and Week 20;
- Had Week 20 assessments within 12 to 21 days of the preceding (Week 18) infusion;
- Did not change their lipid-lowering medications; and
- Did not have any other major protocol violations that would affect interpretation of results for serum transaminases or serum lipids.

This analysis set definition was finalized prior to database lock.

3.2.2.2.2 Multiplicity Adjustment

In order to control the overall study-wise type I error rate, a step-down/closed sequential testing procedure was pre-specified by the applicant to adjust for the multiple comparisons on the study endpoints presented in the order above within Section 3.2.2.1. Starting with the primary endpoint, the applicant stated that the step-down could only be carried to the next endpoint, within the order presented above, if and only if the current endpoint/step was found to be statistically significant in the comparison of sebelipase alfa to placebo (i.e., p-value less than 0.05). If the comparison of sebelipase alfa to placebo was not statistically significant at the current endpoint/step (i.e., p-value greater than or equal to 0.05), then all hypothesis testing for the subsequent endpoints/steps would be deemed as exploratory.

3.2.2.2.3 Primary Endpoint Analysis

The primary endpoint, i.e., normalization of ALT at Week 20, was assessed for patients within the sebelipase alfa and placebo treatment groups. The responder rates at Week 20 (i.e., the proportion of patients who had a normal ALT value at Week 20) were assessed for both treatment groups separately and a 95% Wald CI for the difference of these responder rates was

calculated by the statistical reviewer. The applicant's pre-specified analysis was to compare these proportions utilizing a Fisher's exact test without adjusting for the three aforementioned randomization strata (see Section 3.2.2.1 above). An additional sensitivity analysis was conducted by the statistical reviewer. This sensitivity analysis utilized a Cochran-Mantel-Haenszel (CMH) test which adjusted for all three randomization stratification variables. In tandem with the CMH test, a Breslow-Day test was also conducted in order to test for the homogeneity of the treatment effect across the different randomization strata.

3.2.2.2.4 Secondary Endpoints Analysis

For the normalization of AST at Week 20 and the improvement in liver histopathology at Week 20 secondary endpoints, the same applicant pre-specified analysis and reviewer sensitivity analysis were conducted as described above in Section 3.2.2.2.3.

For the analysis of all percentage change from baseline at Week 20 secondary endpoints, the applicant's pre-specified analysis was to utilize a Wilcoxon Rank Sum Test without adjusting for the three aforementioned randomization strata (see Section 3.2.2.1 above). For each of these continuous secondary endpoints, an additional sensitivity analysis was conducted by the statistical reviewer. This sensitivity analysis utilized an Analysis of Covariance (ANCOVA) model with treatment (i.e., sebelipase alfa or placebo) and the three randomization stratification variables as factors. The baseline value of the lab or imaging parameter of interest was also included in the model as a covariate. The 95% CI for the treatment effect of sebelipase alfa versus placebo was calculated. Note that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were checked by graphically observing residuals along with a normal quantile-quantile plot. Normality was also tested using the Kolmogorov-Smirnov test. As an additional sensitivity analysis, the aforementioned ANCOVA procedures were re-conducted on the corresponding absolute change from baseline at Week 20.

An additional exploratory analysis, that was deemed clinically meaningful and thus motivated by the clinical review team, was conducted by the statistical reviewer in regards to LDL-c. This was a responder analysis that assessed whether patients with abnormal baseline LDL-c (i.e., ≥ 130 mg/dL) ultimately achieved LDL-c normalization (i.e., < 130 mg/dL) at Week 20. Responder rates and corresponding 95% CIs, using the Wald method, were descriptively presented separately for both the sebelipase alfa and placebo treatment groups overall.

3.2.2.2.5 Handling of Dropouts/Missing Data

No missing data handling procedure was pre-specified by the applicant. As can be seen below in Section 3.2.2.3, there was only one discontinuation in this study (i.e., patient 2106-044, who was randomized to receive sebelipase alfa). However, there were other patients who successfully finished the study while also having missing Week 20 data for certain efficacy assessments due to corrupted samples (e.g., laboratory samples) that were not evaluable. A listing of all patients who had missing Week 20 data is presented below.

LAL-CL02 Patients with Missing Week 20 Data

Patient Number	Randomized Treatment	Missing Week 20 Efficacy Data
(b) (6)	Sebelipase Alfa	ALT, AST
	Sebelipase Alfa	Liver Fat Content
	Placebo	Liver Fat Content
	Placebo	Liver Volume, Liver Fat Content
	Sebelipase Alfa	Liver Volume, Liver Fat Content
	Placebo	LDL-c, non-HDL-c, HDL-c
	Sebelipase Alfa	All Week 20 Efficacy Data
	Sebelipase Alfa	AST

Source: Reviewer's Listing generated from the ADBLB, ADXM, and ADXP datasets.

[1]: Patient (b) (6) was the only patient in the LAL-CL02 trial who discontinued the study.

To further assess the sensitivity of the results to this missing/unavailable Week 20 data, the statistical reviewer espoused a worst-case (i.e., designating “failure”) imputation strategy for analyses pertaining to ALT, AST and liver histopathology while also imputing no-change-from-baseline for the analysis of all percentage change from baseline at Week 20 secondary endpoints. As is discussed in Section 3.2.2.4 below, the final results and conclusions were not influenced by the minimal missing data encountered in the study.

3.2.2.2.6 Other Analysis Considerations

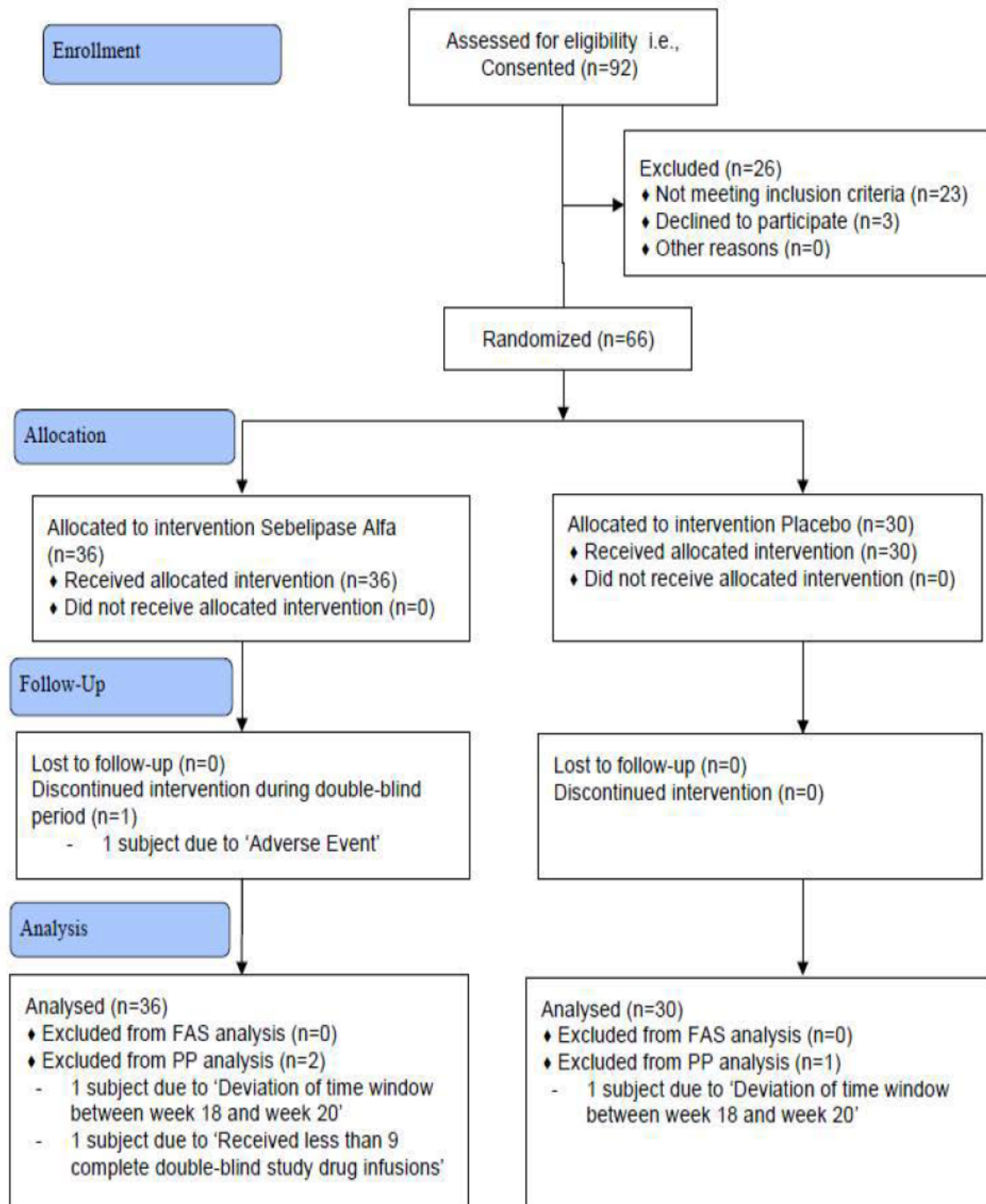
Baseline was defined by the applicant as the last measurement prior to the first infusion of study drug, or, if multiple pre-treatment measurements were available, the arithmetic mean of the last (up to) three measurements preceding the first infusion of study drug. Unscheduled measurements prior to first study drug infusion were considered in the calculation of baseline value.

For sensitivity analysis purposes, all relevant analyses were re-conducted by the statistical reviewer utilizing a traditional baseline definition, i.e., the last non-missing value prior to the first infusion of study drug.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition information for all relevant patients is displayed in Figure 4 and Table 6 below. Figure 4 displays information for all eligible patients who provided informed consent while Table 6 displays information for all randomized patients.

Figure 4
Disposition – LAL-CL02



Source: LAL-CL02 CSR - Figure 2 on pg. 147.

Note: Patient ^{(b) (6)}, randomized to sebelipase alfa, was the only patient in the LAL-CL02 trial who discontinued the study during the double-blind treatment period.

Table 6
Disposition – LAL-CL02
(All-Randomized)

	Sebelipase Alfa (N = 36)	Placebo (N = 30)	Total (N = 66)
Full Analysis Set (FAS)	36 (100%)	30 (100%)	66 (100%)
Per-Protocol Set (PPS)	34 (94.4%)	29 (96.7%)	63 (95.5%)
Completed Double-Blind Treatment Period	35 (97.2%)	30 (100%)	65 (98.5%)
Discontinued Study Early	1 (2.8%)	0	1 (1.5%)
Adverse Event	1 (2.8%)	0	1 (1.5%)
Escape Therapy Introduced	0	0	0
Did not Tolerate Treatment	0	0	0
Withdrawal	0	0	0
Lost to follow-up	0	0	0
Study Terminated by Sponsor	0	0	0
Pregnancy	0	0	0
Other	0	0	0
Participated in Open-Label Treatment Period	35 (97.2%)	30 (100%)	65 (98.5%)

Source: Reviewer's Table generated from ADSL dataset.

Note: Denominators for percentages are N. Patient (b) (6) was the only patient who discontinued the study during the double-blind treatment period, and this was due to an adverse event. All patients completing the double-blind treatment period participated in the open-label treatment period.

The relevant demographics and baseline characteristics for all randomized patients are presented in Table 7 below.

Table 7
Demographic and Baseline Characteristics – LAL-CL02
(All-Randomized)

	Sebelipase Alfa (N = 36)	Placebo (N = 30)	Total (N = 66)
Age (years)			
n	36	30	66
Mean (SD)	16.9 (11.57)	15.2 (10.23)	16.1 (10.93)
Median	13.5	13.0	13.0
Min, Max	4, 55	4, 58	4, 58
Age Group – n (%)			
< 12 years	14 (38.9%)	10 (33.3%)	24 (36.4%)
≥ 12 years	22 (61.1%)	20 (66.7%)	42 (63.6%)
Gender – n (%)			
Female	18 (50.0%)	15 (50.0%)	33 (50.0%)
Male	18 (50.0%)	15 (50.0%)	33 (50.0%)
Race – n (%)			
Asian	3 (8.3%)	0	3 (4.5%)
Black or African American	1 (2.8%)	0	1 (1.5%)
Other	5 (13.9%)	2 (6.7%)	7 (10.6%)
White	27 (75.0%)	28 (93.3%)	55 (83.3%)
Average Screening ALT Level – n (%)			
< 3 × ULN	25 (69.4%)	23 (76.7%)	48 (72.7%)
≥ 3 × ULN	11 (30.6%)	7 (23.3%)	18 (27.3%)
Use of LLM – n (%)			
Yes	14 (38.9%)	11 (36.7%)	25 (37.9%)
No	22 (61.1%)	19 (63.3%)	41 (62.1%)
Geographical Region – n (%)			
Europe	18 (50.0%)	21 (70.0%)	39 (59.1%)
North America	10 (27.8%)	6 (20.0%)	16 (24.2%)
Other	8 (22.2%)	3 (10.0%)	11 (16.7%)

Source: Reviewer's Table generated from ADSL dataset.

Note: Denominators for percentages are N.

It can be seen that there was no noticeable imbalance between the treatment groups regarding the presented demographic and baseline characteristics.

3.2.2.4 Results and Conclusions

The results displayed in this section correspond to the endpoint testing order specified in Section 3.2.2.1 above. All presented results were generated by the statistical reviewer.

Table 8
Proportion of Patients who Achieved ALT Normalization at Week 20 – LAL-CL02
(FAS)

	Sebelipase Alfa (N = 36)	Placebo (N = 30)	Treatment Difference (%) (Sebelipase Alfa – Placebo)
ALT Normalization at Week 20 – n (%)	11 (30.6%)	2 (6.7%)	23.9%
Corresponding 95% CI			6.4%, 41.4%
Fisher’s Exact Test p-value [1]			0.0271
CMH Test p-value			0.0242
Corresponding Breslow-Day Test p-value			0.1780

Source: Reviewer’s Table generated from ADBLB dataset.

Note: Denominators for percentages are N.

[1]: The applicant’s pre-specified analysis.

It can be observed from Table 8 above that sebelipase alfa showed a superior difference in the proportion/percentage of patients achieving ALT normalization at Week 20 when compared to placebo. This analysis was repeated utilizing the PPS, and the conclusions were consistent. The worse-case imputation strategy, implemented by the statistical reviewer for missing data from patients listed in Section 3.2.2.2.5 above, did not impact the study conclusions. It is important to note that no single site influenced or drove the overall study results. It can also be observed from Table 8 that the result from the additional sensitivity analysis conducted by the statistical reviewer (i.e., the CMH test) was consistent with the applicant’s pre-specified analysis findings. The corresponding Breslow-Day test result shows that the treatment effect is homogeneous across the different randomization strata. Considering the applicant’s pre-specified step-down/closed sequential testing procedure as previously described in Section 3.2.2.2.2, formal hypothesis testing can subsequently be continued for percentage change from baseline to Week 20 in LDL-c.

Table 9
Summary of Change from Baseline to Week 20 in LDL-c – LAL-CL02
(FAS)

Time Point	Sebelipase Alfa (N = 36)	Placebo (N = 30)	Treatment Difference (Sebelipase Alfa – Placebo)
Baseline LDL-c (mg/dL)			
n	36	30	
Mean (SD)	189.9 (57.16)	229.5 (69.95)	
Median	193.0	213.0	
Min, Max	70, 280	135, 378	
Week 20 LDL-c (mg/dL)			
n	36	30	
Mean (SD)	138.7 (66.27)	213.3 (65.99)	
Median	137.5	201.0	
Min, Max	32, 348	99, 408	
Absolute Change from Baseline to Week 20 (mg/dL)			
n	36	30	
Mean (SD)	-51.3 (45.34)	-16.1 (34.73)	
Median	-53.5	-10.5	
Min, Max	-130, 109	-119, 32	
Difference in LS Means (SEM) [1]			-42.9 (9.80)
Corresponding 95% CI [1]			-62.11, -23.69
p-value [1]			<0.0001
Percentage Change from Baseline to Week 20 (%)			
n	36	30	
Mean (SD)	-28.4 (22.30)	-6.3 (13.02)	
Median	-28.9	-4.8	
Min, Max	-59, 46	-33, 16	
Difference in Means			-22.2
p-value [2]			<0.0001
Difference in LS Means (SEM) [1]			-22.4 (4.30)
Corresponding 95% CI [1]			-31.24, -13.56
p-value [1]			<0.0001
Responder Analysis – n/n* (%: 95% CI) [3]			
Overall	13/32 (40.6%: 23.6%, 57.6%)	2/30 (6.7%: 0%, 15.6%)	

Source: Reviewer's Table generated from ADBLB dataset.

Note: LS = least squares; SEM = standard error of the LS mean.

[1]: Derived from ANCOVA model adjusted for age post-screening/pre-randomization (<12 years, ≥12 years), average screening ALT level (<3×upper limit of normal [ULN], ≥3×ULN), use of lipid lowering medications (LLM) at baseline (yes, no), and baseline LDL-c concentration.

[2]: Corresponding to unadjusted Wilcoxon Rank Sum Test, which was the applicant's pre-specified analysis.

[3]: Assessing whether patients with abnormal baseline LDL-c (i.e., ≥130 mg/dL) ultimately achieved LDL-c normalization (i.e., <130 mg/dL) at Week 20; n* represents the number of patients with abnormal baseline LDL-c.

It can be observed from Table 9 above that sebelipase alfa showed superior improvement (i.e., reduction) in the percentage change from baseline for LDL-c at Week 20 when compared to

placebo. This analysis was repeated utilizing the PPS, and the conclusions were consistent. The no-change-from-baseline imputation strategy, implemented by the statistical reviewer for missing data from patients listed in Section 3.2.2.2.5 above, did not impact the study conclusions. There were no patients who were designated as outliers (i.e., by having studentized residual values greater than three). It is important to note that no single site influenced or drove the overall study results.

It can also be observed from Table 9 that the result from the additional sensitivity analysis conducted by the statistical reviewer (i.e., ANCOVA) was consistent with the applicant's pre-specified analysis findings. It should be noted that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were appropriate based on graphically observing residuals in addition to the pertinent normal quantile-quantile plot along with conducting the Kolmogorov-Smirnov test, which resulted in failure to reject the null hypothesis that the underlying distribution of the LDL-c data is normal. The aforementioned ANCOVA procedure being re-conducted on the absolute change from baseline for LDL-c at Week 20 resulted in similar findings. The descriptive results of the responder analysis also suggest sebelipase alfa's positive impact on patients with abnormal baseline LDL-c relative to placebo. All of the previously presented analyses were re-conducted utilizing a traditional baseline definition, as described earlier in Section 3.2.2.2.6 above, with no impact on study conclusions.

Considering the applicant's pre-specified step-down/closed sequential testing procedure as previously described in Section 3.2.2.2.2, formal hypothesis testing can subsequently be continued for percentage change from baseline to Week 20 in non-HDL-c.

Table 10
Summary of Change from Baseline to Week 20 in non-HDL-c – LAL-CL02
(FAS)

Time Point	Sebelipase Alfa (N = 36)	Placebo (N = 30)	Treatment Difference (Sebelipase Alfa – Placebo)
Baseline non-HDL-c (mg/dL)			
n	36	30	
Mean (SD)	220.5 (61.48)	263.8 (75.48)	
Median	223.5	241.5	
Min, Max	93, 332	155, 408	
Week 20 non-HDL-c (mg/dL)			
N	36	30	
Mean (SD)	161.9 (69.61)	242.8 (66.82)	
Median	158.0	229.0	
Min, Max	55, 378	127, 424	
Absolute Change from Baseline to Week 20 (mg/dL)			
n	36	30	
Mean (SD)	-58.6 (44.44)	-21.0 (35.22)	
Median	-55.5	-16.5	
Min, Max	-138, 98	-122, 16	
Difference in LS Means (SEM) [1]			-46.8 (9.42)
Corresponding 95% CI [1]			-65.26, -28.34
p-value [1]			<0.0001
Percentage Change from Baseline to Week 20 (%)			
n	36	30	
Mean (SD)	-28.0 (18.61)	-6.9 (10.92)	
Median	-26.4	-6.0	
Min, Max	-53, 35	-31, 7	
Difference in Means			-21.0
p-value [2]			<0.0001
Difference in LS Means (SEM) [1]			-21.0 (3.53)
Corresponding 95% CI [1]			-27.92, -14.08
p-value [1]			<0.0001

Source: Reviewer's Table generated from ADBLB dataset.

Note: LS = least squares; SEM = standard error of the LS mean.

[1]: Derived from ANCOVA model adjusted for age post-screening/pre-randomization (<12 years, ≥12 years), average screening ALT level (<3×upper limit of normal [ULN], ≥3×ULN), use of lipid lowering medications (LLM) at baseline (yes, no), and baseline non-HDL-c concentration.

[2]: Corresponding to unadjusted Wilcoxon Rank Sum Test, which was the applicant's pre-specified analysis.

It can be observed from Table 10 above that sebelipase alfa showed superior improvement (i.e., reduction) in the percentage change from baseline for non-HDL-c at Week 20 when compared to placebo. This analysis was repeated utilizing the PPS, and the conclusions were consistent. The no-change-from-baseline imputation strategy, implemented by the statistical reviewer for missing data from patients listed in Section 3.2.2.2.5 above, did not impact the study conclusions. There were no patients who were designated as outliers (i.e., by having studentized

residual values greater than three). It is important to note that no single site influenced or drove the overall study results.

It can also be observed from Table 10 that the result from the additional sensitivity analysis conducted by the statistical reviewer (i.e., ANCOVA) was consistent with the applicant's pre-specified analysis findings. It should be noted that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were appropriate based on graphically observing residuals in addition to the pertinent normal quantile-quantile plot along with conducting the Kolmogorov-Smirnov test, which resulted in failure to reject the null hypothesis that the underlying distribution of the non-HDL-c data is normal. The aforementioned ANCOVA procedure being re-conducted on the absolute change from baseline for non-HDL-c at Week 20 resulted in similar findings. All of the previously presented analyses were re-conducted utilizing a traditional baseline definition, as described earlier in Section 3.2.2.2.6 above, with no impact on study conclusions.

Considering the applicant's pre-specified step-down/closed sequential testing procedure as previously described in Section 3.2.2.2.2, formal hypothesis testing can subsequently be continued for AST normalization at Week 20.

Table 11
Proportion of Patients who Achieved AST Normalization at Week 20 – LAL-CL02 (FAS)

	Sebelipase Alfa (N = 36)	Placebo (N = 30)	Treatment Difference (%) (Sebelipase Alfa – Placebo)
AST Normalization at Week 20 – n (%)	15 (41.7%)	1 (3.3%)	38.4%
Corresponding 95% CI			21.1%, 55.7%
Fisher's Exact Test p-value [1]			0.0003
CMH Test p-value			0.0037
Corresponding Breslow-Day Test p-value			0.6045

Source: Reviewer's Table generated from ADBLB dataset.

Note: Denominators for percentages are N.

[1]: The applicant's pre-specified analysis.

It can be observed from Table 11 above that sebelipase alfa showed a superior difference in the proportion/percentage of patients achieving AST normalization at Week 20 when compared to placebo. This analysis was repeated utilizing the PPS, and the conclusions were consistent. The worse-case imputation strategy, implemented by the statistical reviewer for missing data from patients listed in Section 3.2.2.2.5 above, did not impact the study conclusions. It is important to note that no single site influenced or drove the overall study results. It can also be observed from Table 11 that the result from the additional sensitivity analysis conducted by the statistical reviewer (i.e., the CMH test) was consistent with the applicant's pre-specified analysis findings. The corresponding Breslow-Day test result shows that the treatment effect is homogeneous across the different randomization strata. Considering the applicant's pre-specified step-down/closed sequential testing procedure as previously described in Section 3.2.2.2.2, formal

hypothesis testing can subsequently be continued for percentage change from baseline to Week 20 in triglycerides.

Table 12
Summary of Change from Baseline to Week 20 in Triglycerides – LAL-CL02 (FAS)

Time Point	Sebelipase Alfa (N = 36)	Placebo (N = 30)	Treatment Difference (Sebelipase Alfa – Placebo)
Baseline Triglycerides (mg/dL)			
n	36	30	
Mean (SD)	152.8 (54.43)	174.4 (65.90)	
Median	138.0	170.0	
Min, Max	65, 307	66, 361	
Week 20 Triglycerides (mg/dL)			
n	36	30	
Mean (SD)	115.8 (54.11)	148.4 (58.62)	
Median	114.0	139.0	
Min, Max	35, 245	60, 301	
Absolute Change from Baseline to Week 20 (mg/dL)			
n	36	30	
Mean (SD)	-37.1 (48.72)	-26.1 (51.72)	
Median	-39.5	-24.0	
Min, Max	-145, 73	-129, 108	
Difference in LS Means (SEM) [1]			-20.3 (7.28)
Corresponding 95% CI [1]			-34.57, -6.03
p-value [1]			0.0311
Percentage Change from Baseline to Week 20 (%)			
n	36	30	
Mean (SD)	-25.5 (29.41)	-11.1 (28.83)	
Median	-32.4	-14.9	
Min, Max	-67, 59	-51, 56	
Difference in Means			-14.3
p-value [2]			0.0375
Difference in LS Means (SEM) [1]			-12.9 (5.21)
Corresponding 95% CI [1]			-23.11, -2.69
p-value [1]			0.0435

Source: Reviewer's Table generated from ADBLB dataset.

Note: LS = least squares; SEM = standard error of the LS mean.

[1]: Derived from ANCOVA model adjusted for age post-screening/pre-randomization (<12 years, ≥12 years), average screening ALT level (<3×upper limit of normal [ULN], ≥3×ULN), use of lipid lowering medications (LLM) at baseline (yes, no), and baseline Triglyceride concentration.

[2]: Corresponding to unadjusted Wilcoxon Rank Sum Test, which was the applicant's pre-specified analysis.

It can be observed from Table 12 above that sebelipase alfa showed superior improvement (i.e., reduction), albeit marginally, in the percentage change from baseline for Triglycerides at Week 20 when compared to placebo. This analysis was repeated utilizing the PPS, and the conclusions were consistent. The no-change-from-baseline imputation strategy, implemented by the

statistical reviewer for missing data from patients listed in Section 3.2.2.2.5 above, did not impact the study conclusions. There were no patients who were designated as outliers (i.e., by having studentized residual values greater than three). It is important to note that no single site influenced or drove the overall study results.

It can also be observed from Table 12 that the result from the additional sensitivity analysis conducted by the statistical reviewer (i.e., ANCOVA) was consistent with the applicant's pre-specified analysis findings. It should be noted that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were appropriate based on graphically observing residuals in addition to the pertinent normal quantile-quantile plot along with conducting the Kolmogorov-Smirnov test, which resulted in failure to reject the null hypothesis that the underlying distribution of the Triglyceride data is normal. The aforementioned ANCOVA procedure being re-conducted on the absolute change from baseline for Triglycerides at Week 20 resulted in similar findings. All of the previously presented analyses were re-conducted utilizing a traditional baseline definition, as described earlier in Section 3.2.2.2.6 above, with no impact on study conclusions.

Due to this positive, albeit marginal, formal hypothesis test result, and considering the applicant's pre-specified step-down/closed sequential testing procedure as previously described in Section 3.2.2.2.2, formal hypothesis testing can subsequently be continued for percentage change from baseline to Week 20 in HDL-c.

Table 13
Summary of Change from Baseline to Week 20 in HDL-c – LAL-CL02
(FAS)

Time Point	Sebelipase Alfa (N = 36)	Placebo (N = 30)	Treatment Difference (Sebelipase Alfa – Placebo)
Baseline HDL-c (mg/dL)			
n	36	30	
Mean (SD)	32.4 (7.09)	33.4 (7.46)	
Median	32.0	33.5	
Min, Max	18, 48	16, 47	
Week 20 HDL-c (mg/dL)			
N	36	30	
Mean (SD)	38.1 (9.54)	33.5 (8.75)	
Median	36.0	35.0	
Min, Max	22, 72	19, 49	
Absolute Change from Baseline to Week 20 (mg/dL)			
n	36	30	
Mean (SD)	5.7 (5.91)	0.1 (3.71)	
Median	5.0	0.0	
Min, Max	-10, 24	-7, 7	
Difference in LS Means (SEM) [1]			5.7 (1.24)
Corresponding 95% CI [1]			3.27, 8.13
p-value [1]			<0.0001
Percentage Change from Baseline to Week 20 (%)			
n	36	30	
Mean (SD)	19.6 (16.83)	-0.3 (12.36)	
Median	19.1	1.2	
Min, Max	-24, 66	-25, 21	
Difference in Means			19.9
p-value [2]			<0.0001
Difference in LS Means (SEM) [1]			18.5 (3.61)
Corresponding 95% CI [1]			11.42, 25.58
p-value [1]			<0.0001

Source: Reviewer's Table generated from ADBLB dataset.

Note: LS = least squares; SEM = standard error of the LS mean.

[1]: Derived from ANCOVA model adjusted for age post-screening/pre-randomization (<12 years, ≥12 years), average screening ALT level (<3×upper limit of normal [ULN], ≥3×ULN), use of lipid lowering medications (LLM) at baseline (yes, no), and baseline HDL-c concentration.

[2]: Corresponding to unadjusted Wilcoxon Rank Sum Test, which was the applicant's pre-specified analysis.

It can be observed from Table 13 above that sebelipase alfa showed superior improvement (i.e., increase) in the percentage change from baseline for HDL-c at Week 20 when compared to placebo. This analysis was repeated utilizing the PPS, and the conclusions were consistent. The no-change-from-baseline imputation strategy, implemented by the statistical reviewer for missing data from patients listed in Section 3.2.2.2.5 above, did not impact the study conclusions. There were no patients who were designated as outliers (i.e., by having studentized

residual values greater than three). It is important to note that no single site influenced or drove the overall study results.

It can also be observed from Table 13 that the result from the additional sensitivity analysis conducted by the statistical reviewer (i.e., ANCOVA) was consistent with the applicant's pre-specified analysis findings. It should be noted that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were appropriate based on graphically observing residuals in addition to the pertinent normal quantile-quantile plot along with conducting the Kolmogorov-Smirnov test, which resulted in failure to reject the null hypothesis that the underlying distribution of the HDL-c data is normal. The aforementioned ANCOVA procedure being re-conducted on the absolute change from baseline for HDL-c at Week 20 resulted in similar findings. All of the previously presented analyses were re-conducted utilizing a traditional baseline definition, as described earlier in Section 3.2.2.2.6 above, with no impact on study conclusions.

Considering the applicant's pre-specified step-down/closed sequential testing procedure as previously described in Section 3.2.2.2.2, formal hypothesis testing can subsequently be continued for percentage change from baseline to Week 20 in liver fat content.

Table 14
Summary of Change from Baseline to Week 20 in Liver Fat Content (%) – LAL-CL02
(FAS Patients for whom this Assessment was performed)

Time Point	Sebelipase Alfa (N = 32)	Placebo (N = 25)	Treatment Difference (Sebelipase Alfa – Placebo)
Baseline Liver Fat Content (%)			
n	32	25	
Mean (SD)	8.7 (3.95)	8.2 (2.80)	
Median	7.7	7.9	
Min, Max	3, 25	2, 13	
Week 20 Liver Fat Content (%)			
n	32	25	
Mean (SD)	5.6 (2.15)	8.1 (3.15)	
Median	5.3	8.1	
Min, Max	2, 11	2, 13	
Absolute Change from Baseline to Week 20 (%)			
n	32	25	
Mean (SD)	-3.1 (3.34)	-0.18 (1.06)	
Median	-2.3	-0.0050	
Min, Max	-14, 2	-2, 3	
Difference in LS Means (SEM) [1]			-2.7 (0.501)
Corresponding 95% CI [1]			-3.68, -1.72
p-value [1]			<0.0001
Percentage Change from Baseline to Week 20 (%)			
n	32	25	
Mean (SD)	-32.0 (26.76)	-4.2 (15.56)	
Median	-35.1	-4.1	
Min, Max	-75, 52	-37, 25	
Difference in Means			-27.8
p-value [2]			<0.0001
Difference in LS Means (SEM) [1]			-27.4 (5.55)
Corresponding 95% CI [1]			-38.28, -16.52
p-value [1]			<0.0001

Source: Reviewer's Table generated from ADXM dataset.

Note: This analysis was conducted in the subset of patients for whom this assessment was performed. LS = least squares; SEM = standard error of the LS mean.

[1]: Derived from ANCOVA model adjusted for age post-screening/pre-randomization (<12 years, ≥12 years), average screening ALT level (<3×upper limit of normal [ULN], ≥3×ULN), use of lipid lowering medications (LLM) at baseline (yes, no), and baseline liver fat content (as a percentage).

[2]: Corresponding to unadjusted Wilcoxon Rank Sum Test, which was the applicant's pre-specified analysis.

It can be observed from Table 14 above that sebelipase alfa showed superior improvement (i.e., reduction) in the percentage change from baseline for liver fat content (as a percentage) at Week 20 when compared to placebo. Note that this analysis was conducted in the subset of patients for whom this assessment was performed. This analysis was repeated utilizing the PPS, and the conclusions were consistent. The no-change-from-baseline imputation strategy, implemented by the statistical reviewer for missing data from patients listed in Section 3.2.2.2.5 above, did not

impact the study conclusions. There were no patients who were designated as outliers (i.e., by having studentized residual values greater than three). It is important to note that no single site influenced or drove the overall study results.

It can also be observed from Table 14 that the result from the additional sensitivity analysis conducted by the statistical reviewer (i.e., ANCOVA) was consistent with the applicant's pre-specified analysis findings. It should be noted that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were appropriate based on graphically observing residuals in addition to the pertinent normal quantile-quantile plot along with conducting the Kolmogorov-Smirnov test, which resulted in failure to reject the null hypothesis that the underlying distribution of the liver fat content (as a percentage) data is normal. The aforementioned ANCOVA procedure being re-conducted on the absolute change from baseline for liver fat content (as a percentage) at Week 20 resulted in similar findings. All of the previously presented analyses were re-conducted utilizing a traditional baseline definition, as described earlier in Section 3.2.2.2.6 above, with no impact on study conclusions.

Considering the applicant's pre-specified step-down/closed sequential testing procedure as previously described in Section 3.2.2.2.2, formal hypothesis testing can subsequently be continued for improvement in liver histopathology at Week 20.

Table 15
Proportion of Patients who Achieved Improvement in Liver Histopathology at Week 20 –
LAL-CL02
(FAS Patients for whom this Assessment was performed)

	Sebelipase Alfa (N = 16)	Placebo (N = 10)	Treatment Difference (%) (Sebelipase Alfa – Placebo)
Liver Histopathology Improvement at Week 20 – n (%)	10 (62.5%)	4 (40.0%)	22.5%
Corresponding 95% CI			-16.0%, 61.0%
Fisher's Exact Test p-value [1]			0.4216
CMH Test p-value			0.2552
Corresponding Breslow-Day Test p-value			0.0573

Source: Reviewer's Table generated from ADXP dataset.

Note: This analysis was conducted in the subset of patients for whom this assessment was performed.

Denominators for percentages are N.

[1]: The applicant's pre-specified analysis.

It can be observed from Table 15 above that there was no difference in the proportion/percentage of patients achieving improvement in liver histopathology at Week 20 between sebelipase alfa and placebo. Note that this analysis was conducted in the subset of patients for whom this assessment was performed. This analysis was repeated utilizing the PPS, and the conclusions were consistent. The worse-case imputation strategy, implemented by the statistical reviewer for missing data from patients listed in Section 3.2.2.2.5 above, did not impact the study conclusions. It is important to note that no single site influenced or drove the overall study

results. It can also be observed from Table 15 that the result from the additional sensitivity analysis conducted by the statistical reviewer (i.e., the CMH test) was consistent with the applicant's pre-specified analysis findings. The corresponding Breslow-Day test result shows that the lack of treatment effect is homogeneous across the different randomization strata. Due to this negative formal hypothesis test result, and considering the applicant's pre-specified step-down/closed sequential testing procedure as previously described in Section 3.2.2.2.2, formal hypothesis testing is stopped at this point. Hypothesis testing for the subsequent endpoint (i.e., percentage change from baseline to Week 20 in liver volume) is deemed as exploratory.

Table 16
Summary of Change from Baseline to Week 20 in Liver Volume (MN) – LAL-CL02
(FAS Patients for whom this Assessment was performed)

Time Point	Sebelipase Alfa (N = 33)	Placebo (N = 27)	Treatment Difference (Sebelipase Alfa – Placebo)
Baseline Liver Fat Content (%)			
n	33	27	
Mean (SD)	1.4 (0.41)	1.5 (0.31)	
Median	1.4	1.4	
Min, Max	1, 3	1, 2	
Week 20 Liver Fat Content (%)			
n	33	27	
Mean (SD)	1.3 (0.30)	1.5 (0.29)	
Median	1.25	1.5	
Min, Max	1, 2	1, 2	
Absolute Change from Baseline to Week 20 (%)			
n	33	27	
Mean (SD)	-0.16 (0.18)	-0.04 (0.15)	
Median	-0.18	-0.04	
Min, Max	-1, 0	-0.4, 0.3	
Difference in LS Means (SEM) [1]			-0.14 (0.035)
Corresponding 95% CI [1]			-0.21, -0.07
p-value [1]			0.0001
Percentage Change from Baseline to Week 20 (%)			
n	33	27	
Mean (SD)	-10.3 (10.51)	-2.7 (10.11)	
Median	-11.7	-4.6	
Min, Max	-36, 12	-22, 19	
Difference in Means			-7.6
p-value [2]			0.0068
Difference in LS Means (SEM) [1]			-7.6 (2.55)
Corresponding 95% CI [1]			-12.60, -2.60
p-value [1]			0.0043

Source: Reviewer's Table generated from ADXM dataset.

Note: This analysis was conducted in the subset of patients for whom this assessment was performed. MN = Multiples of Normal; LS = least squares; SEM = standard error of the LS mean.

[1]: Derived from ANCOVA model adjusted for age post-screening/pre-randomization (<12 years, ≥12 years), average screening ALT level (<3×upper limit of normal [ULN], ≥3×ULN), use of lipid lowering medications (LLM) at baseline (yes, no), and baseline liver volume (in MN).

[2]: Corresponding to unadjusted Wilcoxon Rank Sum Test, which was the applicant's pre-specified analysis.

It can be observed from Table 16 above that sebelipase alfa showed, in an exploratory context, superior improvement (i.e., reduction) in the percentage change from baseline for liver volume (in MN) at Week 20 when compared to placebo. Note that this analysis was conducted in the subset of patients for whom this assessment was performed. This analysis was repeated utilizing the PPS, and the conclusions were consistent. The no-change-from-baseline imputation strategy, implemented by the statistical reviewer for missing data from patients listed in Section 3.2.2.2.5

above, did not impact the study conclusions. There were no patients who were designated as outliers (i.e., by having studentized residual values greater than three). It is important to note that no single site influenced or drove the overall study results.

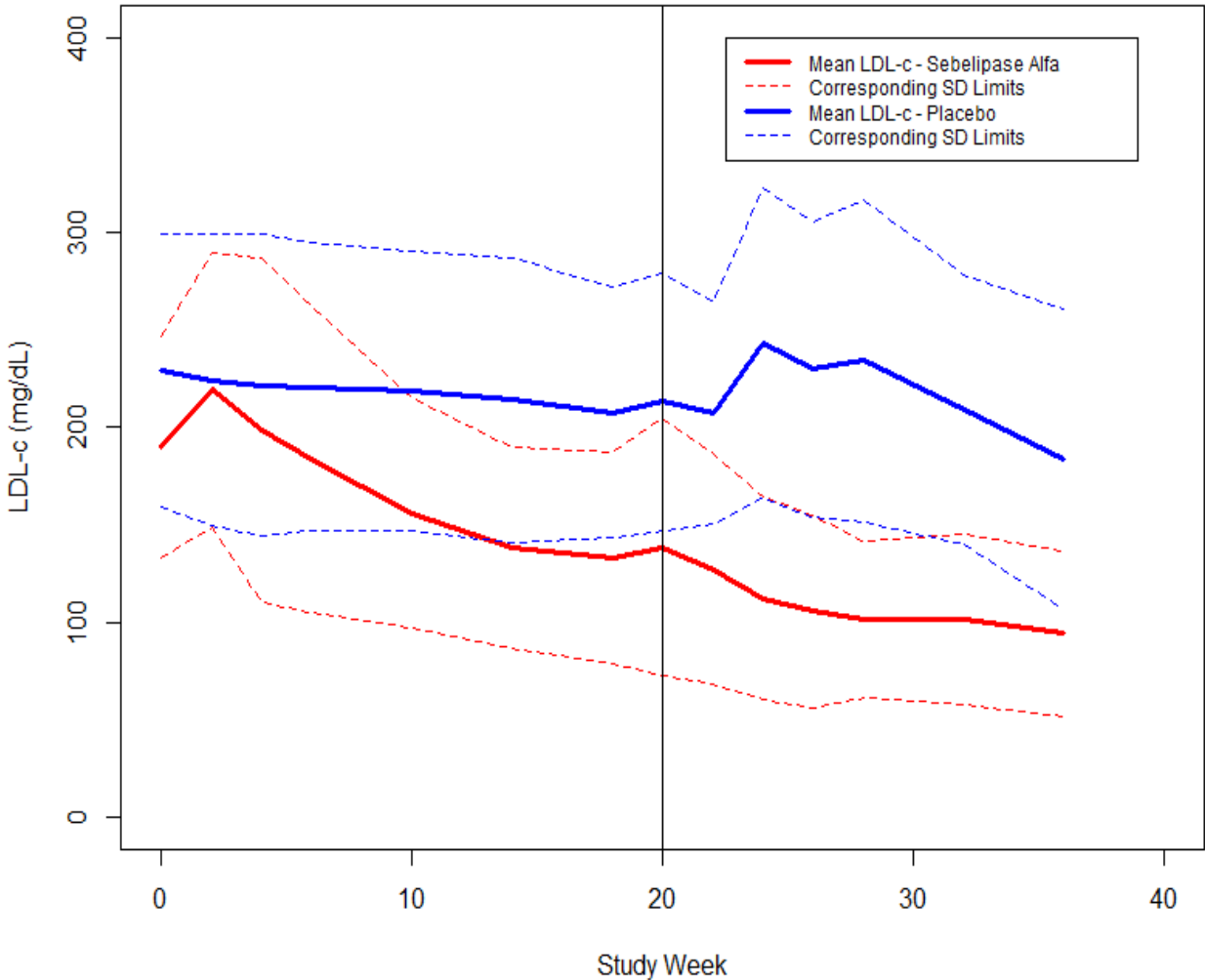
It can also be observed from Table 16 that the result from the additional sensitivity analysis conducted by the statistical reviewer (i.e., ANCOVA) was consistent with the applicant's pre-specified analysis findings. It should be noted that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were appropriate based on graphically observing residuals in addition to the pertinent normal quantile-quantile plot along with conducting the Kolmogorov-Smirnov test, which resulted in failure to reject the null hypothesis that the underlying distribution of the liver volume (in MN) data is normal. The aforementioned ANCOVA procedure being re-conducted on the absolute change from baseline for liver volume (in MN) at Week 20 resulted in similar findings. All of the previously presented analyses were re-conducted utilizing a traditional baseline definition, as described earlier in Section 3.2.2.2.6 above, with no impact on study conclusions. It should again be emphasized that these analysis results are exploratory in nature.

As stated previously in Section 3.2.2.1, after Week 20 assessments were completed, each patient was offered to continue in an open-label treatment period where all patients would receive sebelipase alfa at a dose of 1 mg/kg from post-Week 20 (i.e., Day 1 of the open-label treatment period) through study completion. It can be seen from Section 3.2.2.3 above that all patients completing the double-blind treatment period (i.e., 65 out of the 66 total patients who were randomized) also participated in the open-label treatment period. The duration of each patient's treatment in the study was expected to be at least 78 weeks, and patients were allowed to continue receiving treatment in the study for up to 150 weeks. This open-label treatment period is currently ongoing.

Figures 5, 6, 7, and 8 below present raw values of the clinically meaningful efficacy parameters (as adjudicated by the clinical review team; previously stated above in Section 3.2.2.1) LDL-c, non-HDL-c, triglycerides, and HDL-c, respectively, from baseline through Week 36. Note that patients who were randomized at baseline to receive placebo for the double-blind treatment period are displayed as 'Placebo' patients within these figures although they all began the sebelipase alfa treatment after Week 20. It can be seen that patients who were randomized at baseline to sebelipase alfa for the double-blind treatment period seemed to maintain, or even further improve, their LDL-c, non-HDL-c, triglycerides, and HDL-c values after Week 20. It can also be seen that patients who were randomized at baseline to placebo for the double-blind treatment period seemed to ultimately reverse (i.e., start improving) their LDL-c, non-HDL-c, triglycerides, and HDL-c values sometime after Week 20 when these patients began exclusive treatment with sebelipase alfa. It should be noted that increases in circulating cholesterol and triglycerides (i.e., hyperlipidemia) are observed in all of these figures following the initiation of sebelipase alfa in both groups, as can be seen by spikes in the lipid parameter values shortly after sebelipase alfa initiation. These increases generally occurred within the first two to four weeks and improved within eight weeks of sebelipase alfa treatment. This observed phenomenon was expected and is considered normal by the clinical review team given the nature of CESD, i.e., the pent up storage of the cholesterol and triglycerides within the cells, due to CESD, are all of a sudden being mobilized out of storage and into the blood stream by sebelipase alfa. This

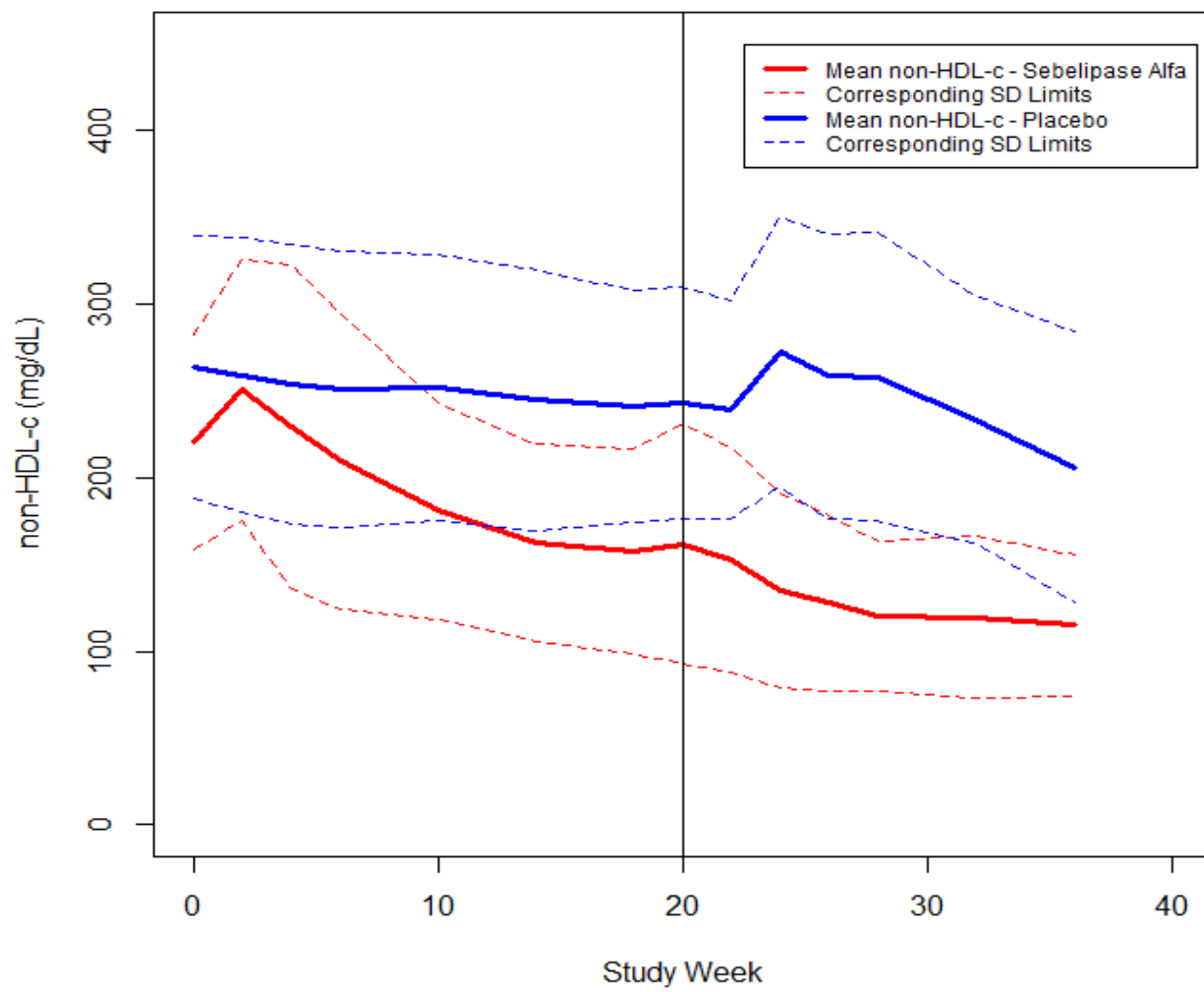
phenomenon actually confirms the mechanism of action and hypothesized treatment effect of sebelipase alfa.

Figure 5
Mean ($\pm$ SD) LDL-c over Time – LAL-CL02
(FAS)



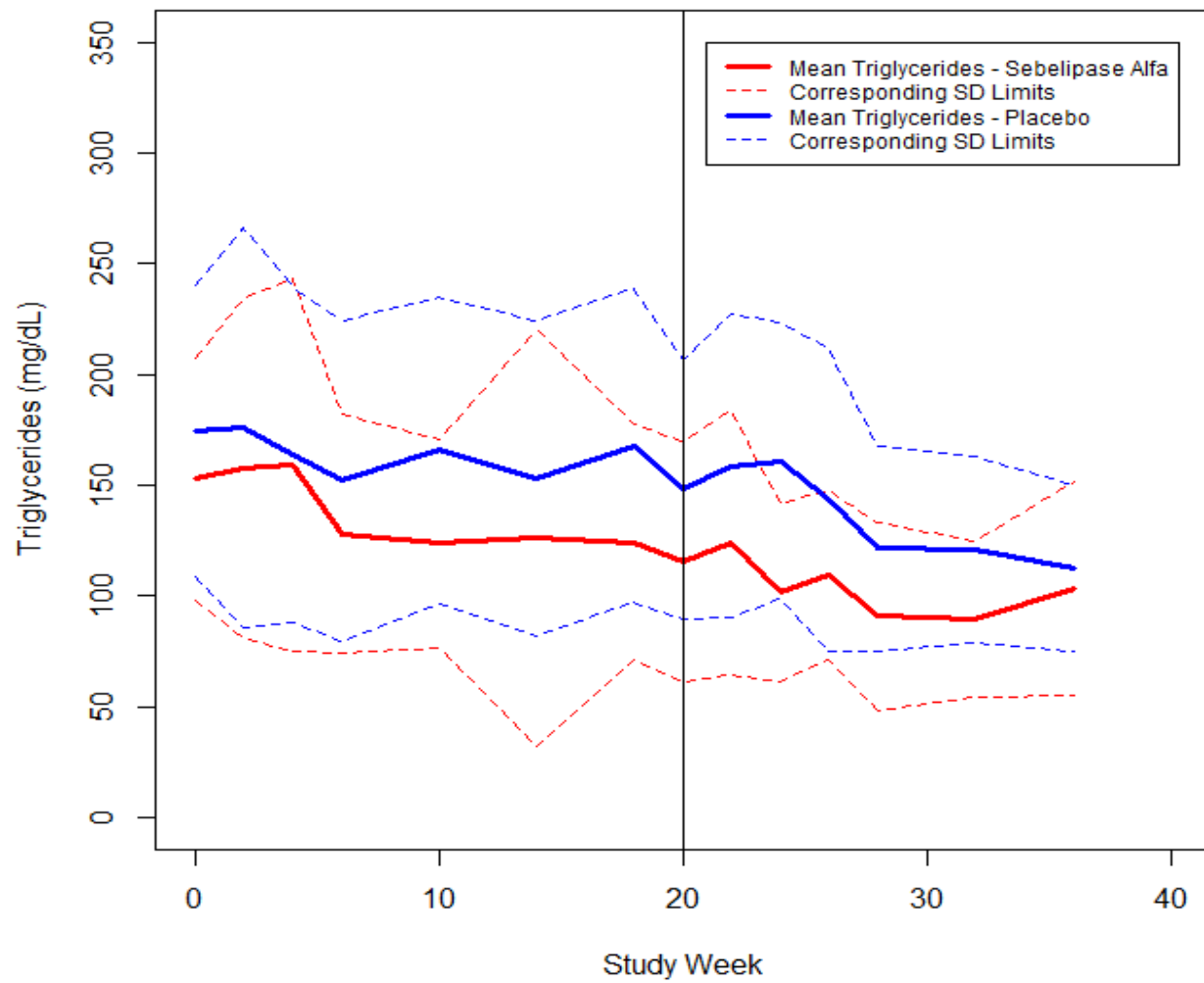
Source: Reviewer’s Figure using R generated from ADBLB dataset.

Figure 6
Mean ($\pm$ SD) non-HDL-c over Time – LAL-CL02
(FAS)



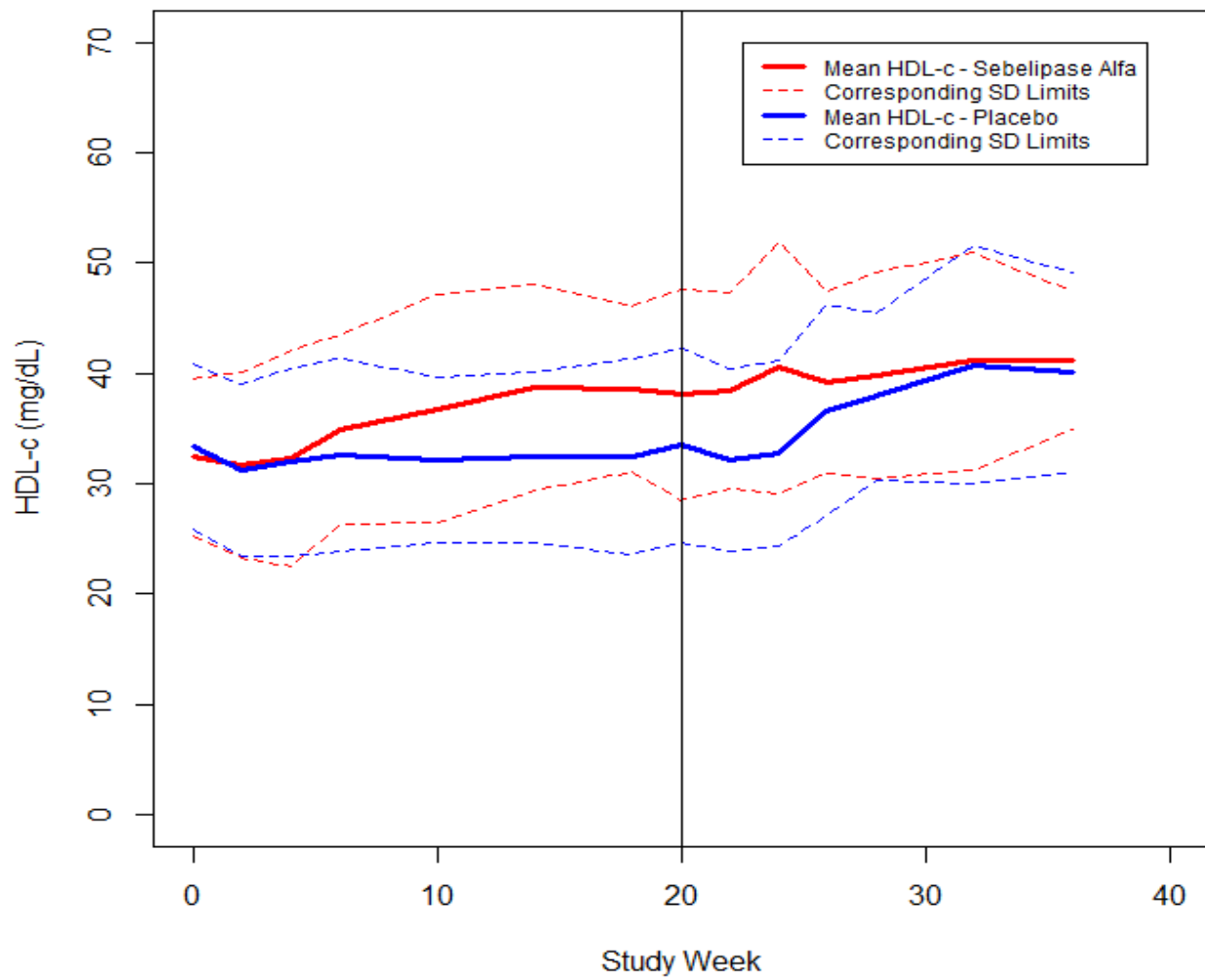
Source: Reviewer's Figure using R generated from ADBLB dataset.

Figure 7
Mean ($\pm$ SD) Triglycerides over Time – LAL-CL02
(FAS)



Source: Reviewer's Figure using R generated from ADBLB dataset.

Figure 8
Mean ($\pm$ SD) HDL-c over Time – LAL-CL02
(FAS)



Source: Reviewer's Figure using R generated from ADBLB dataset.

3.3 Evaluation of Safety

The safety summary by study, presented below, is described in the applicant's respective CSRs. The relatively mild adverse events observed during the clinical development program along with the low risk in developing any type of anti-drug antibody (ADA) indicate the overall low risk associated with sebelipase alfa treatment. Please see Section 7 of both clinical review documents for the full details regarding the safety profile of sebelipase alfa in Wolman and CESD patients, respectively.

3.3.1 Study LAL-CL03

Sebelipase alfa was reasonably tolerated by patients during the LAL-CL03 study. There were no drug-related deaths in the study. Only one (11%) patient experienced a drug-related serious adverse event (SAE), which was an infusion-associated reaction (IAR). The most common treatment-emergent adverse events (TEAEs) with sebelipase alfa (i.e., those occurring in $\geq 30\%$ of patients treated with sebelipase alfa) were diarrhea (67%), vomiting (67%), fever (56%), rhinitis (56%), anemia (44%), cough (33%), nasopharyngitis (33%), and urticarial (33%). Seven of the nine patients were formally tested for ADAs, and four of them (57%) were determined to be ADA-positive at some point during sebelipase alfa treatment. For three of these four ADA-positive patients, ADA titers decreased to undetectable levels by the last time point assessed. Only one of these four ADA-positive patients had persistent ADA titers. Two of these four ADA-positive patients developed neutralizing antibodies during sebelipase alfa treatment, with decreased efficacy surmised for only one of these two patients.

3.3.2 Study LAL-CL02

Sebelipase alfa was well tolerated by patients during the LAL-CL02 study. There were no deaths in the study. The incidence of severe TEAEs and SAEs was low and similar in the sebelipase alfa and placebo groups during the double-blind treatment period. Three (8%) and one (3%) patients, respectively, experienced a severe TEAE and two (6%) and one (3%) patients, respectively, experienced an SAE. No specific SAE was reported in more than one patient. One sebelipase alfa patient (3%), patient (b) (6) discontinued study treatment due to an IAR within the double-blind treatment period. The most common TEAEs with sebelipase alfa (i.e., those occurring in $\geq 10\%$ of patients treated with sebelipase alfa) during the double-blind treatment period were headache (28%), fever (25%), oropharyngeal pain (17%), and nasopharyngitis (11%). All occurrences of these events were deemed unrelated to study drug. Including data from the open-label treatment period, five of 66 patients (8%) exposed to sebelipase alfa were determined to be ADA-positive at some point during the study. Among these ADA-positive patients, ADA titers were low and decreased to undetectable levels by the last time point assessed. Two of these five patients did develop neutralizing antibodies during the open-label treatment period; however, there was no association between the neutralizing ADA and decreased efficacy in these patients. When data from the open-label treatment period are considered, the overall safety profile of sebelipase alfa is consistent with that seen during the double-blind treatment period.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses were conducted only for the LAL-CL02 study. The limited number of patients from the LAL-CL03 study precluded any meaningful subgroup analysis. All LAL-CL02 subgroup analyses are descriptive in nature, and correspond exclusively to the parameter deemed most clinically meaningful by the clinical review team (as previously explained in Section 3.2.2.1 above), i.e., LDL-c. Consequently, all subgroup analysis results formally presented in tables within this section correspond to LDL-c alone.

4.1 Gender, Race, Age and Geographical Region

4.1.1 Study LAL-CL03/LAL-1-NH01

As stated above, no subgroup analyses were conducted for this study.

4.1.2 Study LAL-CL02

As can be observed from Table 7 above, the overwhelming majority (i.e., $\geq 80\%$) of study participants was white; hence, no subgroup analysis for race was conducted. In addition, due to limited number of patients along with the heterogeneity of countries making up the ‘other’ geographical region category (i.e., Argentina, Australia, Japan and Mexico), the ‘other’ category was not included in the subgroup analysis for geographical region.

The gender subgroup analysis results are presented in Table 17 below. It appears that results were consistent across the gender subgroups, and consistent with the overall population as seen in Table 9 above.

Table 17
Summary of Change from Baseline to Week 20 in LDL-c by Gender – LAL-CL02
(FAS)

Timepoint/ Treatment Group	n	Mean	SD	Median	Min	Max
<i>Female</i>						
Baseline LDL-c (mg/dL)						
Placebo	15	240.5	66.52	248.0	135	363
Sebelipase Alfa	18	195.6	61.58	200.5	70	280
Week 20 LDL-c (mg/dL)						
Placebo	15	221.4	56.28	244.0	99	287
Sebelipase Alfa	18	136.6	55.57	138.5	44	248
Absolute Change from Baseline to Week 20 (mg/dL)						
Placebo	15	-19.1	37.81	-18.0	-119	32
Sebelipase Alfa	18	-59.1	37.26	-53.5	-130	16
Percentage Change from Baseline to Week 20 (%)						
Placebo	15	-7.0	13.46	-8.5	-33	16
Sebelipase Alfa	18	-30.6	16.82	-28.7	-54	12
<i>Male</i>						
Baseline LDL-c (mg/dL)						
Placebo	15	218.5	73.83	193.0	145	378
Sebelipase Alfa	18	184.2	53.52	185.5	79	273
Week 20 LDL-c (mg/dL)						
Placebo	15	205.3	75.58	187.0	114	408
Sebelipase Alfa	18	140.8	77.10	124.5	32	348
Absolute Change from Baseline to Week 20 (mg/dL)						
Placebo	15	-13.2	32.41	-1.0	-81	30
Sebelipase Alfa	18	-43.4	52.10	-52.0	-123	109
Percentage Change from Baseline to Week 20 (%)						
Placebo	15	-5.7	12.94	-0.5	-30	8
Sebelipase Alfa	18	-26.4	26.93	-28.6	-59	46

Source: Reviewer's Table generated from ADBLB dataset.

The age subgroup analysis results are presented in Table 18 below. It appears that results were consistent across the age subgroups, and consistent with the overall population as seen in Table 9 above.

Table 18
Summary of Change from Baseline to Week 20 in LDL-c by Age – LAL-CL02
(FAS)

Timepoint/ Treatment Group	n	Mean	SD	Median	Min	Max
<i>< 12 years</i>						
Baseline LDL-c (mg/dL)						
Placebo	10	227.2	58.07	209.0	160	330
Sebelipase Alfa	14	202.0	42.84	192.5	138	273
Week 20 LDL-c (mg/dL)						
Placebo	10	221.6	42.89	224.5	162	287
Sebelipase Alfa	14	169.5	69.78	156.0	84	348
Absolute Change from Baseline to Week 20 (mg/dL)						
Placebo	10	-5.6	30.14	2.5	-70	32
Sebelipase Alfa	14	-32.5	51.48	-42.0	-116	109
Percentage Change from Baseline to Week 20 (%)						
Placebo	10	-0.8	11.11	1.6	-21	16
Sebelipase Alfa	14	-17.0	24.63	-23.6	-54	46
<i>≥ 12 years</i>						
Baseline LDL-c (mg/dL)						
Placebo	20	230.6	76.59	219.0	135	378
Sebelipase Alfa	22	182.2	64.42	195.0	70	280
Week 20 LDL-c (mg/dL)						
Placebo	20	209.2	75.64	189.0	99	408
Sebelipase Alfa	22	119.0	57.16	111.0	32	239
Absolute Change from Baseline to Week 20 (mg/dL)						
Placebo	20	-21.4	36.37	-15.5	-119	30
Sebelipase Alfa	22	-63.2	37.44	-60.5	-130	0
Percentage Change from Baseline to Week 20 (%)						
Placebo	20	-9.1	13.23	-8.5	-33	10
Sebelipase Alfa	22	-35.8	17.42	-41.7	-59	0

Source: Reviewer's Table generated from ADBLB dataset.

The geographical region subgroup analysis results are presented in Table 19 below. It appears that results were consistent across the geographical region subgroups, and consistent with the overall population as seen in Table 9 above.

Table 19
Summary of Change from Baseline to Week 20 in LDL-c by Geographical Region – LAL-CL02 (FAS)

Timepoint/ Treatment Group	n	Mean	SD	Median	Min	Max
<i>Europe</i>						
Baseline LDL-c (mg/dL)						
Placebo	21	236.4	71.09	231.0	145	378
Sebelipase Alfa	18	165.5	56.59	159.5	70	250
Week 20 LDL-c (mg/dL)						
Placebo	21	226.2	69.00	220.0	132	408
Sebelipase Alfa	18	119.7	54.53	126.0	32	224
Absolute Change from Baseline to Week 20 (mg/dL)						
Placebo	21	-10.2	27.39	-7.0	-70	30
Sebelipase Alfa	18	-45.8	32.85	-46.0	-123	16
Percentage Change from Baseline to Week 20 (%)						
Placebo	21	-3.8	9.86	-3.0	-23	10
Sebelipase Alfa	18	-29.0	19.80	-28.6	-59	12
<i>North America</i>						
Baseline LDL-c (mg/dL)						
Placebo	6	189.3	31.00	202.5	135	213
Sebelipase Alfa	10	212.8	52.21	213.5	131	280
Week 20 LDL-c (mg/dL)						
Placebo	6	184.0	46.66	188.0	99	237
Sebelipase Alfa	10	149.3	58.68	152.5	67	248
Absolute Change from Baseline to Week 20 (mg/dL)						
Placebo	6	-5.3	25.53	-10.5	-36	32
Sebelipase Alfa	10	-63.5	44.23	-53.5	-130	0
Percentage Change from Baseline to Week 20 (%)						
Placebo	6	-3.8	15.17	-5.2	-27	16
Sebelipase Alfa	10	-30.8	19.57	-33.3	-56	0

Source: Reviewer's Table generated from ADBLB dataset.

4.2 Other Special Subgroup Populations

The special subgroup population of clinical interest pertained to the baseline usage of LLM (yes, no) in the LAL-CL02 study.

4.2.1 Study LAL-CL03/LAL-1-NH01

As stated above, no subgroup analyses were conducted for this study.

4.2.2 Study LAL-CL02

The LLM usage at baseline subgroup analysis results are presented in Table 20 below. It appears that results were consistent across the LLM usage at baseline subgroups, and consistent with the overall population as seen in Table 9 above.

Table 20
Summary of Change from Baseline to Week 20 in LDL-c by Baseline Usage of LLM –
LAL-CL02
(FAS)

Timepoint/ Treatment Group	n	Mean	SD	Median	Min	Max
<i>LLM Usage at Baseline</i>						
Baseline LDL-c (mg/dL)						
Placebo	11	196.4	66.71	173.0	135	363
Sebelipase Alfa	14	163.1	59.65	151.5	79	271
Week 20 LDL-c (mg/dL)						
Placebo	11	174.6	52.70	177.0	99	272
Sebelipase Alfa	14	105.7	54.06	84.5	32	239
Absolute Change from Baseline to Week 20 (mg/dL)						
Placebo	11	-21.7	40.17	-13.0	-119	24
Sebelipase Alfa	14	-57.4	29.72	-53.5	-113	-13
Percentage Change from Baseline to Week 20 (%)						
Placebo	11	-9.8	15.13	-9.0	-33	10
Sebelipase Alfa	14	-36.8	16.61	-42.5	-59	-9
<i>No LLM Usage at Baseline</i>						
Baseline LDL-c (mg/dL)						
Placebo	19	248.6	65.97	259.0	152	378
Sebelipase Alfa	22	207.0	49.56	214.5	70	280
Week 20 LDL-c (mg/dL)						
Placebo	19	235.7	63.46	237.0	150	408
Sebelipase Alfa	22	159.6	65.76	152.0	44	348
Absolute Change from Baseline to Week 20 (mg/dL)						
Placebo	19	-12.9	31.87	-8.0	-81	32
Sebelipase Alfa	22	-47.4	53.27	-52.5	-130	109
Percentage Change from Baseline to Week 20 (%)						
Placebo	19	-4.3	11.54	-3.0	-30	16
Sebelipase Alfa	22	-23.3	24.06	-25.3	-56	46

Source: Reviewer's Table generated from ADBLB dataset.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Overall, the designs of both the LAL-CL03/LAL-1-NH01 and LAL-CL02 studies were deemed adequate from a statistical perspective for the proposed indication, and the applicant's corresponding SAPs deemed appropriate. There were no statistical review issues identified for this application that would preclude product approval.

For the LAL-CL03/LAL-1-NH01 study, it should be noted that comparisons to a historical control group are not considered to provide results that are as robust or reliable as those from comparisons within a randomized controlled study. Even when there is an observed balance between the non-concurrent groups in regards to identified baseline characteristics/covariates, there may be confounding due to baseline imbalances in latent variables, which can influence outcome to therapy. This potential introduction of bias results from not having a randomization mechanism. In addition, the retrospective nature of the LAL-1-NH01 study introduces the potential for selection bias, i.e., patients ultimately chosen for the historical control group may be those that result in an overly optimistic estimate of efficacy when comparisons are made to the treated patients. Both of these issues are further magnified when operating with very small sample sizes, which is the case for Wolman Disease. Due to the scarcity of this disease population, and the previously discussed limitations of the submitted clinical studies, the determination of the clinical effectiveness of sebelipase alfa will rely more on clinical judgment than on the statistical rigor usually required for larger randomized controlled studies.

5.2 Collective Evidence

The applicant submitted the results from the LAL-CL03 and LAL-CL02 trials to support the efficacy of sebelipase alfa for the treatment of LAL deficiency. For the LAL-CL03 trial, conducted in the Wolman Disease patient population, sebelipase alfa was demonstrated to be superior to an acceptable historical control group, extracted from retrospective natural history study LAL-1-NH01, with respect to survival, i.e., time to death from birth up to Month 12. This result was further supported by longer term survival data. For the LAL-CL02 trial, conducted in the CESD patient population, sebelipase alfa was demonstrated to be superior to placebo in the Week 20 change from baseline in LDL-c, non-HDL-c, triglycerides, and HDL-c. The currently ongoing open-label treatment period suggests a sustained/durable efficacy profile with respect to the aforementioned four parameters.

5.3 Conclusions and Recommendations

There is sufficient evidence in supporting the proposed efficacy claims for sebelipase alfa in the treatment of both Wolman Disease and CESD. The claims reflected within the applicant's submitted product labeling are supported by the results presented in this review. For the CESD patient population, specifically, it is recommended that results from only the following lipid parameters (i.e., LDL-c, non-HDL-c, triglycerides, and HDL-c) be included in the product labeling as these were the only parameters deemed clinically meaningful by the clinical review team.

6 APPENDIX

Table 21
Timeline and Comments for Relevant Meetings under IND 108,460

<u>Milestone</u>	1. July 29, 2010 Pre-IND Meeting	2. June 12, 2012 EOP1 Meeting	3. November 6, 2012 Type C Meeting	4. February 25, 2014 Post Breakthrough Therapy Meeting
<u>Comment</u> (if necessary)	Nonclinical requirements along with dose finding and manufacturing advice, for the overall clinical development program, were communicated to the sponsor. The sponsor agreed to start their clinical trials in older patients (i.e., CESD patients), in order to mitigate risk, before conducting studies for the younger population (i.e., Wolman Disease). In addition, the sponsor agreed to conduct natural history studies for both Wolman Disease and CESD.	Discussions about study design, duration and endpoints were held regarding the LAL-CL02 and LAL-CL03 trials. DGIEP stated that ALT alone would not be sufficient as a basis for approval for the CESD population (i.e., the LAL-CL02 trial).	DGIEP reiterated that ALT alone would not be adequate as a basis for approval for the CESD population, although LDL cholesterol could be so long as sufficient evidence was provided regarding its clinical meaningfulness. DGIEP also stated that demonstration of a survival advantage could be a basis for approval for the Wolman Disease population.	Discussions were held regarding the eventual filing of one BLA covering both the Wolman Disease and CESD patient populations.

<u>Milestone</u>	5. April 1, 2014 Type C Meeting	6. August 15, 2014 Pre-BLA Meeting
<u>Comment</u> (if necessary)	DGIEP stated that the sponsor's biopsy evaluation in CESD patients appears acceptable. DGIEP again reiterated that ALT alone would not be adequate as a basis for approval for the CESD population.	DGIEP communicated its expectations regarding the content and format of the BLA submission.

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/s/

BENJAMIN P VALI
06/12/2015

YEH FONG CHEN
06/12/2015

STATISTICS FILING CHECKLIST FOR A NEW BLA

BLA Number: 125561	Applicant: Synageva BioPharma Corporation	Stamp Date: January 8, 2015
Drug Name: KANUMA™ (sebelipase alfa; SBC-102)	BLA Type: Original Biologic Priority	Indication: (b) (4) (b) (4) for patients with Lysosomal Acid Lipase (LAL) Deficiency

On initial overview of the BLA application for filing:

	Content Parameter for RTF	Yes	No	NA	Comments
1	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			This electronic submission was eCTD compliant and of satisfactory quality.
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)		X		There were adequate and complete clinical study reports (CSRs), which were ICH E3 compliant, along with the ISS submitted. There was no full ISE report submitted in Module 5; however a sufficient summary of efficacy is submitted within Module 2.7.3.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups (if applicable).		X		Subgroup analyses for Gender, Race, and Age were not presented for studies LAL-CL03 and LAL-1-NH01 due to lack of an adequate sample size in this ultra-rare disease. Subgroup analyses for Gender, Race, and Age were presented, however, for study LAL-CL02.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			All data sets provided were of satisfactory quality and were compliant with CDISC data standards (i.e., SDTM and ADaM). Appropriate data definition files in Define.XML and Define.PDF format were included.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

STATISTICS FILING CHECKLIST FOR A NEW BLA

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			The designs utilized for the LAL-CL03, LAL-1-NH01, and LAL-CL02 trials appeared appropriate.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			For the LAL-CL03, LAL-1-NH01, and LAL-CL02 trials, the endpoints and corresponding methods of analysis were pre-specified in the protocols and Statistical Analysis Plans (SAP).
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	There was no formal interim analysis planned for the LAL-CL03, LAL-1-NH01, and LAL-CL02 trials.
Appropriate references for novel statistical methodology (if present) are included.			X	The statistical methodology in the LAL-CL03, LAL-1-NH01, and LAL-CL02 trials did not appear novel, hence no references were presented.
Safety data organized to permit analyses across clinical trials in the NDA.	X			Safety datasets were submitted for each study individually. In addition, ISS datasets were also submitted.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		The sponsor did not investigate the effect of dropouts on the statistical analyses for the LAL-CL03, LAL-1-NH01, and LAL-CL02 studies. This was not an issue, however, as only one patient in total (from the LAL-CL02 study) dropped out of these trials.

I. Background

On October 21, 2014, Synageva BioPharma Corporation initiated the filing of this Biologics Licensing Application (BLA) for KANUMA™ (sebelipase alfa; SBC-102) in accordance with Section 351(a) of the Public Health Service Act and Title 21 of the Code of Federal Regulations (CFR), Part 601.2. The active pharmaceutical ingredient (API) of sebelipase alfa [1 mg/kg of body weight to be administered once every week or every other week as an intravenous (IV) infusion] is recombinant human lysosomal acid lipase (rhLAL). Effective on April 2, 2010, the applicant had initiated clinical development of sebelipase alfa, under IND 108,460, (b) (4)

STATISTICS FILING CHECKLIST FOR A NEW BLA

(b) (4) in patients with Lysosomal Acid Lipase (LAL) deficiency, which is the proposed indication.

LAL deficiency is a lysosomal storage disorder that occurs when the body, specifically the lysosomes within the cells of the body, does not produce enough active LAL enzyme. This enzyme plays an important role in breaking down fatty material (i.e., cholesteryl esters and triglycerides) in the body. Infants, children and adults that suffer from LAL Deficiency experience a range of serious health problems. The lack of the LAL enzyme can lead to a build-up of fatty material in a number of body organs including the liver, spleen, gut, and in the wall of blood vessels and other important organs. This build-up of fatty material can be lethal if not adequately assuaged. Currently there is no available treatment for LAL deficiency. Sebelipase alfa is an ERT whose mechanism of action is to directly replace the non-existent LAL enzyme thereby, as hypothesized by the applicant, reversing the disease process.

There are two distinct forms of this disease. One is in infants which is called Wolman Disease (i.e., “infantile onset”). The other is in children and adults which is called Cholesteryl Ester Storage Disease (CESD). Wolman Disease presents shortly after birth, is homogeneous in its phenotype, and is often highly progressive and thus fatal within the first 6 months of life. Sebelipase alfa is to be administered once every week in the Wolman Disease patient population. In comparison to Wolman Disease, CESD is heterogeneous in its phenotype and is less progressive. However, CESD does ultimately result in death if not treated in a timely manner. Sebelipase alfa is to be administered once every other week in the CESD patient population. Wolman Disease is estimated to occur in 1 per 528,000 births which is roughly 600 total people in the USA. The estimated prevalence of CESD ranges from 1 per 40,000 people to 1 per 300,000 people which corresponds to between roughly 1,055 and 7,925 total people in the USA. As can be readily seen, this is a rare disease in both patient populations with the infant population being much rarer than the children/adult population. Overall, LAL deficiency is a rare, serious and life-threatening condition with an unmet medical need.

The applicant obtained *Orphan Designation* from the Office of Orphan Products Development (OOPD) on July 1, 2010. There is also a pending request for *Rare Pediatric Disease Designation*. Synageva also obtained *Fast Track Designation* from the Division of Gastroenterology and Inborn Errors Products (DGIEP) on June 14, 2011. Consequently, DGIEP has agreed to receive the BLA on a rolling basis with the final component of the BLA having been submitted on January 8, 2015. *Breakthrough Therapy Designation* was also granted by DGIEP on May 15, 2013, (b) (4) for Wolman disease. (b) (4). A priority 8-month review cycle is expected under the Prescription Drug User Fee Act (PDUFA) V Program.

This BLA was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). The content, including the electronic data sets and labeling information, is located in the Center for Drug Evaluation and Research (CDER) electronic document room (EDR) at the location: [\\CDSESUB1\evsprod\BLA125561\0000](#), [\\CDSESUB1\evsprod\BLA125561\0003](#), and [\\CDSESUB1\evsprod\BLA125561\0015](#).

II. Brief Overview and Summary of Relevant Trials

For Wolman Disease (i.e., LAL deficiency in infants), the regulatory pathway is for full approval under 21 CFR Part 601 utilizing survival data. The lone trial used for the basis of this full

STATISTICS FILING CHECKLIST FOR A NEW BLA

approval will be study LAL-CL03 which is phase 1/2, multicenter, open-label, single-arm, dose escalation study in treatment naïve Wolman Disease patients. This study will compare overall survival (up to 12 months) between infants being administered sebelipase alfa and baseline matched infants from a historical control group (i.e., natural history data for 35 total patients collected retrospectively from chart reviews though natural history study LAL-1-NH01). Note that patients being administered sebelipase alfa in this trial can stay on treatment for up to 208 weeks. A total of 10 patients were targeted for enrollment in trial LAL-CL03. Ultimately 9 patients were recruited, and it took 3 years to recruit these 9 patients. LAL-CL03 is still currently ongoing during its follow-up period. The primary analysis has been completed.

For CESD (i.e., LAL deficiency in children and adults), the regulatory pathway is for accelerated approval under 21 CFR Part 601 Subpart E utilizing a surrogate endpoint, i.e., normalization of alanine transaminase (ALT). The lone trial used for the basis of this accelerated approval will be study LAL-CL02 which is a phase 3, multicenter, randomized, double-blind, placebo-controlled, 20 week (followed by an open-label rollover period of up to 130 weeks) trial in treatment naïve children and adults. The double-blind and placebo-controlled portion of this trial has already locked and unblinded. The open-label rollover period is still currently ongoing. A total of 50 patients were targeted for enrollment, and 66 patients were ultimately recruited to participate in this study.

For the LAL-CL03, LAL-1-NH01, and LAL-CL02 studies, the clinical/tabulation datasets were compliant to the CDISC/SDTM v.3.1.2 implementation guide standard. The analysis datasets for study LAL-CL02 were compliant to the CDISC/ADaM v.1.0 implementation guide standard. However, the analysis datasets for the LAL-CL03 and LAL-1-NH01 studies were in legacy format and hence not compliant to CDISC/ADaM. Adequate data definition files (in define.xml and define.pdf formats), a reviewer's guide and software code (in .txt, format) were also submitted for all three studies.

The following table presents information on the relevant trials contained in this submission.

STATISTICS FILING CHECKLIST FOR A NEW BLA

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment
Safety and Efficacy; Phase 1/2	LAL-CL03	Efficacy, Safety, Pharmacokinetics (PK)	Multicenter, Open-label, Single-arm, Dose escalation	Sebelipase Alfa; Dose escalation from 0.35 mg/kg to 1 mg/kg every week, and then up to 3-5 mg/kg every week; IV	Total: 9	LAL Deficiency (Wolman Disease)	Up to 208 weeks
Natural History	LAL-1-NH01	Chart review of infants with LAL Deficiency	Observational, Natural History, Non-interventional	N/A	Zero patients dosed; 35 total patients participated	LAL Deficiency (Wolman Disease)	N/A
Safety and Efficacy; Phase 3	LAL-CL02	Efficacy, Safety, Pharmacokinetics (PK)	Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel group	Sebelipase Alfa; 1 mg/kg every other week; IV	Total: 66	LAL Deficiency (CESD)	20 weeks followed by an open-label period up to 130 weeks

III. Review Issues

There are no review issues identified at this time.

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/s/

BEHRANG VALI
01/20/2015

YEH FONG CHEN
01/20/2015