CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA:	STN 125,561
Submission Type:	Original BLA (New Molecular Entity)
Standard or Priority:	Priority
Brand Name:	KANUMA®
Drug Name:	Sebelipase Alfa (SBC-102)
Submission Date:	01/08/2015
PDUFA Goal Date:	09/08/2015
Proposed Indication:	For the treatment of lysosomal acid lipase (LAL) deficiency in patients with a confirmed diagnosis of LAL deficiency as an enzyme replacement therapy (ERT)
Proposed Dosing Regimen:	▪ Patients with Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life: 1 mg/kg as an intravenous infusion once weekly as an initial dose followed by escalation to 3 mg/kg once weekly. ▪ Pediatric and Adult Patients with LAL Deficiency: 1 mg/kg as an intravenous infusion once every other week.
Dosage Forms and Strength:	20 mg/10 mL (2 mg/mL) solution in a single-use vial for injection
Applicant:	Synageva BioPharma Corporation
Clinical Pharmacology Review Team:	Primary Reviewers: Jing Fang, Ph.D., and Sarah Dorff, Ph.D. Secondary Reviewers/Team Leaders: Christian Grimstein, Ph.D., Nitin Mehrotra, Ph.D., and Yow-Ming Wang, Ph.D.
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1. EXECUTIVE SUMMARY

Sebelipase alfa (SBC-102) is being developed as an enzyme replacement therapy (ERT) for the treatment of lysosomal acid lipase (LAL) deficiency. Sebelipase alfa is a recombinant human lysosomal acid lipase (rhLAL) and is purified from egg white of transgenic hens (Gallus) with the same amino acid sequence as the native human LAL. It received Orphan Drug designation in July 2010 and Fast Track designation in June 14, 2011 for the treatment of LAL deficiency, and Breakthrough Therapy designation for the treatment of patients with rapidly progressive LAL Deficiency within the first 6 months of life (infantile-onset LAL deficiency) on May 13, 2013. Sebelipase alfa is supplied as liquid-in-vial containing approximately 10 (b) (4) mL solution of sebelipase alfa at a concentration of 2 mg/mL. For administration via intravenous infusion, sebelipase alfa is to be diluted in 0.9% Sodium Chloride Injection to a final concentration of 0.1 mg/mL to 1.5 mg/mL with a final volume not exceeding (b) (4) mL.

There are two phenotypes of LAL deficiency: infantile- and late-onset LAL deficiency. Infantile-onset LAL deficiency, historically called Wolman disease (WD), is the most aggressive presentation of LAL deficiency and is usually fatal within the first 6 months of life. Late-onset LAL deficiency, historically called Cholesteryl Ester Storage Disease (CESD), is more heterogeneous with respect to the age of diagnosis and rate of disease progression.

To support the proposed indication in two patient population, i.e., treatment of infantile-onset LAL deficiency and late-onset LAL deficiency, the Applicant submitted results of 4 clinical trials conducted in a total of 84 subjects (9 infants, 47 children, and 28 adults) with LAL deficiency. Study LAL-CL01 (N=9 adults) is completed with an ongoing extension study (LAL-CL04). One study in pediatrics and adults (LAL-CL02, N=66) and one study in infants (LAL-CL03) are ongoing in the extension phase. In these studies, sebelipase alfa was administered as an intravenous infusion over approximately 60 to 120 minutes.

In this review, Sebelipase alfa and SBC-102 were used interchangeably.

1.1. Recommendations

From a clinical pharmacology perspective, information submitted in this BLA is acceptable to support a recommendation for the approval of KANUMA (sebelipase alfa) provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2. Post-Marketing Requirements/Commitments

None.

1.3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

1.3.1 Pharmacokinetics

In adult subjects administered sebelipase alfa, the sebelipase alfa serum concentration rose quickly within the first hour after the start of infusion; C_{max} was reached close to or at the end of infusion. After the end of infusion, sebelipase alfa concentrations was rapidly eliminated from the systemic circulation with a median $t_{1/2}$ ranged between 0.11 and 0.26 h at 1 mg/kg dose and 0.11 and 0.21 h at 3 mg/kg dose.

The exposure of sebelipase alfa in serum increased in a dose proportional manner between 0.35 mg/kg and 1 mg/kg and in a greater than dose-proportional manner between the 1 and 3 mg/kg doses following a single dose and multiple doses of sebelipase alfa. A 3-fold increase in dose from

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1 mg/kg to 3 mg/kg resulted in approximately 10- to 15-fold increases in exposure, including the area under the concentration-time curve from time zero to last quantifiable measurement (AUC_{0-last}), AUC from time zero to infinity (AUC_{0-inf}), and maximum concentration (C_{max}), which is consistent with the reduced clearance at the 3 mg/kg. The PK parameters for sebelipase alfa were comparable following the administration of a single and after multiple doses, indicating no accumulation with repeated dosing.

Body surface area was a significant covariate in the population PK analysis of data in children (4-17 years old) and in adults.

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

1.3.2 Efficacy/Safety

Among 9 patients with infantile-onset LAL deficiency, 67% (95% CI of 30% - 93% based on survival analysis) of subjects (n=7) survived to 12 months of age (Study LAL-CL03). The proportion of subjects surviving at 12 months of age was the primary efficacy endpoint. Compared to 0% (0% - 16%) in a historical control study (LAL-1-NH01), the observed 67% improvement in survival is clinically meaningful. Generally, dosing in these infants began at 0.35 mg/kg weekly which was escalated to 1 mg/kg after two doses although the dosing escalation plan differed across subjects (see Table 3 in Section 2.3.1). The Applicant proposed starting dosage regimen of 1 mg/kg every week with up-titration to 3 mg/kg every week is acceptable considering the limited exposure to lower sebelipase alfa doses prior to escalating to 1 mg/kg followed by 3 mg/kg in all surviving subjects and infantile-onset LAL deficiency is a rapidly progressive, lethal condition.

For patients with late-onset LAL deficiency, the pivotal study (LAL-CL02) only evaluated one dose level (1 mg/kg) once every other week. At Week 20, the mean percentage change from baseline of LDL-cholesterol (LDL-c) (the primary efficacy endpoint) in the sebelipase alfa treatment group (-28%) was significantly higher than that in the placebo (-6%) group. A subgroup analysis of the sebelipase alfa treatment effect across age group (4-11 years of age, 12-17 years of age, and 18 years and older) showed that the Week 20 % LDL-c reduction in all three age categories was statistically greater in sebelipase alfa treated group than in placebo group by 16%, 23%, and 29%, respectively. Another subgroup analysis by age categories showed that the proportion of subjects whose LDL-c level was reduced and achieved the normal range (<130 mg/dL) was statistically greater in the sebelipase alfa treated group than in the placebo group by 28% to 35%. Taken together, the data support the proposed dosing regimen of 1 mg/kg once every other week for children ≥4 years old and for adults.

The greatest safety concern associated with enzyme replacement therapies are hypersensitivity reactions, including anaphylaxis. Hypersensitivity reactions occurred in 5 patients with infantile onset LAL deficiency during the study. In 36 patients with late-onset LAL deficiency treated with sebelipase alfa during the 20-week double-blind treatment period, two experienced hypersensitivity reactions. Refer to clinical reviews for more details.

1.3.3 Proposed Dosing Regimen

The Applicant’s proposed dosing regimens are:

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- Rapidly progressive LAL deficiency in patients with growth failure in the first 6 months of life: starting dose of 1 mg/kg as an intravenous infusion once weekly. In clinical studies, these patients were dose escalated to 3 mg/kg once weekly;
- Pediatric and adult patients with LAL deficiency: 1 mg/kg as an intravenous infusion once every other week.

1.3.4 Immunogenicity

Overall, 10 of 51 sebelipase alfa treated subjects (20%) in the clinical development program developed antibodies against sebelipase alfa (anti-drug antibody-positive or ADA-positive).

Namely, in the pivotal study of infantile-onset LAL deficiency (LAL-CL03), 4 of 7 evaluable infants (57%) developed ADA during treatment with sebelipase alfa. Two patients were determined to be positive for neutralizing antibodies that inhibit in vitro enzyme activity and cellular uptake of the enzyme.

In the pivotal study of late-onset LAL deficiency (LAL-CL02), 5 of 35 evaluable children and adults (14%) treated with sebelipase alfa developed ADA during the 20-week double-blind period of the study. No patient developed neutralizing antibodies that inhibit in vitro enzyme activity or cellular uptake of the enzyme.

In the study of adult patients of late-onset LAL deficiency (LAL-CL04), 1 of 9 had a single ADA-positive result at Week 4.

Overall, it is not feasible to draw a definitive conclusion on the impact of ADA, or lack thereof, on PK, PD, efficacy, and safety. Although one infant who developed ADA with sustained neutralizing capability for LAL enzyme activity and LAL cellular uptake was associated with suboptimal rate of growth leading to dose escalation to 5 mg/kg, the lack of efficacy cannot be directly attributed to the immunogenicity due to other confounding factors.

2. QUESTION BASED REVIEW

2.1 List of the Clinical Pharmacology and the clinical studies with PK and/or PD information submitted in the BLA

A summary of sebelipase alfa clinical studies to support the clinical pharmacology section of this BLA submission is presented in Table 1.

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Table 1: Summary of Sebelipase Alfa Clinical Studies in the BLA Submission

Study Identifier	Study Design	Regimen (Duration of treatment)	Study Population	Number of Subjects Treated[a] / PK[b]	PK Assessment	PD Assessment[d]	PG Assessment	Immunogenicity Assessment
LAL-CL01 (completed)	Phase 1/2, open-label study	0.35, 1, or 3 mg/kg qw for 4 weeks, IV	Adults (≥18 and ≤65 years of age) with liver dysfunction due to LAL deficiency	9/9	Day 0 (single-dose) and Day 21 (multiple-dose)	ALT, Serum lipids (total cholesterol, TGs, HDL-c, LDL-c)	Yes	ADA
LAL-CL04 (ongoing)	Single-arm, open-label, extension study	0.35, 1, or 3 mg/kg qw for 4 weeks, then 1 or 3 mg/kg qow, for up to 3 years, IV	Subjects who completed LAL-CL01	8/8	Weeks 24, 52, and 104	ALT, Serum lipids (LDL-c, TGs, HDL-c, and total cholesterol), and liver fat content	No	ADA
LAL-CL02 (Double-blind period complete, open-label period ongoing)	Phase 3, randomized, double-blind, placebo-controlled study	Double-blind period: 1 mg/kg or placebo qow for 20 weeks, IV; Open-label period: 1 mg/kg qow (irrespective of treatment in double-blind period) for up to 130 weeks	Pediatric (≥ 4 years old) and adult subjects with LAL deficiency	66/65[c] (47/47 children and 19/18 adults)	Day 0 and at Weeks 22 and 56	ALT, Serum lipids (LDL-c, TGs, HDL-c, non-HDL-c), and liver fat content	Yes	ADA, Nab
LAL-CL03 (Primary analysis complete, subject follow-up ongoing)	Phase 2/3, Single-arm, open-label, dose escalation study	0.35 mg/kg qw for 2 infusions, IV, then 1 mg/kg qw, then 3 mg/kg qw if a suboptimal clinical response, and to 5 mg/kg qw if a continued suboptimal clinical response. Maximum treatment up to 4 years. Subjects treated for at least 96 weeks and with a stable dose for at least 6 months could transition to a qow regimen at same dose as qw regimen.	Infants with LAL deficiency who developed growth failure or other clinical evidence of a rapidly progressive disease course before 6 months of age	9/5[c]	Day 0 and Weeks 22 and 52	No	Yes	ADA, Nab

[a] Number of subjects includes only those subjects who received at least 1 infusion of sebelipase alfa. The number of subjects included in the PK, PD/efficacy, and exposure-response analyses may have been less, and may have varied over time or between parameters, depending on data availability.
[b] Analysed for PK. [c] Population PK analysis. [d] Exposure-response analysis.
PK: Pharmacokinetics. PD: Pharmacodynamics. PG: Pharmacogenomics. ADA: Anti-drug antibody. Nab: Neutralizing antibody.

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2.2. General Attributes

2.2.1. What are the highlight of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The drug substance is a recombinant human lysosomal acid lipase (rhLAL) enzyme, purified from egg white of transgenic Gallus, with the same amino acid sequence as the native human enzyme. It has a molecular weight of approximately 55 kD with 6 N-linked glycosylation sites.

Sebelipase alfa is supplied as a clear to slightly opalescent, colorless to slightly colored liquid, in sterile vials containing approximately 10 (b) (4) mL (including (b) (4) % overfill) of a (b) (4) solution of sebelipase alfa at a concentration of 2 mg/mL. Each single-use vial of sebelipase alfa contains 2 mg/mL rhLAL, 13.7 mg/mL trisodium citrate dihydrate, 1.57 mg/mL citric acid monohydrate, and 10 mg/mL human serum albumin. No preservatives are added. For administration, sebelipase alfa is diluted in 0.9% Sodium Chloride Injection to a final concentration of 0.1 mg/mL to 1.5 mg/mL with a final infusion volume determined by the dose to be administered and not exceeding (b) (4) mL.

2.2.2. What are the proposed mechanism of action and therapeutic indication?

Sebelipase alfa is intended as ERT for patients with LAL deficiency, an autosomal recessive lysosomal storage disease in which mutations affecting the gene encoding lysosomal acid lipase/ cholesteryl esterase (*LIPA*) result in a marked reduction or absence of LAL enzyme activity. LAL deficiency is associated with accumulation of substrates for LAL, namely cholesteryl esters and triglycerides, in the lysosomes of various tissues and cell types throughout the body.

Administration of sebelipase alfa is intended to provide the exogenous enzyme LAL that will be taken up into the lysosomes to hydrolyze accumulated substrates (cholesteryl esters and triglycerides) in LAL-deficient cells, thus reducing the pathological effects in affected tissues. Sebelipase alfa uptake by cells into lysosomes is most likely mediated by the binding of N-linked glycans (b) (4)) of LAL to cell surface macrophage mannose or mannose-6-phosphate receptors.

2.2.3. What are the proposed dosing regimen and route of administration?

- Rapidly progressive LAL deficiency in patients with growth failure in the first 6 months of life: starting dose of 1 mg/kg as an intravenous infusion once weekly. In clinical studies, these patients were dose escalated to 3 mg/kg once weekly;
- Pediatric and adult patients with LAL deficiency: 1 mg/kg as an intravenous infusion once every other week.

2.2.4. What drugs (substances, products) indicated for the same indication are approved in the US?

No approved drugs are available for the proposed indications.

2.3. General Clinical Pharmacology

2.3.1. What are the design features of the clinical pharmacology, biopharmaceutics and clinical studies used to support dosing or claims?

Table 1 (in Section 2.1 above) shows a summary of the design features of 4 studies, including two pivotal clinical trials that contribute to the clinical pharmacology assessment: Study LAL-CL03 in infants with LAL deficiency and Study LAL-CL02 in children and adults with LAL deficiency.

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Briefly, infantile-onset LAL deficiency was studied in Phase 2/3 study LAL-CL03, a multicenter, open label, intra-subject dose escalation study. Sebelipase alfa dose was administered as an IV infusion once weekly. The dose escalation scheme differed across individuals and the decision to dose escalate was based on suboptimal response in one or more clinical measures. All subject received 0.35 mg/kg as the starting dose except for one subject who received the starting dose of 0.2 mg/kg before getting 0.35 mg/kg dose. Seven surviving subjects were dose escalated to 1 mg/kg and remained at this dose for varying duration before escalating to 3 mg/kg or further to 5 mg/kg (Table 2).

Table 2. Individual Subject Data on Dose Escalations to 3 mg/kg or 5 mg/kg due to Suboptimal Clinical Response in Study LAL-CL03.

Subject ID	No. of infusions at ≤0.35 mg/kg qw	No. of infusions at 1 mg/kg qw	First Infusion at 3 mg/kg qw	Infusion at 3 mg/kg qow	First Infusion at 5 mg/kg qw	Criterion Not Met (Dose escalation to 3 mg/kg)
(b) (6)	2	21	Week 23		Week 88[c]	WFA plateaued; also hepatomegaly
	2	10	Week 14			WFA plateaued
	4[a]	86	Week 91	Weeks 122 to 154[b]		Mesenteric lymphadenopathy
	2	10	Week 12			Failure to gain an average of 5 g /kg body weight per day, and WHO LFA/HFA Z-score < -2
	2	4	Week 6			Failure to gain an average of 5 g /kg body weight per day, and WHO LFA/HFA Z-score < -2
	2	8	Week 10			Failure to gain an average of 5 g /kg body weight per day, and WHO LFA/HFA Z-score < -2

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

Source: LAL-CL03 CSR, Table 15

Pediatric (aged ≥ 4) and adult patients with LAL deficiency were studied in Phase 3 study LAL-CL02, which was a multi-national, multi-center randomized, double-blind placebo-controlled study that evaluated 1 mg/kg dose of sebelipase alfa administered as an IV infusion once every other week for 20 weeks.

2.3.2. What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Infantile-onset LAL deficiency (Study LAL-CL03):

Primary efficacy endpoint: the proportion of subjects surviving at 12 months of age

The primary efficacy endpoint was selected because Infantile-onset LAL deficiency is a rapidly progressive presentation of LAL deficiency and patients typically die within the first 6 months of life.

Secondary efficacy endpoints: the proportion of subjects surviving beyond 12 Months of age, anthropometrics, liver and serum biochemical parameters, etc.

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Secondary efficacy endpoints were selected because growth failure and rapidly progressive hepatic disease are prominent features of infantile-onset LAL deficiency, and key contributors to mortality in these patients.

Late-onset LAL deficiency (Study LAL-CL02):

Primary efficacy endpoint: LDL-cholesterol (% change from baseline)

Per protocol the primary efficacy endpoint for Study LAL-CL02 was normalization of alanine aminotransferase (ALT). However, normalization of ALT neither directly measures clinical benefit of treatment (i.e., how a patient feels, functions, or survives) nor represents a surrogate endpoint reasonably likely to predict clinical benefit in patients with late-onset LAL deficiency.

The FDA communicated to the Applicant by mid-cycle communication that "the Division has reviewed all available clinical and laboratory parameters for which there were pre- and on-treatment data, and has concluded that LDL, the first-ranked key secondary endpoint, is the most suitable endpoint to assess efficacy in patients with CESD." LDL-cholesterol (LDL-c) is included in the causal pathway of LAL deficiency and contributes to disease manifestations seen in patients with late-onset LAL deficiency, because LDL-c is made up in part by cholesteryl esters and triglycerides that accumulate in the lysosome when LAL is deficient. In addition, elevation of LDL-c is a well-established risk factor for coronary heart disease, and hyperlipidemia and accelerated atherosclerosis are known complications of LAL deficiency.

Secondary efficacy endpoints are serum lipids and liver fat content because they represent important PD parameters directly related to the mechanism of action for sebelipase alfa. Liver fat content was also selected for demonstrating reductions in abnormal substrate accumulation. Below is a partial list of endpoints monitored:

- %Change from baseline non-high-density lipoprotein cholesterol (non-HDL-c)
- %Change from baseline in triglycerides (TG)
- %Change from baseline in high-density lipoprotein cholesterol (HDL-c)
- %Change from baseline in liver fat content using multi-echo gradient-echo proton density fat fraction (MEGE PDFF) magnetic resonance imaging (MRI)
- Normalization of ALT

2.3.3. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Yes, the serum sebelipase alfa concentration was measured using an enzyme activity assay which was appropriate for the evaluation of PK parameters and the exposure-response relationships.

However, sebelipase alfa in systemic circulation is expected to be inactive until internalized into the lysosomal compartment because the plasma has a neutral pH whereas sebelipase has an acidic pH optimum which occurs in the lysosomes. The exposure-response relationships based on systemic exposure measures are considered supportive evidence of effectiveness because the biological activity of sebelipase alfa is primarily driven by the exposure in the lysosomes of target tissues, and the

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relationship between systemic exposure and the concentration of sebelipase alfa in the lysosomes is unknown.

2.4. Exposure-Response

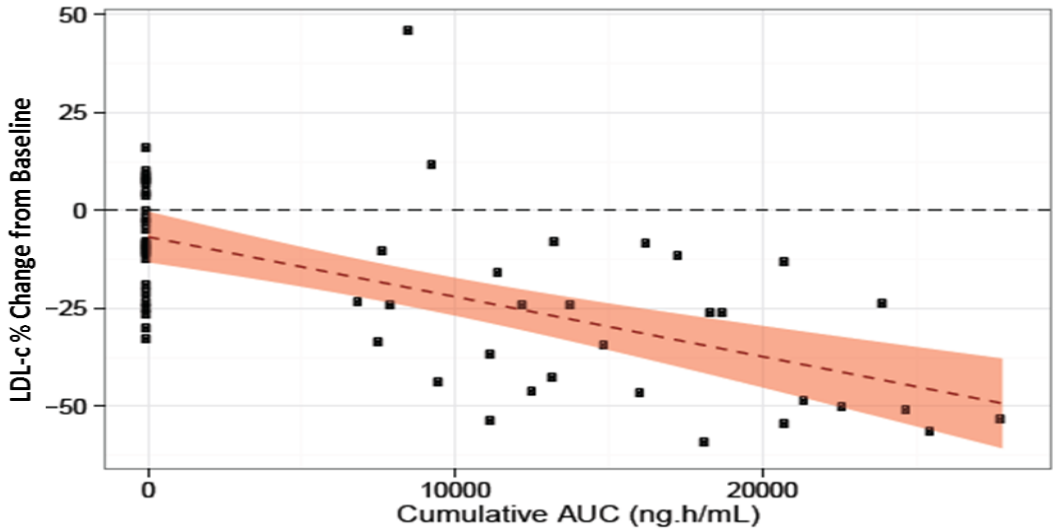
2.4.1. What are the characteristics of the exposure-response relationship for effectiveness?

Because the biological activity of sebelipase alfa is primarily driven by the exposure in the lysosomes of target tissues, and the relationship between systemic exposure and the concentration of sebelipase alfa in the lysosomes is unknown, the exposure-response relationships described below based on systemic exposure measures are considered supportive evidence of effectiveness.

In infantile-onset LAL deficiency, the exposure-response analysis was not feasible due to extremely limited PK sampling and overall sample size (n=9) in the pivotal phase 2/3 study (LAL-CL03).

In late-onset LAL deficiency, the Applicant evaluated the exposure-response relationship using cumulative AUC from time zero to Week 20 as the exposure variable and the primary efficacy endpoint of LDL-c % change from baseline at Week 20 as the response variable. As shown in Figure 1, the LDL-c % change from baseline increased with increasing exposure, which provides supportive evidence of effectiveness of sebelipase alfa treatment in late-onset LAL deficiency. Overall, no clear exposure-response was shown in five additional secondary efficacy endpoints (HDL-c, Cholesterol, Triglycerides, ALT and liver fat %).

Figure 1. Exposure-Response Relationship for the Primary Efficacy Endpoint (%LDL-c Change from baseline) with Sebelipase Alfa Cumulative AUC at Week 20 (Study LAL-CL02).



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

Source: Applicant's Updated Clinical Pharmacology Response 2 to IRs dated 04/16/2015, Figure 11

2.4.2. What are the characteristics of the exposure-response relationships for safety?

The safety results presented below were based on the Applicant's analysis.

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Overall, as shown in Table 3 a very low percentage of infusion-associated adverse event occurred: the rate of moderate and severe infusion-associated reactions (IAR) was below 1%. Therefore, the exposure-response relationship will provide limited value for safety assessment and a dedicated analysis was not conducted.

Table 3. Percentage of infusion-associated adverse event data in 4 clinical studies LAL-CL01, LAL-CL02, LAL-CL03 and LAL-CL04

Severity	No AEs	Mild	Moderate	Severe
N (%)	2009 (96.5%)	46 (2.2%)	13 (0.6%)	14 (0.7%)

Data Source: Module 5.3.3.5, AE-WITH-PK

Please refer to clinical reviews for more details of the overall safety analyses.

2.4.3. Does this drug prolong QT/QTc Interval?

No formal QT/QTc studies were performed for sebelipase alfa, as the drug is a therapeutic protein which has minimal potential for prolongation of QT/QTc interval.

2.4.4. Is the dose and dosing regimen selected consistent with the known E-R relationship?

It was not possible to evaluate the dosing regimen for infantile and late-onset LAL deficiency from an exposure-response perspective because the relevance of E-R based on systemic exposure of sebelipase alfa is not clear (see Section 2.3.3 and Section 2.4.1). Therefore, the selected doses and dosing regimens for patients with infantile-onset LAL deficiency and late-onset LAL deficiency were based on the efficacy and safety data in the pivotal study of the respective patient population.

In patients with infantile-onset LAL deficiency, the E-R relationship has not been established. In patients with late-onset LAL deficiency, the E-R relationship (higher exposures appear to be associated with a greater LDL-c% change from baseline) provides supportive evidence of effectiveness.

2.5. Pharmacokinetics

2.5.1. Data from which studies were used to determine the PK characteristics of the drug?

Data from 3 studies were used to determine the PK characteristics of sebelipase alfa in pediatric and adult patients. As shown in Table 4, intensive PK sampling was conducted in adult patients received 0.35, 1, and 3 mg/kg dose of sebelipase alfa once every week (qw) or once every other week (qow) for up to 104 weeks (Studies LAL-CL01, LAL-CL02, and LAL-CL04). Whereas the intensive PK data in adults were amenable to estimating PK parameters using non-compartmental analysis (NCA), population PK analysis was used to estimate PK parameters in pediatric patients receiving 1 mg/kg dose of sebelipase alfa once every other week (LAL-CL02) because of sparse PK sampling.

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Table 4. PK Sampling Scheme and Data Analysis Method

Study no.	Age group	Intensive PK sampling (Yes/No)	Doses (mg/kg) studied; dosing frequency	PK Analysis Method	N with PK data
LAL-CL01	Adults	Yes (Day 1 and Day 21)	0.35, 1 or 3; qw x4	NCA	9
LAL-CL04 (extension of LAL-CL01)	Adults	Yes (Weeks 24, 52, 104)	0.35, 1, or 3; qw x4 followed by 1 or 3; qow	NCA	8
LAL-CL02	Adults	Yes (Day 0, Week 22) No (Week 56)	1; qow	NCA Population PK	19 (Day 0) 13 (Week 22)
LAL-CL02	Ages 4-17	No (Day 0, Weeks 22 and 56)	1; qow	Population PK	46
LAL-CL03	Infants	No (Day 0, Weeks 22, 52)	0.2 – 5; qw	Population PK	5

N: number of subjects included in the population PK analysis

2.5.2. What are the single and multiple dose PK parameters of sebelipase alfa in patients with LAL deficiency?

In patients with infantile-onset LAL deficiency, PK of sebelipase alfa is not well-characterized due to limited PK sampling in Study LAL-CL03; 21 samples collected in 5 subjects who were receiving various sebelipase alfa dosing regimens. Although the Applicant conducted population PK analysis with the available concentration data, the model did not fit the data satisfactorily and was deemed not suitable for simulating PK profiles or estimating PK parameters in infants.

In adult patients, sebelipase alfa serum concentration rose quickly after the start of infusion, reached C_{max} close to or at the end of infusion, and rapidly declined after the end of infusion (Figures 2 to 3). The temporal PK profiles on Day 1 and Day 21 were similar. The median half-life ($t_{1/2}$) values ranged from 0.11 – 0.51 h after a single dose at 1 and 3 mg/kg (Table 5). The PK parameters for sebelipase alfa were comparable at multiple time points for up to 104 weeks in two studies, indicating no accumulation with repeated dosing (Table 6).

Whereas the sebelipase alfa exposure at 1 mg/kg dose was approximately 3-fold of the exposure at 0.35 mg/kg dose, there was a greater than dose-proportional increase in exposure between 1 mg/kg and 3 mg/kg doses. Based on median values for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}, a 3-fold increase in dose from 1 to 3 mg/kg resulted in approximately 10- to 15-fold increase in exposure of sebelipase alfa at multiple visits through Week 104 (Table 5 and more details in the Individual Study Review).

(b) (4)

However, the Applicant did not provide experimental data to support the hypothesis.

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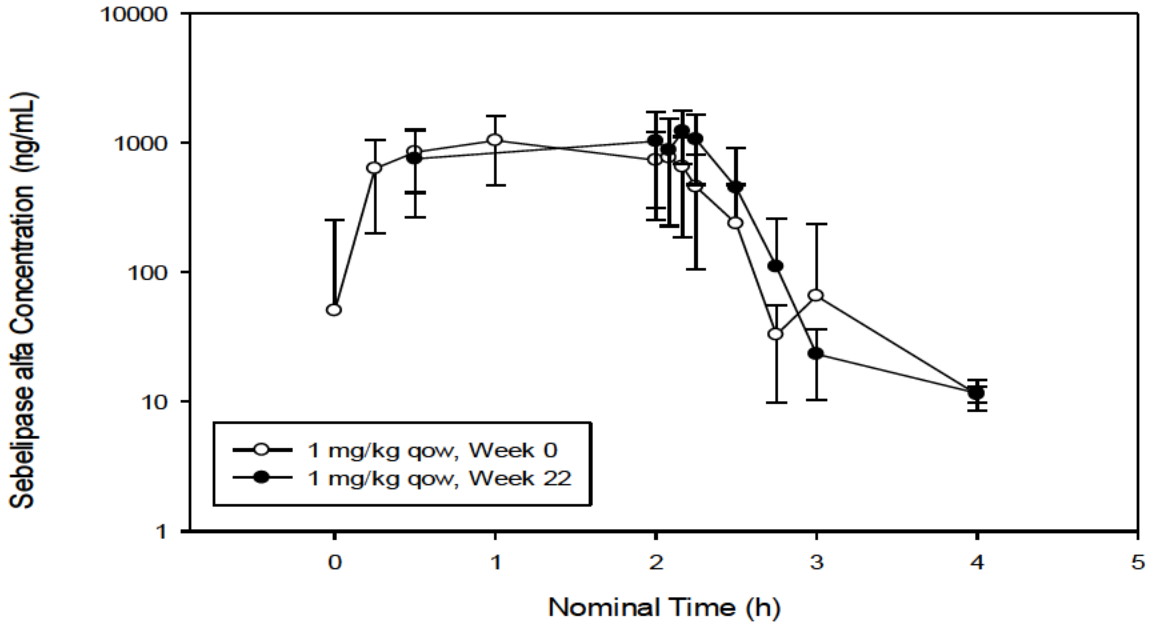
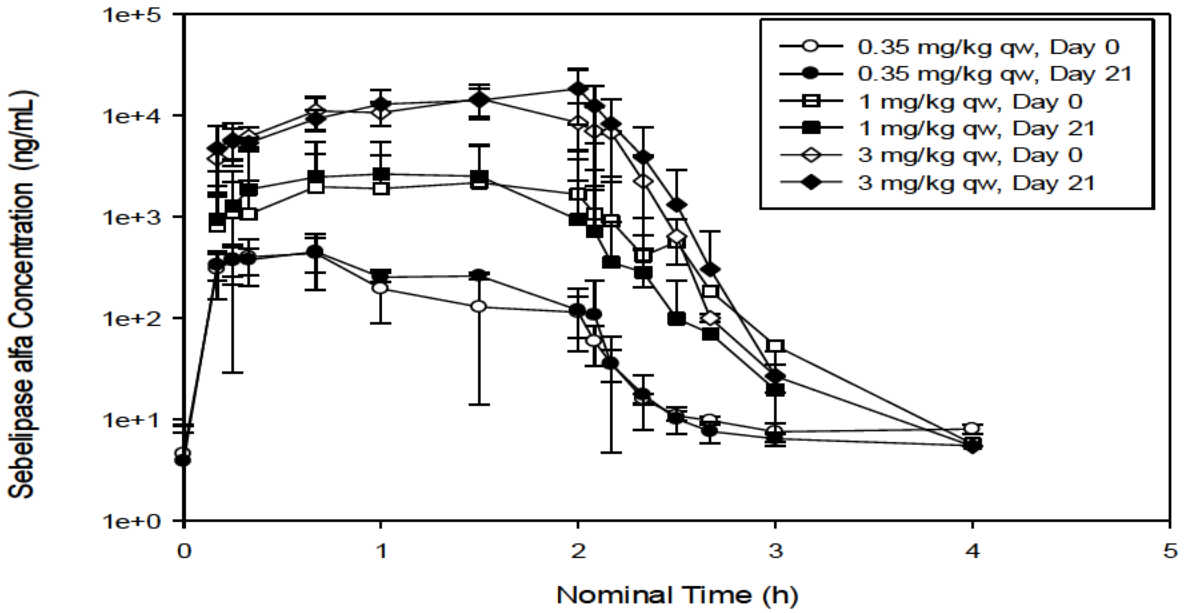
Figure 2. Mean (±SD) sebelipase alfa serum concentration over time in Adults from Study LAL-CL02.



Source: plot generated by the reviewer

Figure 3. Mean (+SD) sebelipase alfa serum concentration over time in Adults from Study LAL-CL01.



Source: plot generated by the reviewer

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Table 5. The PK parameters After Single-Dose (Day 0) and Multiple-Dose (Day 21) Administration (qw) in Study LAL-CL01.

	Median (Range)					
	Day 0			Day 21		
	0.35 mg/kg (N=3)	1 mg/kg (N=3)	3 mg/kg (N=3)	0.35 mg/kg (N=3)	1 mg/kg (N=3)	3 mg/kg (N=3)
C_{max} (ng/mL)	370 (262-718)	836 (561-5484)	15027 (9080-19904)	379 (330-655)	1212 (814-5991)	16080 (9616-29613)
$AUC_{0\text{-last}}$ (ng.h/mL)	449 (441-663)	1091 (846-8254)	22030 (12796-27029)	509.9 (494-757)	1687 (1026-9198)	22137 (16661-31437)
T_{max} (h)	0.67 (0.33-1.58)	1.00 (1.00-1.50)	1.50 (1.50-1.50)	0.67 (0.67-0.67)	1.25 (1.00-1.50)	1.80 (1.75-2.08)
$t_{1/2}$ (h)	1.37 (0.60-3.51)	0.11 (0.11-0.28)	0.13 (0.10-0.24)	0.78 (0.07-2.05)	0.11 (0.08-0.14)	0.13 (0.09-0.16)
CL (mL/h/kg)	722 (524-755)	916 (121-1180)	136 (111-229)	665 (462-700)	541 (109-974)	136 (95.4-180)

C_{max}: maximum observed serum concentration; $T_{max:}$ time of maximum observed serum concentration; $AUC_{(0\text{-last})}$, area under the serum concentration-time curve (AUC) from the start of the infusion to the time of the last quantifiable concentration; $t_{1/2:}$ apparent terminal half-life; CL: total body clearance.

Source: LAL-CL01CSR, Table 7; results from non-compartmental analysis

Table 6. The PK parameters of sebelipase alfa in adult patients After Multiple-Dose Administration of 1 mg/kg* in Studies LAL-CL01 and LAL-CL04

Parameter	Median (Range)				
	Day 0 (N=3)	Day 21 (N=3)	Week 24 (N=5)	Week 52 (N=4)	Week 104 (N=5)
C_{max} (ng/mL)	836 (561-5484)	1212 (814-5991)	1110 (815-1780)	1095 (628-1280)	595 (498-1050)
$AUC_{0\text{-last}}$ (ng.h/mL)	1091 (846-8254)	1687 (1026-9198)	1683 (1310-2433)	1600 (1089-1873)	1108 (991-1585)
T_{max} (h)	1.00 (1.00-1.50)	1.25 (1.00-1.50)	1.00 (0.38-1.00)	0.50 (0.33-1.03)	1.50 (0.67-2.70)
$t_{1/2}$ (h)	0.11 (0.11-0.28)	0.11 (0.08-0.14)	0.258 (0.15-0.46)	0.147 (0.09-0.22)	0.212 (0.14-0.25)
CL (mL/h/kg)	916 (121-1180)	541 (109-974)	592 (410-762)	627 (533-916)	900 (630-1003)

* Subjects were administered IV infusions of sebelipase alfa 1 mg/kg qw for 4 weeks in Study LAL-CL01, and 1 mg/kg qow in Study LAL-CL04

Source: LAL-CL04 CSR, Table 21; results from non-compartmental analysis

2.5.3. How does the PK of sebelipase alfa in healthy subjects compare to that in patients with the target disease?

No studies were conducted in healthy volunteers.

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2.5.4. What is the inter-subject variability of the PK parameters in patients with the target disease?

The inter-subject variability of sebelipase alfa was 33% to 48% for AUC, 26% to 41% for C_{max}, and 30-58% for CL in adult patients with LAL deficiency from Study LAL-CL02 (Table 7) based on results from the non-compartmental analysis.

Table 7. Summary of PK Parameters for Adult Subjects receiving 1 mg/kg once every other week (Study LAL-CL02).

Parameter	Week 0 (N=17)		Week 22 (N=11)	
	Median (Range)	Mean (SD, %CV)	Median (Range)	Mean (SD, %CV)
AUC_{last} (ng*hr/mL)	1713.5 (690.2 – 3362.7)	1732.5 (640.7, 37.0%)	1706.8 (638.7- 3439.7)	1914.1 (879.5, 45.9%)
AUC_{inf} (ng*hr/mL)	1798.6 (1147.2 – 3365.4)	1901.9 (634.3, 33.4%)	1768.8 (645.2 – 3447.5)	1940.5 (924.2, 47.6%)
C_{max} (ng/mL)	1113.9 (672.3 - 2555)	1196.0 (519.9, 26.0)	1285.7 (501.0 – 2167.1)	1352.1 (553.0, 40.9%)
T_{max} (hr)	1.1 (0.5 – 2.45)	1.4 (0.68, 48.6%)	1.8 (0.5 – 2.3)	1.7 (0.63, 37.1%)
CL (mL/hr/kg)	556.4 (297.1 – 871.7)	575.5 (172.0, 29.9%)	570.4 (290.1 – 1549.9)	656.5 (377.3, 57.5%)
$T_{1/2}$ (hr)	0.5 (0.1 – 2.3)	0.80 (0.83, 103.8%)	0.13 (0.09 – 0.9)	0.30 (0.28, 93.3%)

Source: Clinical Pharmacology Report for Study LAL-CL02 version 1.0, Table 2, 7 & 8; results from non-compartmental analysis

The inter-subject variability of sebelipase alfa was 28.5% (95% CI: 10.4% – 38.9%) for CL and 79.1% (95% CI: 57.1% – 96.2%) for V_c based on results from population PK analysis.

2.5.5. What are the characteristics of drug absorption, distribution, metabolism, and elimination?

Absorption:

Not applicable as sebelipase alfa is administered by IV infusion.

Distribution:

The central volume of distribution (V_c) in patients with LAL deficiency ranged between 3.3 L and 5.4 L in pediatric and adult patients (Tables 9).

Metabolism:

The metabolic pathway of sebelipase alfa has not been characterized. It is assumed that sebelipase alfa is degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous proteins.

Excretion:

The excretion of sebelipase alfa in urine has not been evaluated.

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2.5.6. Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

The PK of sebelipase alfa was nonlinear over the dose range of 0.35 mg/kg to 3 mg/kg based on NCA derived PK parameters in adults patients received 0.35 mg/kg, 1 mg/kg, and 3 mg/kg in Study LAL-CL01 and 1 mg/kg in Study LAL-CL02.

Whereas the sebelipase alfa exposure at 1 mg/kg dose was approximately 3-fold of the exposure at 0.35 mg/kg dose, there was a greater than dose-proportional increase (approximately 10- to 15-fold) in exposure between 1 mg/kg and 3 mg/kg doses.

2.6. Intrinsic Factors

2.6.1. What are the major intrinsic factors responsible for the inter-subject variability in exposure in LAL deficiency patients and how much of the variability is explained by the identified covariates?

Among multiple covariate tested in the population PK analysis with data from patients with late-onset LAL deficiency, body surface area (BSA) was the only influential covariate identified for clearance of sebelipase alfa, and no covariates were significant for V_c.

For the population PK analysis, the structural PK model was a one-compartment model. Potential covariates including age, body weight, body surface area, race, sex, serum creatinine, creatinine clearance, and anti-drug antibody titer were tested in covariate analyses and only the BSA was found to be a statistically significant covariate on CL. In the final PK model, the covariate of body surface area (BSA) on CL was implemented empirically as a step function to distinguish the CL at 3 mg/kg dose from CL at 0.35 and 1 mg/kg doses and estimate the difference in CL between 3 mg/kg and the other two lower dose levels. Refer to the *Pharmacometrics Review* for more detailed information.

Age was not found to be a significant covariate on CL and V_c in the population PK analysis.

Body Surface Area

The sebelipase alfa clearance increased with increasing body surface area (Figure 4), supporting a body size (e.g., body weight) based dosing regimen.

Figure 4. Sebelipase Alfa CL versus BSA

Source: Population PK Report SYN201301 Figure 46

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Elderly

No PK information is available for the elderly patient population with LAL deficiency as the median age (range) of the enrolled subjects was 13 (4 – 58) years old in the pivotal trial LAL-CL02, and 29 (19 -45) in Study LAL-CL01.

Pediatric Patients

The PK of sebelipase alfa in pediatric patients < 6 months of age has not been adequately characterized (Study LAL-CL03).

Table 8 summarized the population PK model-derived PK parameters stratified by age groups for 47 pediatric subjects (4-17 years) and 18 adults enrolled in Study LAL-CL02 who received 1 mg/kg dose once every two weeks. The data showed that the 4-11 years old pediatric group appeared to have lower exposure compared to the 12-17 years old pediatric and adults group.

The efficacy data (% LDL-c change from baseline) summarized in Table 9 showed that sebelipase alfa treated subjects in all three age groups experienced a statistically greater response than placebo treated subjects. There was no clear trend of differences in the sebelipase alfa treatment effect across the three age groups based on two subgroup analyses. The first subgroup analysis showed that the %LDL-c reduction was higher in sebelipase alfa treated subjects than in the placebo treated subjects by 16%, 23%, and 29% for 4-11 year-olds, 12-17 year-old, and adults, respectively. The second subgroup analysis showed that, among patients whose baseline LDL-c levels were abnormal (≥ 130 mg/dL), the proportion of subjects who had the LDL-c level reduced to within the normal range (<130 mg/dL) at Week 20 was greater in sebelipase alfa treated group than in the placebo group by 36%, 36% and 28% in 4-11 year-olds, 12-17 year-old, and adults, respectively. These data support the use of 1 mg/kg dosing regimen in all three age groups.

Table 8: Mean (SD) Population Pharmacokinetics Parameters in Study LAL-CL02

Parameter	Study LAL-CL02 – Children and Adults 1 mg/kg once every other week					
	4-11 years old n=24		12-17 years old n=23		≥18 years old n=18	
	Week 0	Week 22*	Week 0	Week 22*	Week 0	Week 22*
AUC_{ss} (ng·hr/mL)	1133.8 (989.8)	941.6 (388.2)	1436.4 (605.6)	1453.6 (699.2)	1989.3 (991.2)	1861.0 (598.6)
C_{max} (ng/mL)	571.7 (421.5)	489.6 (205.2)	736.4 (323.4)	783.6 (479.6)	1076.9 (555.7)	957.0 (302.8)
T_{max} (hr)	1.2 (0.5)	1.3 (0.6)	1.2 (0.5)	1.1 (0.3)	1.4 (0.6)	1.3 (0.6)
CL (L/hr)	28.8 (9.1)	31.1 (7.1)	35.1 (10.1)	37.4 (12.4)	36.4 (9.9)	38.2 (12.5)
V_c (L)	3.3 (2.5)	3.6 (3.0)	5.0 (2.3)	5.4 (2.4)	5.5 (1.7)	5.3 (1.6)
$T_{1/2}$ (hr)	0.1 (0.09)	0.1 (0.07)	0.1 (0.06)	0.1(0.06)	0.1 (0.08)	0.1 (0.06)

Source: Response to Clinical Pharmacology IR dated 05/07/2015.

AUC_{ss} = Area under the plasma concentration time curve at steady-state C_{max} = Maximum concentration T_{max} = Time to maximum concentration CL = Clearance V_c = Central volume of distribution T1/2 = Half-life

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Table 9: Percent Change from Baseline in LDL-c and the Number of Subjects with Abnormal LDL-c (>=130 mg/dL) at baseline Who Achieved Normal LDL-c (<130 mg/dL) at Week 20 by Age in Study LAL-CL02

	4 – 11 years		12 – 17 years		≥ 18 years old	
	SA	Placebo	SA	Placebo	SA	Placebo
Total number of subjects enrolled in the study	14	10	9	14	13	6
% Change from Baseline LDL-c (Mean ± SD)	-17 ± 25	-0.7 ± 11.1	-32 ± 17	-9 ± 13	- 38 ± 18	-9 ± 16
Differences in % Change from Baseline LDL-c	-16		-23		-29	
Total number of subjects with abnormal LDL-c (≥ 130 mg/dL)	14	10	7	14	11	6
Total number (proportion) of subjects who achieved normal LDL-c (<130 mg/dL)	5 (36%)	0	3 (43%)	1 (7%)	5 (45%)	1 (17%)
Proportion Difference	36		36		28	

Source: Study LAL-CL02 tables-figures, pages 133/11252 and Response to Drug Trials Snapshots IR dated 05/14/2015.

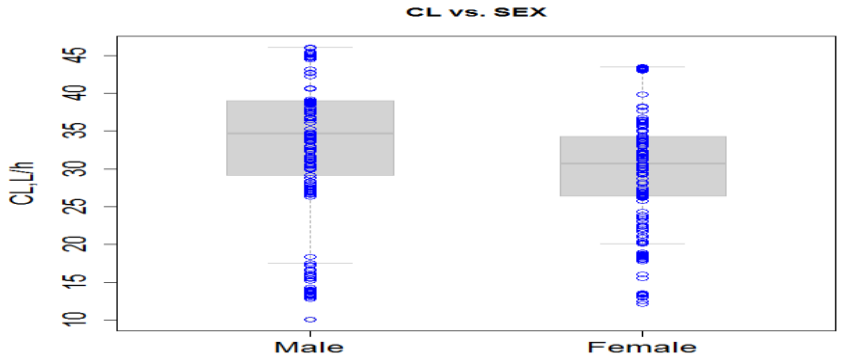
Race

Among the 79 subjects who had PK data in 4 clinical studies, there were 65 Caucasians, 2 Asians, 2 Japanese, 2 Black, 1 Hispanic, 4 other and 3 not provided. Because of extremely limited number of subjects in each of the non-Caucasian race categories, comparing the PK parameters across different race categories will not be informative.

Sex

Male (n= 42) and female (n=37) subjects appeared to have comparable sebelipase alfa CL (Figure 5).

Figure 5. Boxplot of sebelipase alfa Clearance (CL) in Male and Female subjects with overlay of individual subject data in Studies LAL-CL01 and LAL-CL02 (Source: plot generated by the reviewer based on population estimated CL values).



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Renal impairment

No formal studies were conducted to examine the effects of renal impairment on the PK of sebelipase alfa.

Hepatic impairment

No formal studies were conducted to examine the effects of hepatic impairment on the PK of sebelipase alfa.

2.6.2. Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended?

None.

2.6.3. Does genetic variation impact exposure and/or response?

No, genetic variation of the *LIPA* gene (the gene encoding the lysosomal acid lipase/cholesteryl esterase) did not appear to impact sebelipase alfa exposure or clinical response in pediatric and adult patients with LAL deficiency. However, potential impact of genetic mutation on exposure and response was not evaluated in patients with infantile-onset LAL deficiency.

The genetic mutation for allelic variants of the *LIPA* gene was performed in all 4 studies. The c.849G>A mutation was the most commonly found mutation in children and adults with LAL deficiency. Subjects who have the common mutation were further divided into two groups (homozygous and confirmed or presumed compound heterozygous for the mutation)

All 6 infants who had *LIPA* genetic testing in Study LAL-CL03 were classified as with "other" mutations and distinct mutations were identified in each of the 6 subjects. Therefore, the Applicant did not evaluate the potential relationship between genotype mutation status and exposure and/or response to sebelipase alfa.

Among 66 pediatric and adult patients in Study LAL-CL02, 32% (21/66) were homozygous for the c.849G>A mutation, 53% (35/66) were heterozygous for the c.849G>A mutation, and 15% (10/66) were classified as having “other” mutations. Of the 9 adult subjects enrolled in Study LAL-CL01/LAL-CL04, 8 subjects were heterozygous and 1 subject was a homozygous for the c.849G>A mutation.

The Applicant evaluated the effect of mutation on PK, efficacy, and immunogenicity for subjects in Study LAL-CL02.

PK

Graphical comparison of the population PK model estimated AUC for Week 0 among the 3 mutation categories as described (Figure 6) showed a high degree of overlap in the observed AUC and C_{max} values observed among these 3 mutation categories, suggesting a consistency in the exposure to sebelipase alfa irrespective of the genotype mutation status.

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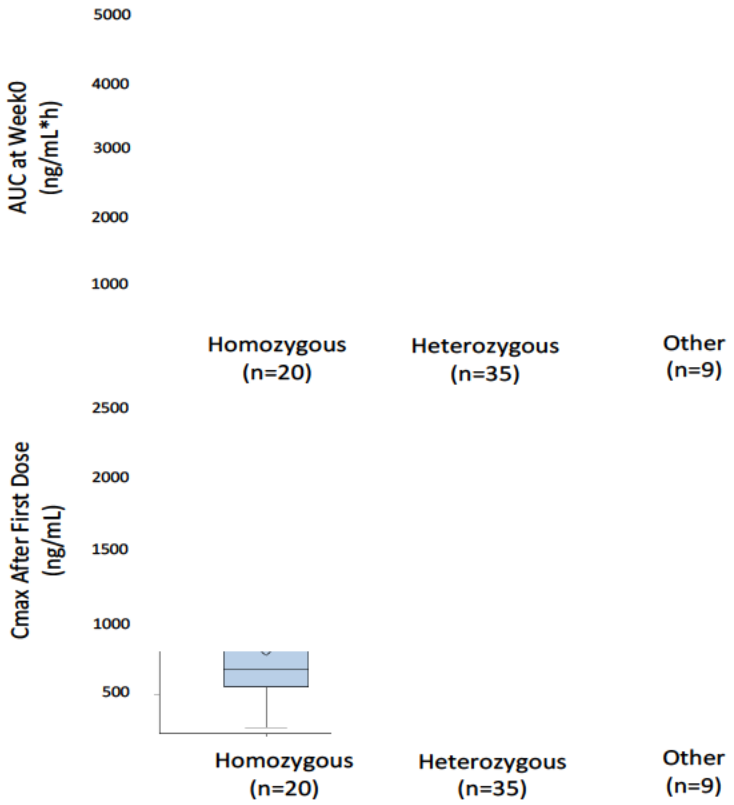
Figure 6. Boxplots of Sebelipase Alfa Estimates of AUC and C_{max} at Week 0 (Population Pharmacokinetic Analysis) According to Genotype Mutation Category in Study LAL-CL02



Source: Summary of Clin Pharm, Figure 8.

Efficacy

The Applicant evaluated the impact of genetic mutation on the efficacy endpoints in Study LAL-CL02 at the end of the double blind period (Week 20). No differences were observed among the three mutation categories for LDL-c (Table 10).

Table 10: Summary of % LDL-c Reduction at Week 20 Among Sebelipase Alfa-treated Subjects, by Genetic Mutation Category (Double-blind Treatment Period)

	LDL-c reduction (percentage change from baseline)		
Genetic Mutation Category	**Homozygous (n=11)**	**Heterozygous (n=17)**	**Other Mutation (n=8)**
N	11	17	8
Mean	-29.0	-29.1	-26.3
(SD)	(15.51)	(22.04)	(32.05)

Source: LAL-CL02 Study Report, Table 36.

Immunogenicity

Table 11 summarizes the ADA + incidence by mutation category for each clinical trial. Results showed that the majority (7/10) of ADA+ subjects had "other" mutations and the remaining fraction (3/10) of ADA+ subjects had heterozygous c.849G>A mutation.

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Table 11. The Summary of ADA Positive Incidence by Mutation Category

	Number of ADA+ subjects / number of subjects in mutation category			
Patient population	Infants	Children and Adults	Adults	All
Study number	(Study LAL-CL03)	(Study LAL-CL02)	(Study LAL-CL01 / LAL-CL04)	4 studies combined
Total N tested for LIPA gene mutation	6	66	9	81
Homozygotes for c.849G>A mutation	-	0/21	0/1	0/22
Heterozygotes for c.849G>A mutation	-	2/35	1/8	3/43 (7%)
"Other" mutations	4/6	3/10	0/0	7/16 (44%)
Sub-total	4/6	5/66	1/9	10/81 (12%)

2.6.4. Immunogenicity

2.6.4.1. What is the incidence of the formation of the anti-sebelipase alfa antibodies (ADA)?

In the overall study population enrolled in 4 clinical trials, the immunogenicity incidence was 20%; 10 of 51 were ADA positive and 41 of 51 were ADA-negative (Table 12).

Table 12. Summary of Immunogenicity Incidence for 4 clinical trials

Patient population	Infants	Children and Adults	Adults	All
Study number	(Study LAL-CL03)	(Study LAL-CL02)	(Study LAL-CL01 / LAL-CL04)	4 studies combined
Total number of subjects*	7[a]	35[b]	9[c]	51
ADA-negative	3/7 (43%)	30/35 (86%)	8/9 (89%)	41/51 (80%)
ADA-positive	4/7 (57%)	5/35 (14%)	1/9 (11%)	10/51 (20%)

[a] Number of subjects evaluable in Study LAL-CL03. [b] Number of sebelipase alfa-treated subjects that completed the 20-week double-blind period of Study LAL-CL02. [c] Number of subjects enrolled in Study LAL-CL01.

Among infants with LAL deficiency (Study LAL-CL03), 4 of 7 evaluable subjects (57%) had positive ADA titers at 1 or more post-dose assessments. In these 4 subjects, positive titers first occurred at Week 5 (n=1), Week 8 (n=2), or Week 59 (n=1). As shown in Figure 9, one subject had a single positive titer and 3 subjects had positive ADA titers at multiple time-points during the study; the maximum titers ranged from 1/153 to 1/790 between Weeks 8 and 96. All 3 subjects who had multiple positive ADA titers decreased from with continued dosing, and 2 of these subjects became ADA negative.

For pediatric and adult patients enrolled in Study LAL-CL02, 5 of 35 treated subjects (14%) that completed the 20-week double-blind period of the study were ADA positive. Among 5 ADA-positive subjects, 3 subjects had positive ADA titers at only a single time point, and 2 subjects had positive titers at more than one time point; the maximum ADA titers were 1/448 and 1/816, both observed at Week 4. Thereafter, the ADA titers decreased over time. After Week 28, none of the ADA+ subjects

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had positive ADA titers. None of the subjects in the placebo group had a positive ADA titer during the double-blind period. Among adult patients enrolled in Study LAL-CL04, 1 of 9 had a single ADA-positive result at Week 4.

2.6.4.2. Do the anti-sebelipase alfa antibodies have neutralizing capability and what is the incidence (rate) of the formation of the anti-sebelipase alfa neutralizing antibody (NAb)?

Yes, in 50% (2 of 4) of ADA-positive infants the anti-sebelipase alfa antibodies had neutralizing capability for both LAL enzyme activity and LAL cellular uptake; on the other hand, none of the ADA-positive pediatric and adult subjects developed neutralizing antibodies.

Two infant subjects tested positive for neutralizing antibodies that inhibit both LAL enzyme activity and LAL cellular uptake in Study LAL-CL03. One subject (b) (6)) had 18.9% inhibition of LAL enzyme activity at Week 5, which subsequently increased to 70.9% at Week 8, 90.3% inhibition at Week 16, and remained above 80% inhibition at all subsequent assessments. This subject also tested positive for neutralizing antibody that inhibits cellular uptake at Week 72. The other subject (b) (6) had 83.2% inhibition of LAL enzyme activity at Week 8 which sustained through Week 48 (82.1% to 89.8%). This subject also tested positive for neutralizing antibody that inhibits cellular uptake at unscheduled assessments at approximately Week 23 and at Week 25. However, the subject was ADA negative at the last assessment at Week 58 (an unscheduled visit)

2.6.4.3. What are the impacts of ADA on sebelipase alfa PK, efficacy and safety?

Overall, it is not feasible to draw a definitive conclusion on the impact of ADA, or lack thereof, on PK, PD, efficacy, and safety. Although one infant who developed ADA with sustained neutralizing capability for LAL enzyme activity and LAL cellular uptake was associated with suboptimal rate of growth leading to dose escalation to 5 mg/kg, the lack of efficacy cannot be directly attributed to the immunogenicity due to other confounding factors.

<u>PK:</u>

Among 4 ADA positive infants in Study LAL-CL03, one subject (Subject (b) (6)) had no detectable sebelipase alfa concentration while the other 3 subjects had detectable concentration after ADA formation (Figure 7). Although Subject (b) (6) had the highest ADA titer at the time when the sebelipase alfa serum concentration was undetectable, it was not feasible to evaluate the effect of ADA on PK because this subject had only one PK sample collected in the study. Among 5 pediatric and adult subjects who developed positive ADA titers in Study LAL-CL02, one subject had notably higher sebelipase alfa concentrations at Week 22 compared to Week 0 whereas the remaining subjects had qualitatively similar concentrations at Week 0 and Week 22 (Figure 8). Of note, the ADA titers were below 100 at the time of PK sampling in all subjects.

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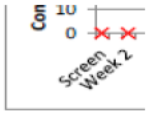
Figure 7. Sebelipase Alfa Concentrations and ADA Titers Over Time in Infant Subjects with Positive ADA Titers in Study LAL-CL03

(b) (6)

(b) (6)

(b) (6)

(b) (6)



Note: Bars indicate serum concentrations of sebelipase alfa (measured only at time points indicated by bars or, if a concentration was below the limit of quantification, an arrow on the x-axis); crosses indicate anti-drug antibody dilution titer; crosses with shading indicate detection of neutralizing antibodies capable of inhibiting LAL enzymatic activity. Source: Summary of Clin Pharm, Figure 20.

Figure 8. Sebelipase Alfa Concentrations and ADA Titers Over Time in Pediatric and Adult Subjects with Positive ADA in Study LAL-CL02

(b) (6)

(b) (6)

(b) (6)

(b) (6)

(b) (6)

Note: Bars indicate serum concentrations of sebelipase alfa (measured only at Weeks 0 and 22); crosses indicate anti-drug antibody dilution titer. Source: Summary of Clin Pharm, Figure 17.

Efficacy:

During the double-blind period of Study LAL-CL02, 5 subjects in the sebelipase alfa group had positive ADA titers on at least 1 occasion, but evidence for the effectiveness of sebelipase alfa treatment in terms of clinical outcome measurements (serum lipids) was seen in all 5 subjects.

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For 1 of 4 infants in Study LAL-CL03, the neutralizing antibodies may have been a factor in the continued suboptimal rate of growth (weight-for-age), leading to a dose increase to 5 mg/kg. However, other factors may have contributed to the observed suboptimal growth rate, such as infection, feeding difficulties, and chronic prednisolone premedication. Other clinical outcome measures (serum lipids) showed no notable or unexplained changes during the period when ADAs and neutralizing antibodies were present. The remaining 3 ADA+ subjects showed no evidence of a potential loss of response in any clinical outcome measures.

Safety:

The Table 13 summarizes treatment-emergent adverse events (TEAEs) by ADA status and overall for subjects in the Pooled Safety Set from 4 clinical studies LAL-CL01, LAL-CL02, LAL-CL03 and LAL-CL04. Although some differences in the frequency of TEAEs by ADA status were noted, due to small number of subjects who were ADA + (n=10) compared with the ADA - group (n=74), no definitive conclusions of the impact of antibody positivity on the occurrence or nature of TEAEs could be made.

Table 13: Overview of Treatment-Emergent Adverse Events in the Pooled Safety Set, by Antibody Status and Overall

Category Subcategory	**Antibody Status[c, d], n (% of N)**		**Pooled Safety Set (N=84), n (% of N)**
	Positive (N=10)	**Negative (N=74)**	
Any TEAE	**10 (100.0%)**	**57 (77.0%)**	**67 (79.8%)**
Onset during infusion and ≤4 hours after end of infusion	8 (80.0%)	30 (40.5%)	38 (45.2%)
Onset during infusion and ≤24 hours after end of infusion	8 (80.0%)	36 (48.6%)	44 (52.4%)
Any Related TEAE[a]	4 (40.0%)	15 (20.3%)	19 (22.6%)
Onset during infusion and ≤4 hours after end of infusion	4 (40.0%)	8 (10.8%)	12 (14.3)
Onset during infusion and ≤24 hours after end of infusion	4 (40.0%)	10 (13.5%)	14 (16.7%)
Any Treatment-Emergent SAE	4 (40.0%)	8 (10.8%)	12 (14.3%)
Any Treatment Related SAE[a]	1 (10.0%)	1 (1.4%)	2 (2.4%)
Any IAR[b]	4 (40.0%)	6 (8.1%)	10 (11.9%)
Any TEAE Leading to Death	0	3 (4.1%)	3 (3.6%)
Any TEAE Leading to Study Discontinuation	0	0	0
Any TEAE Leading to Study Drug Discontinuation	0	1 (1.4%)	1 (1.2%)

Source: Summary of Clinical Safety, Table 26.
IAR=infusion-associated reaction; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Note: Events that started on placebo, including those that continued during transition to sebelipase alfa, are not included.
[a] Based on Investigator's assessment of whether event is at least possibly related to study drug.
[b] Based on Investigator's assessment of whether event is an infusion-associated reaction.
[c] All TEAEs are included, regardless of antibody positive status and the timing of the event relative to first antibody positive result, where applicable.
[d] Subjects who had at least one positive ADA result during treatment are referred to as ADA positive, and subjects who never tested positive for ADA (including subjects who did not have available post-Baseline ADA testing) are referred to as ADA negative.

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2.7. Extrinsic Factors

2.7.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

No formal studies on extrinsic factors have been conducted.

2.8. General Biopharmaceutics

2.8.1. Was the manufacturing process changed during the development program? (Include a table listing all the products used throughout the clinical development programs.)

The sebelipase alfa formulation used in clinical studies is the formulation proposed for marketing.

Some changes were made to the Drug Substance (DS) manufacturing process during development. The process for sebelipase alfa DS purification has evolved with improvements over time. The initial process was used to support non-clinical and clinical studies. The process was modified during clinical development to assure that materials used in pivotal clinical studies were manufactured by a process that was representative of the intended commercial process. This modified process (referred to as the "Pivotal Clinical" process) was originally performed at [redacted] (b) (4) and subsequently transferred and also performed at [redacted] (b) (4). Two different manufacturing sites were established for pivotal clinical material to ensure robust supply.

According to the Applicant, no significant changes have been made to the overall process since initiation of pivotal clinical development, although some additional controls and process optimization were implemented for the proposed commercial process. These process changes were developed and implemented to ensure batch-to-batch consistency of the quality, safety and potency of the DS, [redacted] (b) (4). The final to-be marketed product was deemed comparable to those used in the clinical studies based on CMC evaluations (See CMC review by Dr. Downey, Christopher for more details).

2.8.2. Was the proposed to-be-marketed formulation/presentation comparable to the formulation used in the pivotal clinical trials with respect to pharmacokinetics and/or pharmacodynamics?

Not applicable. The proposed to-be-marketed formulation was used in two pivotal clinical trials LAL-CL02 and LAL-CL03.

2.9. Analytical Section

2.9.1. What bioanalytical methods are used to assess therapeutic protein concentrations? Briefly describe the methods and summarize the assay performance.

A validated bioanalytical method (ELISA-0558-VAL-002) was used throughout the clinical development of sebelipase alfa for the quantification of sebelipase alfa activity in human serum (Validation Report 8285-709).

Briefly, Sebelipase alfa concentrations were determined using an enzyme-based quantitative assay for the measurement of SBC-102 activity in human serum. [redacted] (b) (4)

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(b) (4)

Table 14 summarizes the assay performances from the validation report and the in-study quality control.

Table 14. Quantitative serum sebelipase alfa assay performance characteristics (VR #8285-709)

Assay description and validation parameters	**Results**
Method	Enzymatic Assay
Plate Type	Costar ELISA plate Cat.: 3590
Compound analyzed	SBC102 (sebelipase alfa)
Matrix	Human serum
Sample volume	0.5 mL requested (0.25 mL minimum)
Minimum required dilution (MRD)	1/3
*LLOQ**	3.125 ng/mL
*ULOQ**	100.000 ng/mL
QC samples	Six concentrations in non-diluted human serum: 300, 225, 40, 14.063, 9.375 and 4.688 ng/mL. After dilution with Assay Buffer at 1/3, the concentrations of QCs are changed to 100, 75, 13.333, 4.688, 3.125 and 1.563 ng/mL.
QC Acceptance Criteria	▪ Two sets of QCs (Low, Medium, and High) are included at the front and back of each plate. ▪ (b) (4)
Inter-assay Precision and Accuracy	%RE - QCs ≤ 25%, ≤ 30% at LOQs %CV - QCs ≤ 25%, ≤ 30% at LOQs Except concentration at 4.688 ng/mL in non-diluted human serum (1.563 ng/mL after dilution at 1/3 of Assay Buffer), it has a CV% of (b) (4)% , therefore, the LLOQ at this level is not acceptable.
Intra-assay Precision and Accuracy	%RE - QCs ≤ 25%, ≤ 30% at LOQs %CV - QCs ≤ 25%, ≤ 30% at LOQs Except one out of the six sets of QCs failed for percent CV for the following validation runs: VAL-022, 225 ng/mL (in non-diluted human serum) failed at (b) (4) CV. VAL-021, 40 ng/mL (in non-diluted human serum) failed at (b) (4) CV.
Method Selectivity	Normal Human Serum Samples: 90% tested samples passed acceptance criteria Hemolyzed serum samples: 5/5 samples passed acceptance criteria lipaemic serum samples: 4/5 of lot tested with low recovery of the SBC-102

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	activity, not acceptable
Stability	Up to 6 Freeze/Thaw (F/T) cycles at -60 to -80°C Three hour on bench top Twenty-four hour refrigerator One-month storage stability at -60 to -80 ^{o}C
Dilution Linearity	% RE ≤ 25%, ≤ 30% at LOQs %CV ≤ 25%,≤ 30% at LOQs Demonstrated acceptable with dilution factor ranging from 400 to 12800 using the Ultra-high QC (111,000 ng/mL).
Calibration curve	9 calibration samples (0.000 ng/mL to100.000 ng/mL in 33% human serum matrix diluent) with 4-Parameter fit. The assay acceptance criteria for calibrators are: (b) (4)

LLOQ, lower limit of quantification; ULOQ, upper limit of quantification; LOQs include both the LLOQ and the ULOQ. QC, quality control. *The LLOQ and ULOQ are freshly prepared from SBC-102 stock at in-well concentrations at the assay. RE: relative error; CV: coefficient of variation.

Reviewer's comments: *The Applicant did not include the plan and results for the reanalysis of the incurred samples, which is recommended in the 2013 FDA guidance on "Bioanalytical Method Validation.*"

2.9.2. What bioanalytical methods are used for pharmacodynamic/biomarker studies? Briefly describe the performance of the assays.

Pharmacodynamic assessments incorporated multiple PD endpoints including liver enzymes (Alanine aminotransferase, etc.); serum lipids (total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c). All were conducted at central laboratories using standard clinical biochemistry assay methodology.

2.9.3. What bioanalytical methods are used for immunogenicity assessment? Briefly describe the performance of the assays.

ADA assay

A bridging enzyme linked immunosorbent assay (ELISA) method was implemented to evaluate the ADA in immunogenicity samples using a stepwise approach for screening, confirmation, and titration. In brief, plates are coated with SBC-102, followed by blocking, washing, and then incubating with 1/20 diluted controls and samples. After incubation and plate washing, biotinylated SBC-102 is added to detect any bound anti-SBC-102 antibodies. Poly-HRP Streptavidin conjugate is used to detect the immobilized biotinylated SBC-102. The bound HRP conjugate is detected with the HRP substrate tetramethyl benzidine (TMB), the plate is read colorimetrically on a plate reader. The ADA assay has a sensitivity of 500 ng/mL and a drug tolerance of 50 mcg/mL when 1250 ng/mL of positive control antibody was used (Table 15).

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Reviewer's assessment on the drug tolerance of the binding assay: *Overall, the drug tolerance of the assay appeared to be appropriate for measuring the ADA responses in four clinical trials. The samples for ADA analysis were taken at pre-dose of each dosing cycle (weekly or once every other week), when SBC-102 is present at low or not quantifiable concentrations. Therefore, drug interference does not appear to be an issue.*

See Product Quality Review (immunogenicity section) by João A. Pedras-Vasconcelos, Ph.D., for more detailed information regarding the immunogenicity assay validation.

Table 15. Drug tolerance level of the immunogenicity assays. ADA, anti-drug antibodies; Nab, neutralizing antibodies; PC, positive control.

Assay	Report Study#	ADA PC	Sensitivity	Drug Tolerance Level	
				Sebelipase alfa	ADA PC (ng/mL)
ADA	8285-711	Mouse anti-Lysosomal acid lipase monoclonal antibody	500 ng/mL	50 mcg/mL	1500 ng/mL
				200 ng/mL	2500 ng/mL or 5000 ng/mL
Nab ADA	BxSD R1180094-ig	rabbit anti-sera Igor-2	1.48 mcg/mL	25 mcg/mL	10 mcg/mL
				15 mcg/mL	2.5 mcg/mL

Neutralizing ADA assay that inhibits LAL enzyme activity

For the detection of the neutralizing ADA (Nab) that inhibits LAL enzyme activity, an enzymatic activity based neutralizing assay was used. Briefly, the enzyme activity was measures in the presence of SBC-102 at a constant concentration (25 ng/mL) and the changes in the activity were used as method endpoint. Baseline human serum matrix pool was used as negative control (NC), while the positive control was generated by spiking a commercial rabbit anti-lysosomal acid lipase (LAL) polyclonal antibody into baseline human serum matrix pool. The PCs, NC and samples were incubated with SBC-102, and then they were mixed with the SBC-102 substrate, 4-MUO and incubated at 37°C for 30 minutes. At the end of the incubation the stop solution was added to terminate the enzymatic reaction and fluorescence signals (from 4MUO cleaved product,4-methylumbelliferone, or 4MU) from controls and samples were measured using a microplate reader. Fluorescence signals (relative fluorescence unit, RFU) generated from positive controls and samples were used to calculate the % inhibition.

The Nab assay has a sensitivity of 25 mcg/mL in human serum but the assay did not tolerate sebelipase alfa at the lowest concentration tested (final concentration at 500 ng/mL) in the presence of the positive control ranging from 1.563 to 50 μg/mL.

According to the Applicant, this assay limitation may not impact the sample analysis because of the following reasons: 1) The SBC-102 distributes to the targeted tissue quickly after infusion with half – life of less than 2 hours after infusion; and 2) The drug is administered at weekly intervals and the antibody samples are taken at pre-dose when the estimated circulating concentration of SBC-102 should below the quantification level.

Reviewer's assessment on the drug tolerance of the binding assay: *The neutralizing ADA assay appears to be insensitive. See Product Quality Review (immunogenicity section) by João A. Pedras-Vasconcelos, Ph.D., for more detailed information regarding the immunogenicity assay validation.*

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Neutralizing ADA assay that inhibits cellular uptake of LAL in a rat macrophage cell line

For the detection of the neutralizing ADA (Nab) that inhibits cellular uptake of LAL, a cell based neutralization assay that utilizes NR8383.1 cell line (Normal Rat Macrophage cell line, suspension cell line) as a test system was used. Briefly, NR8383.1 cells could uptake SBC-102 through macrophage mannose receptors (MMR). In the presence of anti-SBC-102 neutralization antibodies, the SBC-102 uptake by cells was blocked. The presence of anti-SBC-102 antibodies that blocked the uptake of SBC-102 could be evaluated by measurement of SBC-102 activity from cell lysates in cells exposed to controls and samples. The activity of sebelipase alfa in these cell lysates was measured by sebelipase alfa enzymatic assay, from which the % neutralization (% inhibition) of the positive controls and samples were calculated.

The assay could only tolerate sebelipase alfa at 0.5 µg/mL with positive controls concentration at 50 µg/mL.

According to the Applicant, an ADA-positive sample could contain antibody that neutralized enzyme activity, cellular uptake, or both. For samples in which both inhibition of enzyme activity and cellular uptake were reported, it should be noted that the presence of antibodies that inhibit enzyme activity could potentially interfere with measurement of cellular enzyme activity and thus complicate interpretation of data from the assay measuring inhibition of cellular uptake.

Reviewer's assessment on the drug tolerance of the binding assay: *The neutralizing ADA assay appears to be insensitive. See Product Quality Review (immunogenicity section) by João A. Pedras-Vasconcelos, Ph.D., for more detailed information regarding the immunogenicity assay validation.*

3. LABELING RECOMMENDATIONS

Detailed labeling revisions are summarized as below. The currently recommended draft labeling text by the review team was based on the clinical study results and the Guidance for Industry: "Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, Content, and Format" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm109739.pdf).

Proposed labeling by the Applicant	Labeling recommendations by the FDA
12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action (b) (4)	12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action Sebelipase alfa binds to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes. Sebelipase alfa catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol and free fatty acids. The primary site action of the LAL enzyme is the lysosome, where the enzyme causes the breakdown of lipid particles including LDL-cholesterol (LDL-c). Deficient LAL enzyme activity results in the lysosomal accumulation of cholesteryl esters and triglycerides in multiple organs, including the liver, spleen, intestine, and the walls of blood vessels. Lipid accumulation in the intestinal wall leads to malabsorption and growth failure. Dyslipidemia is common with elevated LDL-c

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(b) (4)

12.2 Pharmacodynamics

(b) (4)

12.3 Pharmacokinetics

(b) (4)

and triglycerides and low HDL-c, and contributes to increased liver fat content and progression of liver disease.

12.2 Pharmacodynamics

In clinical trials, after initiation of dosing with Kanuma, breakdown of accumulated lysosomal lipid led to initial increases in circulating cholesterol and triglycerides within the first 2 to 4 weeks of treatment. Improvements in dyslipidemia related to LAL deficiency were seen within 8 weeks of treatment with Kanuma.

12.3 Pharmacokinetics

The pharmacokinetic profile of sebelipase alfa was nonlinear with a greater than dose-proportional increase in exposure between 1 and 3 mg/kg based on non-compartmental analysis of data from 26 adults. No accumulation was observed following once weekly or once every other week dosing.

Using a population pharmacokinetic model, sebelipase alfa pharmacokinetic parameters were estimated for 65 pediatric and adult patients who received intravenous infusions of Kanuma at 1 mg/kg at Week 22 (Table 4); 24 patients were 4 to 11 years old, 23 were 12 to 17 years old, and 18 were adults. The pharmacokinetic profiles of sebelipase alfa were similar between adolescents and adults. The T_{max} and $T_{1/2}$ were similar across all age groups.

Table 4: Mean (SD) Population Pharmacokinetics Parameters in Pediatric and Adult Patients Receiving 1 mg/kg Once Every Other Week

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

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(b) (4)	AUC = Area under the plasma concentration time curve. C_{max} = Maximum concentration. T_{max} = Time to maximum concentration. CL = Clearance. V_c = Central volume of distribution. $T_{1/2}$ = Half-life. (b) (4)

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4. APPENDIX

4.1 PHARMACOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Primary Reviewer	Jing Fang, Ph.D.
Secondary Reviewer	Nitin Mehrotra, Ph.D.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Has the most appropriate dosage regimen of sebelipase alfa (dose escalation plan, if applicable) been identified for the infantile-onset LAL deficiency?

We agree with the proposed starting dosage regimen of 1 mg/kg every week with up-titration to 3 mg/kg every week; however, we cannot confirm whether the dosage regimen is most appropriate or not. There was no independent pharmacometric analysis conducted to answer this question.
As demonstrated by the results for the primary efficacy endpoint (the proportion of subjects surviving at 12 months of age) from the pivotal trial LAL-CL03: the proportion (exact 95% CI) of subjects in Study LAL-CL03 surviving to 12 months of age was 67% (29.93%, 92.51%); In contrast, the proportion (exact 95% CI) of patients surviving to 12 months of age in the natural history Study LAL-1-NH01 was 0% (0%, 16.11%).

It is important to note that there is different inter-patient dosing escalation plan in the trial (See Table 3 in Section 1.3.3). Although the starting dosage regimen was 0.35 mg/kg every week in majority of subjects in the trial (8 out of 9), the exposure is limited (1 to 2 infusions). Two subjects died after receiving a single infusion dose of 0.35 mg/kg. In addition, due to extremely limited sample size (n=9) from the pivotal trial LAL-CL03, the exposure-response analysis would not be informative. The data at individual level were looked from a clinical perspective to understand the effect of treatment on various biomarkers, which provided supportive evidence of the proposed dosing regimen (see Clinical review from Dr. Lauren Weintraub for more details). Considering that infantile-onset LAL deficiency is a rapidly progressive, lethal condition, from a clinical pharmacology perspective, we agree with the Applicant's proposed starting dosage regimen of 1 mg/kg every week with an option of up-titration to 3 mg/kg every week.

1.1.2 Does the Dose/Exposure-response relationship for efficacy support the proposed dose of 1 mg/kg IV every other week in late-onset LAL deficiency?

Yes, the proposed dose and dosing interval is acceptable. Based on the results for the primary efficacy endpoint (LDL at Week 20) from the pivotal trial LAL-CL02, the mean percentage change from baseline of LDL in the sebelipase alfa treatment group (-28.42%) was significantly higher than placebo (-6.25%). Note that there is only one dosing regimen in sebelipase alfa treatment group; no dose-response relationship could be performed. Analysis was performed by the Applicant to explore relationships between the percentage change from baseline and cumulative area under the plasma concentration-time

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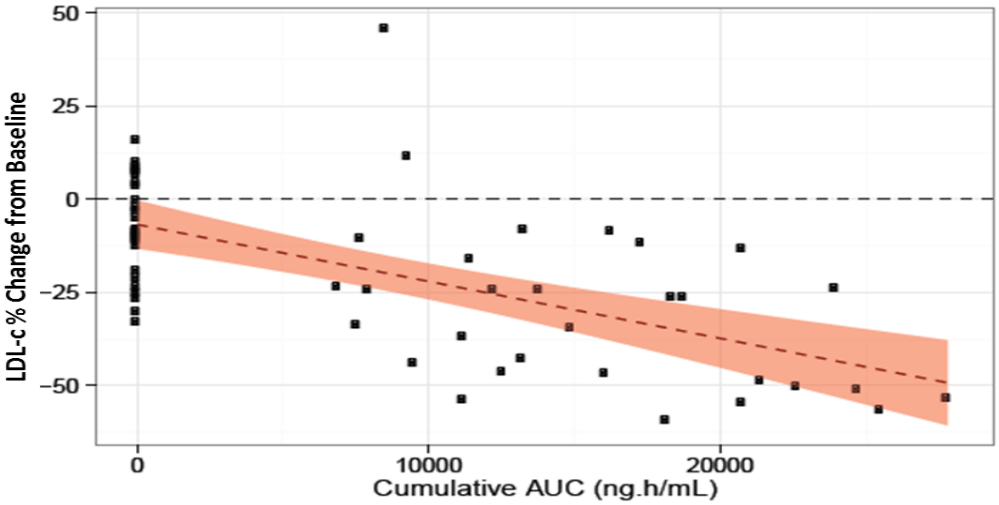
curve (AUC_{cum}) at Week 20 (Figure 1). The trend of exposure-response (higher exposures associated with higher efficacy) with the primary efficacy endpoint of LDL provides supportive evidence of effectiveness. No exposure-response was evident in any of the other secondary efficacy endpoints (HDL-c, Cholesterol, Triglycerides, ALT and liver fat %).

It is important to note that the relevance of systemic exposure is unknown. Sebelipase alfa has a very short plasma half-life (~ 6 minutes) and lysosomes are the site of action. The biological activity is primarily driven by enzyme concentrations and duration of exposure in the lysosomes of target tissue. In addition, it is unclear about the relationship between the systemic exposure and the concentration of sebalipase alfa at the site of action.

The sebelipase alfa clearance increased with increasing body surface area (Figure 2), supporting a body size (e.g., body weight) based dosing regimen.

Taken together, the systemic exposures achieved by Week 20 were shown to be adequate to achieve clinical efficacy. Therefore, we agree with the Applicant proposed dosing regimen of 1 mg/kg IV every other week in patients with late-onset LAL deficiency.

Figure 2. Exposure-Response Relationship for the Primary Efficacy Endpoint (%LDL-c Change from baseline) with Sebelipase Alfa Cumulative AUC at Week 20 (Study LAL-CL02).



The dashed red line represents a least squares linear regression, the shaded regions are the 95% CIs of the regression lines, and the dashed grey line indicates no change from baseline.
Source: Applicant's Updated Clinical Pharmacology Response 2 to IRs dated 04/16/2015, Figure 11

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Figure 2. Sebelipase Alfa CL versus BSA

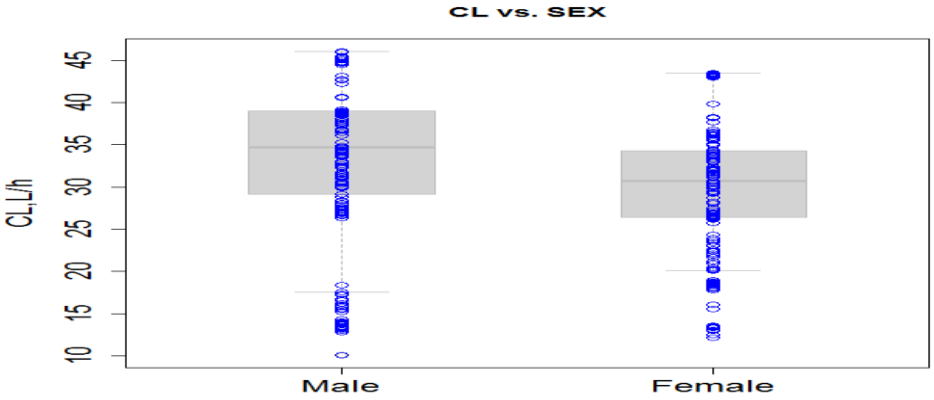
Source: Population PK Report SYN201301 Figure 46

1.1.3 Is there a need for dose adjustment based on age, race or sex?

No, Based on the population PK analysis, after adjusting for BSA, there was no effect of sex on PK of sebelipase alpha (Figure 3). Since about 82% % of the patients were Caucasians, information on dosing by race is limited.

It is important to note that even after body weight based dosing, younger age patients had lower exposures, however, subgroup analysis of efficacy by age indicated that % reduction of LDL from baseline was statistically greater in sebelipase alfa treated group than in placebo group in all age categories. Also, the relevance of systemic exposures for efficacy is unknown, therefore, no dose adjustment is recommended based on age. For details, please refer to Section 2.6.1 of the QBR.

Figure 3. Boxplot of sebelipase alfa Clearance (CL) in Male and Female subjects with overlay of individual subject data in Studies LAL-CL01 and LAL-CL02.



1.2 Recommendations

The proposed dosing regimens are acceptable.

1.3 Label Statements

Detailed labeling recommendations are included in Section 3.

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2 PERTINENT REGULATORY BACKGROUND

Synageva is seeking FDA approval for sebalipase alfa, a recombinant human lysosomal acid lipase (rhLAL), for the treatment of patients with Lysosomal Acid Lipase (LAL) deficiency. There are two phenotypes of LAL deficiency: infantile- onset (historically called Wolman disease, WD) and late-onset LAL deficiency.

The Applicant is providing data from 4 clinical studies containing a total of 84 patients with LAL deficiency. The pivotal trial of infantile-onset LAL deficiency (Study LAL-CL03) succeeded to meet its primary endpoint of the proportion of subjects surviving at 12 months of age. And the pivotal trial of late-onset LAL deficiency (Study LAL-CL02) succeeded to meet its primary endpoint (the mean percentage change from baseline of low-density lipoprotein - cholesterol (LDL-c) at the end of the double-blind treatment period.. At the last time point in the double-blind period, a greater mean percent decrease from baseline in LDL-c was seen in the sebelipase alfa treatment group than in the placebo group (-28% versus -6%); and the difference between groups was statistically significant. Please refer to the Individual Study Review for more details of the study results.

3 RESULTS OF APPLICANT'S ANALYSIS

3.1 Infantile-onset LAL Deficiency

The evidence for efficacy of sebelipase alfa for the treatment of infantile-onset LAL deficiency is based on the results of Study LAL-CL03, an ongoing Phase 2/3 multicenter, multinational, single-arm, open-label, repeat-dose, dose escalation study of sebelipase alfa in 9 infants with LAL deficiency (documented growth failure or other clinical evidence of a rapidly progressive course of LAL Deficiency prior to the age of 6 months) and Study LAL-1-NH01, a completed multinational, multicenter, retrospective natural history study of patients presenting with LAL Deficiency before 2 years of age.

The primary efficacy endpoint for Study LAL-CL03 was the proportion of subjects who survived to 12 months of age with sebelipase alfa treatment. Sebelipase alfa demonstrated a clinically meaningful improvement in survival in subjects with LAL Deficiency presenting in infancy. In Study LAL-CL03, the proportion of the 9 subjects surviving to 12 months of age was 67% (95% CI = 29.93%, 92.51%); and the ages of the 6 surviving subjects at their last available assessment ranged from 12.0 to 42.2 months. In contrast, the proportion (exact 95% CI) of patients surviving to 12 months of age in Study LAL-1-NH01 was 0% (0%, 16.11%).

Due to extremely small sample size (n=9) and limited exposure data in Study LAL-CL03. No exposure-response (E-R) analysis could be done to support the Applicant proposed starting dosage regimen of 1 mg/kg every week with up-titration to 3 mg/kg every week in infantile-onset LAL deficiency.

3.2 Late-onset LAL Deficiency

The evidence for efficacy of sebelipase alfa for the treatment of late-onset LAL deficiency is based on the results of Study LAL-CL02, a Phase 3 multicenter, multinational, randomized, placebo-controlled study of sebelipase alfa in 66 subjects (Age ≥ 4 years) with LAL deficiency.

The Applicant proposed primary efficacy endpoint for Study LAL-CL02 was normalization of ALT. However, normalization of ALT neither directly measures clinical benefit of treatment (i.e., how a patient feels, functions, or survives) nor represents a surrogate endpoint reasonably likely to predict clinical benefit in late-onset LAL deficiency. Because LDL is included in the causal pathway of LAL deficiency,

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as LDL cholesterol is made up in part by cholesteryl esters and triglycerides that accumulate in the lysosome when LAL is deficient, thereby contributing to disease manifestations seen in patients with late-onset LAL deficiency. In addition, elevation of LDL is a well-established risk factor for coronary heart disease, and hyperlipidemia and accelerated atherosclerosis are known complications of LAL deficiency. Hence, the Agency has concluded that LDL is the most suitable primary endpoint to assess efficacy in patients with late-onset LAL deficiency (See Mid-Cycle Communication dated 04/24/2015).

3.2.1 Exposure-Response for Effectiveness

The Applicant conducted an exposure-response analysis utilizing data from patients with late-onset LAL deficiency (Study LAL-CL02) to evaluate the relationships between the percentage change from baseline and cumulative AUC at Week 20 (See Figures 1- 2 in Section 2.4.1). The trend of exposure-response (higher exposures appear to be associated with higher efficacy) with the primary efficacy endpoint of LDL provides supportive evidence of effectiveness. Refer to Section 2.4.1 for details.

3.3 Population Pharmacokinetics of Sebelipase Alfa in LAL Deficiency

The population PK dataset was developed from pooled data from adults (studies LAL-CL01 and LAL-CL04), infants (Study LAL-CL03), and children (≥ 4 years old) and adults (Study LAL-CL02). The sebelipase alfa population PK dataset was comprised of 79 subjects contributing a total of 987 evaluable sebelipase alfa serum concentrations.

The population PK analysis was performed using mixed effects modelling methods as implemented in NONMEM (version VII level 2.0, ICON, Hanover, MD), compiled using the Intel Fortran Compiler 14.0.0 for Linux. Models were fitted to either the untransformed data using the FOCE method in NONMEM with the INTERACTION option.

The population PK model for sebelipase alfa was a 1-compartment model described by central volume of distribution (V_c) and clearance (CL). Input was described by a complex dual input model to allow for variability in infusion rate during the recorded infusion time due to the flush. Due to limited PK data available across the dose range, nonlinearity in the PK of sebelipase alfa was described by a reduction in CL for a dose of 3 mg/kg compared to CL for doses < 3 mg/kg. The covariates assessed for the population PK analysis included age, body weight, body surface area (BSA), race, sex, serum creatinine, creatinine clearance, and anti-drug antibody titer. Only BSA was found to be a signicant covariate on CL for doses < 3 mg/kg. Exponential nonlinear relationship centered on the median BSA was incorporated for the CL for doses < 3 mg/kg (CL_{Linear}). According to the Applicant, inclusion of BSA on CL_{Linear} only was more significant than for inclusion on CL for all dose levels. Due to the limited data available across the dose range, a separate covariate analysis was unable to be performed for nonlinear CL.

The parameter estimates for the final population PK model for sebelipase alfa and diagnostic/goodness of fit plots are shown in Table 2 and Figure 4. In addition, the stratified visual predictive check (VPC) and individual PK fitting results for subjects with infantile-onset LAL deficiency from Study LAL-CL03 are shown in Figures 5 - 6.

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Table 2. Parameter estimates for the final sebalipase alfa population PK model.

Proportional
Additive RU
SE = NONM
BOV = betw
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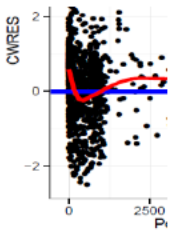
model devel

Source: Population PK Report SYN201301 Table 19.

Figure 4. Diagnostic/Goodness-of-fit plots for the final sebalipase alfa population PK model.



Blue line = line of unity; red line = loess smooth.
Source: Population PK Report SYN201301 Figures 39 -40.

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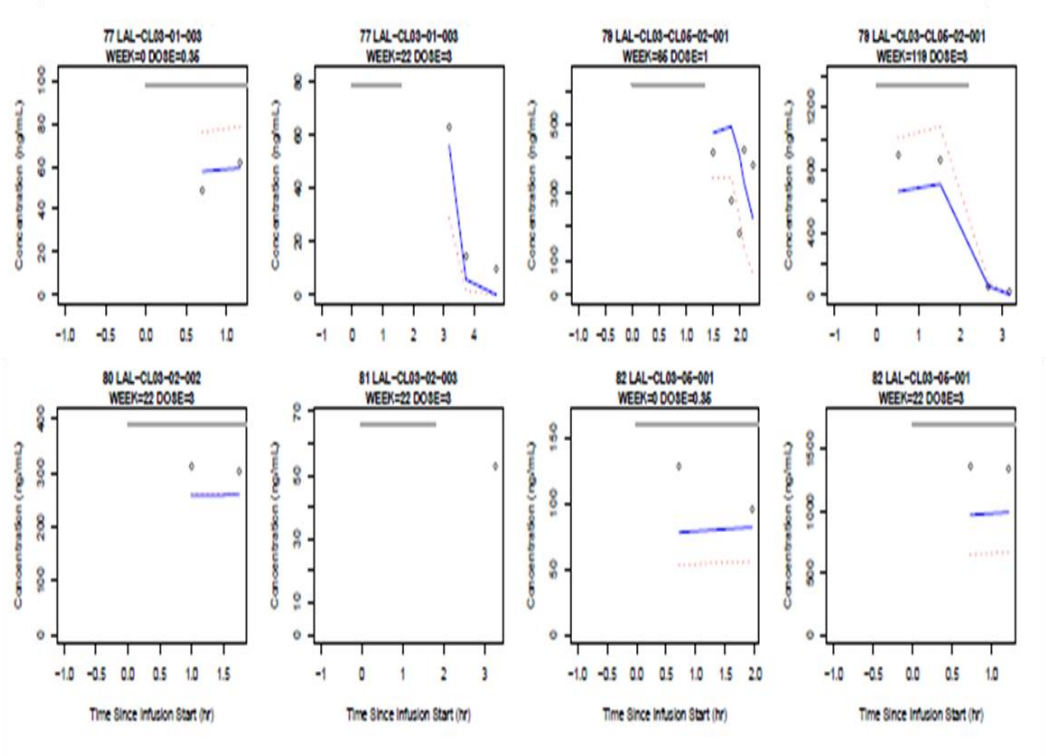
Figure 5. Visual Predictive Check (VPC) for the Final Population PK Model (Study LAL-CL03)

Source: Applicant's Updated Clinical Pharmacology Response 2 to IRs dated 04/16/2015, Figure 9

Figure 6. Individual Sebelipase Alfa Concentration-Time Goodness of Fit Plots for the Final Population PK Model (Study LAL-CL03)



Black circles: observed sebelipase alfa concentration, red dashed line: population predicted concentration, blue line: individual predicted concentration, grey line: recorded infusion duration
Source: Population PK Report SYN201301 Section 13.30.

Applicant's conclusions:
Standard graphical and numerical evaluation techniques suggested that the final model's performance was acceptable and could describe the data with little bias and good precision.

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The BSA was found to be the only significant covariate for inclusion on CL for doses of 0.35 and 1 mg/kg. The relationship was described as an exponential nonlinear relationship centered on the median BSA with an exponent of 0.479.

Reviewer's Comments:
Based on the observed data, the pharmacokinetics of sebelipase alfa is nonlinear with a greater than dose-proportional increase in exposure between 1 and 3 mg/kg dosing. In the population PK model, the Applicant characterized the nonlinearity in the PK of sebelipase alfa as a reduction in CL for a dose of 3 mg/kg compared to CL for doses < 3 mg/kg. As the limited PK data in the nonlinear PK range did not allow characterize the nonlinear PK across all the dose ranges, the Applicant's approach appears to be acceptable.

The Applicant's population PK analysis results appear to be appropriate to characterize the sebalipase alfa PK in pediatric and adult patients with late-onset LAL deficiency from Study LAL-CL02. Based on the population predicted vs. observed concentrations figure, there appears to be some bias but individual predicted vs. observed concentration relationship appears reasonable. However, the stratified VPC and the individual fitting results for patients with infantile-onset LAL deficiency from Study LAL-CL03 indicated that the population PK model is unable to well characterize the PK data in patients with infantile-onset LAL deficiency. Therefore, it appears acceptable to report population PK model derived individual PK parameters for pediatric and adult patients with late-onset LAL deficiency from Study LAL-CL02 in the proposed product labeling.

The sebelipase alfa clearance increases with increasing body surface area (Figure 3 above), supporting inclusion body surface area as a covariate to describe variability in sebelipase alfa CL.

Reference ID: 3777040

4.2 GENOMICS AND TARGETED THERAPY GROUP REVIEW

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS AND TARGETED THERAPY GROUP REVIEW

NDA/BLA Number	BLA 125561
Submission Date	01/08/2015
Applicant Name	Synageva BioPharma Corp.
Generic Name	Sebelipase Alfa
Proposed Indication	Lysosomal Acid Lipase (LAL) Deficiency
Primary Reviewer	Sarah Dorff, Ph.D.
Secondary Reviewer	Christian Grimstein, Ph.D.

Executive Summary

Sebelipase alfa is a new molecular entity for the treatment of patients with lysosomal acid lipase (LAL) deficiency. The purpose of this review is to evaluate the sponsor's analyses regarding the impact of *LIPA* genotype on the PK, efficacy, and immunogenicity/safety of sebelipase alfa. *LIPA* genotype was assessed in 81/84 (96%) of patients in the sebelipase alfa clinical development program. Across clinical studies, 65/84 (77%) of patients were homozygous or heterozygous for a splice-site mutation (c.894G>A) affecting exon 8. No difference by c.894G>A genotype was observed for PK or efficacy in study LAL-CL02. Anti-drug antibodies (ADAs) were found to develop in patients from all studies (LAL-CL01/04, LAL-CL02, and LAL-CL03) across a variety of *LIPA* mutation combinations, and infusion-associated reactions (IARs) were observed in patients with and without ADA-positivity. Therefore, specific mutations or the functional impact of the disease causing mutations are not likely to influence exposure or response to sebelipase alfa.

1 Background

Sebelipase alfa (SBC-102) is an intravenously administered enzyme replacement therapy (ERT) designed to replace the LAL enzyme in patients with LAL deficiency. LAL deficiency is a lysosomal storage disorder (LSD) caused by mutations in the *LIPA* gene, which result in accumulation of cholesteryl esters and triglycerides in various tissues and cells throughout the body. LAL deficiency has traditionally been described as having early-onset (Wolman disease) and late-onset (cholesteryl ester storage disease, CESD) forms. The purpose of this review is to evaluate the influence of *LIPA* genotype on the PK, efficacy, and immunogenicity/safety of sebelipase alfa.

2 Submission Contents Related to Genomics

LIPA genotype was assessed in patients with LAL deficiency in 3 clinical trials (and 1 extension study) of sebelipase alfa (see Table 1).

Reference ID: 3777040

Table 1. Studies with *LIPA* genotype data

Study ID	Title	Enrolled patient age requirement (inclusion criteria)	Patients with genotype n/N (%)
LAL-CL01 LAL-CL04 (extension)	An Open-Label Multicenter Study to Evaluate the Safety, Tolerability and Pharmacokinetics of SBC-102 in Adult Patients with Liver Dysfunction Due to Lysosomal Acid Lipase Deficiency An Open Label Multicentre Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of Sebelipase Alfa in Adult Subjects with Liver Dysfunction Due to Lysosomal Acid Lipase Deficiency who Previously Received Treatment in Study LAL-CL01	Adults ≥ 18 and ≤ 65 years	9/9 (100%)
LAL-CL02	A Multicenter, Randomized, Placebo-Controlled Study of SBC-102 in Patients with Lysosomal Acid Lipase Deficiency	Children ≥ 4 years	66/66 (100%)
LAL-CL03	An Open Label, Multicenter, Dose Escalation Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics, and Pharmacodynamics of SBC-102 in Children with Growth Failure Due to Lysosomal Acid Lipase Deficiency	Infants ≤ 8 months (growth failure < 6 months)	6/9 (67%)

3 Key Questions and Summary of Findings

3.1 Does *LIPA* genotype impact the PK, efficacy, or immunogenicity/safety of sebelipase alfa?

No, genetic variation does not appear to impact sebelipase alfa exposure or response.

3.1.1 Distribution of *LIPA* genotypes

Sequencing of the *LIPA* gene was performed by (b) (4) using the Sanger method. *LIPA* genotype was assessed in all patients enrolled in studies LAL-CL01/04 (N = 9) and LAL-CL02 (N = 66), and in 6/9 (67%) of patients from study LAL-CL03. The most common mutation detected (found in 65/84 (77%) of patients in the sebelipase development program) was an exon 8 splice-site mutation (c.894G>A), which results in a 24 amino acid deletion and some residual enzyme activity. This mutation is associated with LAL Deficiency presenting in children and adults (CESD). The distribution of *LIPA* genotypes using this common c.894G>A mutation as a reference are summarized in Table 2.

Reference ID: 3777040

Table 2. Distribution of *LIPA* genotype across studies

LIPA Genotype	LAL-CL01/04 (N = 9)	LAL-CL02 (N = 66)	LAL-CL03 (N = 9)	Total (N = 84)
Homozygous c.894G>A	1 (11%)	21 (32%)	0	22 (26%)
Heterozygous c.894G>A	8 (89%)	35 (53%)	0	43 (51%)
Other[1]	0	10 (15%)	6 (67%)	16 (19%)
Not Determined	0	0	3 (33%)	3 (4%)

Source: LAL-CL-01 CSR Addendum 1 Appendix 1, LAL-CL-02 DS.xpt and XB.xpt, LAL-CL03 ZS.xpt
[1] 'Other' defined as having at least 1 allele with a defined mutation and not having the c.894G>A mutation

The genotypes found in patients from study LAL-CL01/04 are summarized in Table 3. Out of the 8 patients who were heterozygous for the c.894G>A mutation, 3 patients had insertions and/or deletions resulting in frameshifts leading to premature stop codons. The remaining 5 patients had single nucleotide polymorphisms (SNPs) resulting in missense (3 patients) or nonsense (2 patients) mutations.

Table 3. Genotypes of patients in LAL-CL01/04

Allele 1	Allele 2	Allele 1 Effect	Allele 2 Effect	Number of Patients
c.894 G>A	c.894 G>A	Gln298Gln (splice site)	Gln298Gln	1
	c.967_968delAG		Ser323Leufs*44	1
	c.455 T>C[1]		Leu152Pro	1
	c.796 G>T		Gly266*	1[2]
	c.193 C>T		Arg65*	1
	c.599 T>C		Leu200Pro	2
	c.684delT		Phe228Leufs*13	1
	c.568_627del60insAAATTTTC[1]		Leu190Lysfs*10	1

Source: LAL-CL-01 CSR Addendum 1 Appendix 1 and LAL-CL-04 CSR
[1] Previously unreported
[2] Patient positive for ADA
* = Stop codon

The genotypes found in patients from study LAL-CL01/04 are summarized in Table 4. In the 35 patients who were heterozygous for the c.894G>A mutation, 8 patients had insertions or deletions resulting in frameshifts leading to premature stop codons and 1 patient had an in-frame deletion resulting in the loss of 5 amino acids. SNPs resulting in missense mutations (10 patients), nonsense mutations (8 patients), or intronic mutations (2 patients) were found in 26 patients. The remaining 6 patients did not have a second allele identified. Of the 10 patients who were identified as having a genotype of 'Other' (not having the c.894G>A mutation), no insertions or deletions were reported, but SNPs resulting in missense mutations of both alleles were found in 7 patients, the combination of a missense and a nonsense mutation was found in 2 patients, and the combination of a missense and intronic mutation was found in 1 patient.

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Table 4. Genotypes of patients in LAL-CL02

Allele 1	Allele 2[2]	Allele 1 Effect	Allele 2 Effect	Number of Patients
c.894 G>A	c.894 G>A	Gln298Gln (splice site)	Gln298Gln	21
	c.1024G>A		Gly342Arg	1
	c.256C>T[1]		His86Tyr	2[6]
	c.309C>A[1]		Ser103Arg	1
	c.398delC		Ser133*	4
	c.526G>A[1]		Gly176Ser	1
	c.538+5G>A[1]		Intronic	2
	c.928dupT[1]		Trp310Leufs*58	1
	c.931G>A[1]		Gly311Arg	1
	c.57_60delTGAG[1,3]		Glu20Glyfs*6	1
	c.455T>C[1,3]		Leu152Pro	1
	c.297_311delTGCCAACAGCAGCCT[1,4]		p.Ala100_Leu104del	1
	c.796G>T[4]		Gly266*	3
	c.419G>A[5]		Trp140*	2
	c.193C>T[4]		Arg65*	1
	c.796G>T[3,4]		p.Gly266*	2
	c.594dupT[3,4]		Ala199Cysfs*13	2
	c.386A>C[3,4]		His129Pro	2
	c.1033G>A[3,4]		Asp345Asn	1[6]
	Not Identified[3]		-	1
	Not Identified		-	5
c.386A>G	c.386A>G	His129Arg	His129Arg	1
	c.386A>G[3(homozygous), 4(homozygous)]		p.His129Arg	1[6]
	c.253C>A[1,4]		Gln85Lys	1
	c.260G>T[5]		Gly87Val	1
c.193C>T	c.417C>A[1,4]	Arg65*	Phe139Leu	1
c.607G>C[1]	c.153C>A[1, 4(homozygous)]	Val203Leu	Tyr51*	1[6]
	c.791T>C[1,4]		Leu264Pro	1
c.294C>G[1]	c.253C>A[1,4]	Asn98Lys	Gln85Lys	2
c.676-2A>G	c.974C>T[5]	Intronic	Pro325Leu	1[6]

Source: LAL-CL-02 DS.xpt, XB.xpt, and CSR
[1] Previously unreported
[2] For patients with more than two alleles identified, all alleles identified are reported under allele 2 but may not be on the same chromosome
[3] Patient(s) also carry rs1051338, a common SNP (1000 Genomes minor allele frequency (MAF) = 0.29)
[4] Patient(s) also carry rs2297472, a common SNP (1000 Genomes MAF = 0.32)
[5] Patient(s) also carry rs1051339, a common SNP (1000 Genomes MAF = 0.12)
[6] 1 Patient positive for ADA
* = Stop codon

The genotypes found in patients from study LAL-CL03 are summarized in Table 5. In this study, no patients carried the c.894G>A mutation. Three patients had homozygous mutations including 1 patient with deletions resulting in frameshifts and premature stop codons, 1 patient with intronic 3' splice site

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SNPs resulting in the skipping of exon 7 [PMID: 23652569], and 1 patient with missense mutation SNPs. Of the 3 patients with heterozygous mutations, 2 had missense SNPs combined with an insertion or deletion resulting in frameshifts leading to premature stop codons, and 1 patient had a missense SNP with an unidentified second allele.

Table 5. Genotypes of patients in LAL-CL03

Allele 1	Allele 2[2]	Allele 1 Effect	Allele 2 Effect	Number of Patients
c.398delC	c.398delC	Ser133*	Ser133*	1[4]
c.884A>G[1]	Not Identified	His295Arg	-	1[4]
c.482delA	c.538G>A[1,3]	Asn161Ilefs*19	GLY180SER	1[4]
c.419G>C[1]	c.419G>C[1]	Trp140Ser	Trp140Ser	1
c.676-2A>G	c.676-2A>G	Intronic	Intronic	1[4]
c.350_351insCC[1]	C.797G>T[1]	Met117Ilefs*45	Gly266Val	1
Not Determined	Not Determined	-	-	3

Source: LAL-CL03 ZS.xpt and ADAE.xpt
[1] Previously unreported
[2] For patients with more than two alleles identified, all alleles identified are reported under allele 2 but may not be on the same chromosome
[3] Patient(s) also carry rs2297472, a common SNP (1000 Genomes MAF = 0.32)
[4] 1 Patient positive for ADA
* = Stop codon

3.1.2 Applicant's analyses

Study LAL-CL01/LAL-CL04

Beyond descriptive statistics of the subject level genotypes observed in the study, the applicant did not conduct analyses regarding the impact of genotype on the PK, efficacy, or immunogenicity/safety of sebelipase alfa in study LAL-CL01 or LAL-CL04.

Reviewer comment: One patient was ADA-positive in LAL-CL04 (Table 3).

Study LAL-CL02

The allocation of patients to treatment with sebelipase alfa or placebo by LIPA genotype category in study LAL-CL02 is summarized in Table 6.

Table 6. Genotype by treatment arm in study LAL-CL02

LIPA Genotype	Treatment	
	Sebelipase Alfa (N = 36)	Placebo (N = 30)
Homozygous c.894G>A	11 (31%)	10 (33%)
Heterozygous c.894G>A	17 (47%)	18 (60%)
Other[1]	8 (22%)	2 (7%)

Source: LAL-CL-02 CSR Table 20
[1] 'Other' defined as having at least 1 allele with a defined mutation and not having the c.894G>A mutation

Based on popPK estimates of AUC and Cmax at Week 0, similar exposures across mutation categories are predicted (Figure 1). Efficacy results were similar across mutation categories (Table 7).

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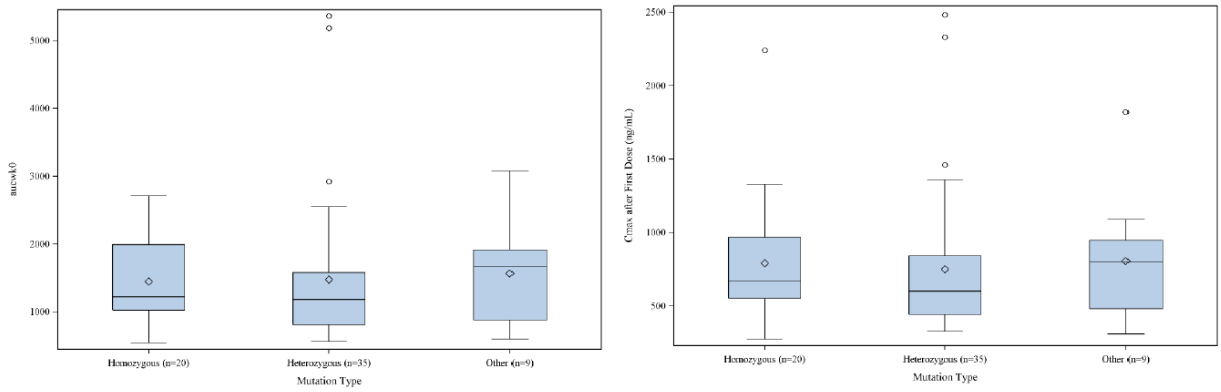
Figure 1. Boxplots of Sebelipase Alfa Estimates of AUC and Cmax at Week 0 (Population Pharmacokinetic Analysis) According to Genotype Mutation Category in Study LAL-CL02.



Source: Summary of Clinical Pharmacology Figure 8.

Table 7. Primary and First Secondary Efficacy Endpoints in Sebelipase Alfa-treated Patients (Study LAL-CL02)

Endpoint	Genetic Mutation Category		
	Homozygous c.894G>A (N = 11)	**Heterozygous c.894G>A (N = 17)**	**Other[1] (N = 8)**
Primary: ALT normalization [n (%)]	4 (36%)	5 (29%)	2 (25%)
First Secondary: LDL Reduction (% change from baseline) [Mean (SD)]	-29.0 (15.51)	-29.1 (22.04)	-26.3 (32.05)

Source: LAL-CL02 CSR Table 36.
[1] 'Other' defined as having at least 1 allele with a defined mutation and not having the c.894G>A mutation

With respect to immunogenicity, 5 patients who received sebelipase alfa developed anti-drug antibodies (ADAs) during the double-blind period. Two of these patients were heterozygous for the c.894G>A mutation and missense mutation SNPs and the remaining 3 patients were in the 'Other' category with 1 patient having SNPs resulting in the combination of missense and nonsense mutations, 1 patient having SNPs resulting in missense and intronic mutations, and 1 patient who was homozygous for SNPs resulting in missense mutations (Table 4). Of the 4 patients who experienced IARs, 3 patients were not ADA-positive and 1 patient (genotype 'Other' with missense and intronic mutations) experienced an IAR but was successfully re-treated.

Study LAL-CL03

Beyond descriptive statistics of the subject level genotypes observed in the study, the applicant did not conduct analyses regarding the impact of genotype on the PK or efficacy of sebelipase alfa in study LAL-CL03. Regarding immunogenicity, 4 of the patients with available genotypes were ADA positive (Table 5). IARs occurred in 4 patients (3 ADA positive) and were manageable, and no cases of anaphylaxis were reported.

4 Summary and Conclusions

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The applicant evaluated *LIPA* genotype in the majority of patients 81/84 (96%) in the sebelipase development program. The most common mutation detected was the exon 8 splice-site mutation (c.894G>A). This mutation was found in children and adults, but not in infants, with LAL deficiency, which is consistent with literature reports suggesting read-through to produce some residual enzyme activity. Novel mutations were identified in 23/84 (27%) of patients.

The impact of genotype on PK and efficacy was assessed in children in study LAL-CL02. According to the applicant's analyses and conclusions, there was no relationship observed between genotype and PK or efficacy. Patients from all 3 study cohorts (LAL-CL01/04, LAL-CL02, and LAL-CL03) with a variety of *LIPA* mutation combinations were found to be ADA positive during treatment with sebelipase alfa and IARs were observed in patients with and without ADA-positivity, suggesting that ADA development and IARs may not be explained solely by specific mutations or the functional impact of the disease causing mutations. The reviewer concurs with the applicant's assessments.

5 Recommendations

The submission is acceptable from a Genomics and Targeted Therapy Group perspective.

5.1 Post-marketing studies

None.

5.2 Label Recommendations

None.

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4.3 CLINICAL PHARMACOLOGY FILING REVIEW

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA/BLA Number	**125561**	**Brand Name**	**Kanuma (proposed)**
OCP Division (I, II, III, IV, V)	**DCP III**	**Generic Name**	**Sebelipase alfa (proposed)**
Medical Division	**DGIEP**	**Drug Class**	**Lysosomal enzyme – recombinant human lysosomal acid lipase**
OCP Reviewer	**Jing Fang, Ph.D.**	**Indication(s)**	**Lysosomal Acid Lipase Deficiency**
OCP Team Leader	**Yow-Ming Wang, Ph.D.**	**Dosage Form**	**Concentrated solution for IV infusion after dilution**
Pharmacometrics Reviewer		**Dosing Regimen**	**1) 1 mg/kg once every other week as an IV infusion** **2) In infants presenting with rapidly progressive disease, starting dose is 1 mg/kg once weekly as an IV infusion, dose escalation to 3 mg/kg once weekly based on clinical response**
Date of Submission	**11/21/14**	**Route of Administration**	**IV**
Estimated Due Date of OCP Review	**4/21/15**	**Sponsor**	**Synageva BioPharma Corp.**
Medical Division Due Date		**Priority Classification**	**Priority**
PDUFA Due Date	**7/21/15**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

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Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**X**	**1**	**1**	
multiple dose:	**X**	**4**	**4**	
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**	**1**	
fasting / non-fasting multiple dose:	**X**	**2**	**2**	
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**	**2**	**2**	
Phase 3:	**X**	**2**	**2**	
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**2**	**2**	
Phase 3 clinical trial:	**X**	**2**	**2**	
Population Analyses -				
Data rich:	**X**	**2**	**2**	
Data sparse:	**X**	**2**	**2**	
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	**X**	**3**	**3**	
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**	**1**	**1**	
Total Number of Studies		**4**	**4**	

Reference ID: 3777040

On **initial** review of the NDA/BLA application for filing (01/20/2015):

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The to-be-marketed formulation was used in the clinical trials.
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			X	
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

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	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			(b) (4) [redacted] in the proposed labeling
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____X____

Please convey the below IR to the sponsor:

1. Table 9 of the LAL-CL02 Clinical Study Report suggests that rich pharmacokinetic (PK) sampling was performed in patients ≥18 years of age at Weeks 0 and 22. These data would allow a non-compartmental analysis (NCA) that could determine PK parameters for each subject. We request that you perform the NCA for all subjects who are ≥18 years of age in Study LAL-CL02 and provide the following:

- All datasets for the NCA PK analyses, including the original PK data, PK analysis dataset, and PK parameter dataset. All data files should be submitted in the sas transport file (.xpt) format. If you have already submitted the requested analysis and the datasets, clarify the location within the eCTD where they are located.

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- A tabular summary of the PK parameters of sebelipase alfa from Day 0 (single dose) and Week 22 (multiple-Dose) for Study LAL-CL02

- Updated assessment of dose proportionality after single dose administration using combined NCA results from Study LAL-CL01 and LAL-CL02.

2. Section 6.5.5.2 in LAL-CL01 Report Body (eCTD 5.3.3.2) states that "Results of any such pharmacogenetic analysis will be presented in a separate report". We recommend that you submit available pharmacogenetic study results from Study LAL-CL01 including patient-level LIPA genotype data as well as provide information on the assay(s) used. In addition, we recommend that you evaluate the impact of LIPA genotype on the safety, efficacy, PK, PD, and immunogenicity of SBC-102 for subjects in Studies LAL-CL01 and LAL-CL04. If you have already submitted the requested analysis and the datasets, clarify the location within the eCTD where they are located.

Note: The first IR was sent out to the sponsor on 12/19/14 and the response was received on 01/09/15.
The second IR was sent out to the sponsor on 01/09/14 and the response was received on 01/12/15.

Filing Review Summary

SBC-102 is a recombinant human lysosomal acid lipase (rhLAL) with a molecular weight of 55,000 Daltons, and is purified from egg white of transgenic hens (Gallus) with the same amino acid sequence as the native human LAL. It received Orphan Drug designation in July 2010 and Fast Track designation in June 14, 2011 for the treatment of LAL deficiency, and Breakthrough Therapy designation for the treatment of LAL deficiency presenting in infants in May 13, 2013.

SBC-102 is proposed for (b) (4)) for patients with Lysosomal Acid Lipase (LAL) Deficiency which is an autosomal recessive lysosomal storage disease characterized by a genetic defect resulting in a marked decrease in activity of LAL enzyme. There are two phenotypes of LAL deficiency: infantile- and late-onset LAL deficiency. LAL deficiency in infants, historically called Wolman disease, is the most aggressive presentation of LAL deficiency. LAL deficiency in children and adults, historically called Cholesteryl Ester Storage Disease (CESD), is more heterogeneous with respect to age of diagnosis and onset.

Proposed dosing regimens

- 1 mg/kg administered as an intravenous (IV) infusion once every other week.
- In patients presenting with rapidly progressive disease in infancy, the recommended starting dose is 1 mg/kg administered as an IV infusion once weekly. In clinical studies, these patients were dose escalated to 3 mg/kg once weekly.

Proposed dosage forms and strengths

- Concentrated solution for IV administration after dilution
- 20 mg/10 mL vial (2 mg/mL) in single-use vials

To support the proposed indication, the applicant submitted this BLA containing 4 clinical studies that contributed information on the clinical pharmacology of SBC-102. One study was completed (LAL-CL01) and 3 studies are in the ongoing extension study or follow-up period. A total of 84 subjects with LAL deficiency received SBC-102 treatment in 2 open-label Phase 1/2 studies in adults (Study LAL-CL01, and its ongoing extension study, Study LAL-CL04), 1 Phase 3 study (Study LAL-CL02, double-blind, placebo-controlled period for 20 weeks followed by an open label extension period) in children (≥ 4 years old) and adults, and 1 dose escalation Phase 2/3 study in infants (Study LAL-CL03). The pivotal studies to demonstrate the efficacy of SB-102 in LAL deficient patients are Study LAL-CL02 in adults and children >4 years old and Study LAL-CL03 in infants. The dose regimens investigated in all of the 4 studies ranged from 0.35 mg once every week (qw) to 3 mg/kg qw and once every other

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week (qow) with the maximum treatment duration ranging between 3 and 4 years. Additionally, Study LAL-CL03 evaluated 0.2 mg/kg as the starting dose in one subject and dose escalated to 5 mg/kg in another subject.

The clinical development program of SBC-102 contains additional 5 studies which were included in the Clinical Overview (eCTD 2.5) and not included in the clinical pharmacology summary (eCTD 2.7.2). The natural history study LAL-1-NH01 served as a historical control for the pivotal Phase 2/3 study in infants (Study LAL-CL03). An observational Study LAL-2-NH01 of children and adults with LAL deficiency and its associated Substudy (assess hepatic and splenic volume and fat content in a subset of subjects in Study LAL-2-NH01) provided case record review of patients with LAL deficiency in order to improve the understanding of the clinical phenotype. Two open-label Phase 2 clinical studies LAL-CL06 in pediatric (> 8 months) and adults and LAL-CL08 in infants (< 8 months) were initiated in 2014 and no data was submitted.

A summary of four key SBC-102 clinical studies in this BLA submission is presented in Table 1.

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Table 1: Table 2. Summary of four Key SBC-102 Clinical Studies in the BLA Submission

Study Identifier	Study Design	Regimen (Duration of treatment)	Study Population	Number of Subjects Treated[a] / PK[b]	PK Assessment	PD Assessment	PG Assessment	Immunogenicity Assessment
LAL-CL01 (completed)	Phase 1/2, open-label study	0.35, 1, or 3 mg/kg qw for 4 weeks, IV	Adults (≥18 and ≤65 years of age) with liver dysfunction due to LAL deficiency	9/9	Day 0 (single-dose) and Day 21 (multiple-dose)	ALT, Serum lipids (total cholesterol, TGs, HDL-c, LDL-c)	Yes	ADA
LAL-CL04 (ongoing)	Single-arm, open-label, extension study	0.35, 1, or 3 mg/kg qw for 4 weeks, then 1 or 3 mg/kg qow, for up to 3 years, IV	Subjects who completed LAL-CL01	8/8	Weeks 24, 52, and 104	ALT, Serum lipids (LDL-c, TGs, HDL-c, and total cholesterol), and liver fat content	No	ADA
LAL-CL02 (Double-blind period complete, open-label period ongoing)	Phase 3, randomized, double-blind, placebo-controlled study	Double-blind period: 1 mg/kg or placebo qow for 20 weeks, IV; Open-label period: 1 mg/kg qow (irrespective of treatment in double-blind period) for up to 130 weeks	Pediatric (≥ 4 years old) and adult subjects with LAL deficiency	66/65[d]	Day 0 and at Weeks 22 and 56	ALT, Serum lipids (LDL-c, TGs, HDL-c, non-HDL-c), and liver fat content	Yes	ADA, NAb
LAL-CL03 (Primary analysis complete, subject follow-up ongoing)	Phase 2/3, Single-arm, open-label, dose escalation study	0.35 mg/kg qw for 2 infusions, IV, then 1 mg/kg qw, then 3 mg/kg qw if a suboptimal clinical response, and to 5 mg/kg qw if a continued suboptimal clinical response. Maximum treatment up to 4 years. Subjects treated for at least 96 weeks and with a stable dose for at least 6 months could transition to a qow regimen at same dose as qw regimen.	Infants with LAL deficiency who developed growth failure or other clinical evidence of a rapidly progressive disease course before 6 months of age	9/5[c]	Day 0 and Weeks 22 and 52	No	Yes	ADA, NAb

[a] Number of subjects includes only those subjects who received at least 1 infusion of sebelipase alfa. The number of subjects included in the PK, PD/efficacy, and exposure-response analyses may have been less, and may have varied over time or between parameters, depending on data availability.
[b] Analysed for PK.
[c] Population PK analysis.

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SBC-102 Drug Product (DP)

The to-be-marketed formulation for SBC-102 was used in the 4 aforementioned clinical studies.

Pharmacokinetic (PK) Assessment

The submission contains SBC-102 single dose and multiple-dose PK data collected with a rich sampling design and a sparse sampling design (see Table 2 below). The applicant performed non-compartmental analysis (NCA) with SBC-102 concentration data from adult subjects in 2 clinical studies (N=9 in LAL-CL01 and N=8 in LAL-CL04). PK data were sparse for all infant subjects in study LAL-CL03 and for subjects < 18 years of age in study LAL-CL02, which are not amenable for the NCA analysis.

In study LAL-CL02, a rich PK sampling scheme was employed with up to 12 samples being collected at each study visit for 19 subjects who are ≥18 years of age. However, NCA PK analysis was not performed for these subjects in Study LAL-CL02.

Table 2. PK Sampling Scheme and Data Analysis Method

Study no.	**Age group**	**Rich PK sampling (Yes/No)**	**Doses (mg/kg) studied; dosing frequency**	**PK Analysis Method**	**N**
LAL-CL01	Adults	Yes (Day 1 and Day 21)	0.35, 1 or 3; qw x4	NCA	9
LAL-CL04 (extension of LAL-CL01)	Adults	Yes (Weeks 24, 52, 104)	0.35, 1, or 3; qw x4 followed by 1 or 3; qow	NCA	8
LAL-CL02	Adults	Yes (Day 0, Week 22) No (Week 56)	1; qow	NCA* Population PK	19 (Day 0) 13 (Week 22)
LAL-CL02	Ages 4-17	No (Day 0, Weeks 22 and 56)	1; qow	Population PK	46
LAL-CL03	Infants	No (Day 0, Weeks 22, 52)	0.2 – 5; qw	Population PK	5

* To be requested

A population PK model with full covariate analysis was developed to describe SBC-102 concentration-time data collected in adult and pediatric subjects. The model was developed using all available data from studies LAL-CL01, LAL-CL04, LAL-CL03, and LAL-CL02, with a total of 987 SBC-102 concentrations datapoints from 79 subjects. In addition, the model was used to identify and quantify covariate effects that described variability in the PK of SBC-102, and then to estimate PK parameters in subjects participated in pivotal studies LAL- CL02 and LAL-CL03.

Reviewer's comment

The current submission contains NCA data in only 8-9 adult subjects. Given an additional 19 adult subjects in study LAL-CL02 had rich PK sampling, their NCA PK data can potentially strengthen the overall understanding of the adult PK and to support the labeling. We will request NCA results for these subjects from the applicant.

Based on the initial review of the population PK analysis report, the model development utilized the data from all subjects. The applicant did not set aside a subset of data to perform an external validation of the model. Further evaluation of the population PK analysis will be a review focus.

Effect of renal impairment on PK

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The applicant did not conduct a dedicated study to evaluate the effect of renal impairment on the PK of SBC-102. The potential effect of renal impairment was assessed in the population PK model by testing the creatinine clearance as a covariate and the results did not show any potential positive relationship with the variability random effects parameter for CL and V_c. (b) (4) The appropriateness of this conclusion will be a review issue.

Efficacy/Safety/Pharmacodynamics (PD) Assessment

The pivotal efficacy data are from Study LAL-CL02 for adults and children >4 years old and from Study LAL-CL03 for infants. Studies LAL-CL01 and LAL-CL04 contributed to additional PD assessments. A summary of study endpoints are described below:

Efficacy Endpoints for adults and children ≥4 years of age (LAL-CL02)

The primary efficacy endpoint is the proportion of subjects who achieved ALT normalization (i.e., ALT below the age- and gender-specific upper limit of normal [ULN] provided by the central laboratory performing the assay) at the end of the double-blind period at Week 20.

Efficacy Endpoints for infants (Study LAL-CL03)

The primary efficacy endpoint is the proportion of subjects surviving at 12 months of age. The proportion of subjects surviving to 12 months of age as well as the Kaplan-Meier plots of survival to 12 months of age from birth were compared with those of a historical control study (LAL-1-NH01) in subjects who had confirmed growth failure and were untreated (i.e., no hematopoietic stem cell transplant or liver transplant).

Efficacy Endpoints for adults (Study LAL-CL04)

To assess the long-term efficacy (the secondary objective), the efficacy endpoints include liver and spleen volumes and fat content by magnetic resonance imaging (MRI) or ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) and liver biopsy (ongoing). The primary objective of the study was to evaluate the long-term safety and tolerability of SBC-102 in subjects with liver dysfunction due to LAL deficiency.

Safety Endpoints

The safety assessment was conducted in all 4 clinical studies, which includes the infusion-associated reactions (IARs) data.

PD Endpoints used in the E-R analyses

Liver enzymes include Alanine aminotransferase (ALT); serum lipids include total cholesterol, triglycerides (TGs), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and liver fat content.

Evaluation of Exposure-Response (E-R) Relationship

The applicant has conducted graphical exposure-response analyses to assess potential relationships between exposure to SBC-102 and the PD endpoints (for studies LAL-CL01, LAL-CL04, and LAL-CL02) and safety endpoints (all 4 studies combined). For Study LAL-CL03, due to the limited data, the applicant did not perform graphical exposure-response analyses. Additionally, the applicant did not conduct a statistical analysis of the dose-response relationship for Study LAL-CL03 either because subjects received variable doses and dosing frequencies of SBC-102 and were dose-escalated at different times.

For the E-R analyses on PD responses, the response parameters were absolute, change from baseline, and percent change from baseline values of the PD endpoints mentioned above. The exposure parameters were the area under

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the concentration-time curve (AUC), the cumulative area under the plasma concentration-time curve (AUC_{cum}), and the maximum concentration (C_{max}); which were derived from the population PK model.

For the E-R analyses with the safety data from all 4 clinical studies, the response parameter was IAR and the exposure parameter was AUC_{cum}. In addition, potential relationships between the occurrence of IARs were assessed and SBC-102 dose or rate of infusion, together with potential relationships between subject age and the occurrence of IARs.

The E-R analyses were submitted in a population PK-PD report. The applicant claimed that the E-R relationships supported the dose and dosing regimen selection and the rationale was summarized in the Summary of Clinical Efficacy. The appropriateness of the proposed dose and dosing regimen in patients with LAL deficiency and in infants presenting with rapidly progressive disease will be a review issue.

Pharmacogenetic (PG) Assessment

The assessment of genetic mutations for allelic variants of the LIPA gene was performed and submitted for subjects in Studies LAL-CL02 (adults and children > 4 years old) and LAL-CL03 (infants). The applicant also assessed the potential impact of the genetic mutation on the PK exposure to SB-102 and the efficacy as well as PD parameters at baseline. Blood samples for pharmacogenetic analyses were collected from subjects in Study LAL-CL01/LAL-CL-04; however, the results of any such pharmacogenetic analysis were not submitted.

The c.849G>A mutation is the most commonly found mutation in children and adults with LAL deficiency. Subjects who have the common mutation are further divided into two groups (homozygous and confirmed or presumed compound heterozygous for the mutation)

In Study LAL-CL03, the genetic mutation was reported in two categories as either "common" or "other". All 6 subjects who had LIPA genetic testing were classified as "other" mutations. Distinct mutations were identified in each of the 6 subjects.

In Study LAL-CL02, three categories were used: Group 1: homozygous c.849G>A mutation, Group 2: heterozygous c.849G>A mutation, and Group 3: “other”. Of 66 subjects in Study LAL-CL02, 32% (21/66) were homozygotes, i.e., in Group 1, 53% (35/66) were heterozygotes, i.e., Group 2, and 15% (10/66) were “other”, i.e., in Group 3.

The applicant evaluated the impact of genetic mutation on baseline parameters of disease activity as well as on the efficacy endpoints in Study LAL-CL02 at the end of the double blind period (Week 20). For the baseline parameters, serum transaminases appeared to be higher in Group 3 compared to Groups 1 or 2. No differences or trends were observed among the three mutation catetories for LDL-c, non HDL-c, TG, or HDL-c. For the efficacy endpoints, the results were generally similar within each group. The applicant concluded that these data suggest that SBC-102 was effective regardless of genetic mutation category.

In addition, to evaluate the potential relationship between the genotype mutation status and the systemic exposure to SBC-102 in Study LAL-CL02, the applicant conducted an analysis using boxplot to compare the population PK estimates of AUC for Week 0 among the 3 mutation categories as described above. The applicant stated that there was a high degree of overlap in the observed AUC and C_{max} values observed among these 3 mutation categories, suggesting a consistency in the exposure to SBC-102 irrespective of the genotype mutation status. In Study LAL-CL03, the genotype mutation status for all 4 of the ADA-positive subjects was “other”. Therefore, the applicant did not evaluate the potential relationship between genotype mutation status and exposure to SBC-102.

The conclusions regarding the impact of genetic mutation status on PK, PD and efficacy will be further reviewed.

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Immunogenicity Assessment

The applicant has included SBC-102 immunogenicity results for all 4 clinical studies. Samples were tested for the presence of anti- SBC-102 antibodies (ADA). Samples from subjects with positive ADA titers were also tested for the presence of neutralizing antibodies (NAb) that inhibit LAL enzyme activity. The incidence as well as the titer of ADA (for positive ADA status) was reported for the 4 aforementioned clinical studies. The effects of antibodies on PK, PD, efficacy, and safety were evaluated and submitted. Samples with positive ADA were tested for the presence of NAb that inhibited LAL enzyme activity and NAb that inhibited cellular uptake of LAL in a rat macrophage cell line.

Bioanalytical Assays

The applicant submitted 4 method validation reports that contain an enzymatic method to determine the activity of SBC-102 in human serum, an ELISA method to examine antibody to SBC-102 (ADA) in human serum (contains three components: screening, confirmatory and titration assay), an enzymatic activity-based neutralizing assay for the detection of the anti-SBC-102 neutralizing antibodies (NAb, inhibition of enzyme activity), and a cell-based assay for the detection of NAb (inhibition of cellular uptake) in human serum.

No ADA samples have been further characterized to date for IgE subtype analysis. The applicant has developed an IgE assay and it is undergoing validation.

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/s/

JING FANG
06/10/2015

SARAH E DORFF
06/10/2015

MICHAEL A PACANOWSKI on behalf of CHRISTIAN GRIMSTEIN
06/10/2015

NITIN MEHROTRA
06/10/2015

YOW-MING C WANG
06/10/2015

LEI ZHANG
06/10/2015
Acting Deputy Director, DCP-3

CLINICAL PHARMACOLOGY INDIVIDUAL STUDY SUMMARY

BLA:	STN 125,561
Submission Type:	Original BLA (New Molecular Entity)
Brand Name:	KANUMA®
Drug Name:	Sebelipase Alfa (SBC-102)
Submission Date:	01/08/2015
PDUFA Goal Date:	09/08/2015
Priority:	Priority
Proposed Indication:	(b) (4) for patients with lysosomal acid lipase (LAL) deficiency.
Applicant:	Synageva BioPharma Corporation
Clinical Pharmacology Reviewer:	Jing Fang, Ph.D.
Clinical Pharmacology Team Leader:	Yow-Ming Wang Ph.D.
OCP Division:	Division of Clinical Pharmacology 3 (DCP-3)
OND Division:	CDER/ODEIII/DGIEP

1. STUDY LAL-CL01 ..... - 2 -
2. STUDY LAL-CL04 ..... - 5 -
3. STUDY LAL-CL02 ..... - 8 -
4. STUDY LAL-CL03 ..... - 12 -

This document provides the Individual Study Summary for clinical pharmacology and clinical studies listed in Table 1 of the Clinical Pharmacology Review of the BLA. The name of the drug product either SBC-102 or sebelipase alpha was used interchangeably in this document. Refer to the Clinical Pharmacology Review for the regulatory recommendations from a Clinical Pharmacology standpoint.

Reference ID: 3776330

1. STUDY LAL-CL01

1.1. Title

- An Open-label Multicenter Study to Evaluate the Safety, Tolerability and Pharmacokinetics of SBC-102 in Adult Patients with Liver Dysfunction Due to Lysosomal Acid Lipase Deficiency

1.2. Study period

- 27 April 2011 (study initiation date) to 06 January 2012 (study completion date)

1.3. Primary objective

- To evaluate the safety and tolerability of SBC-102 in patients with liver dysfunction due to LAL Deficiency (vital signs, physical examination, clinical laboratory tests, immunogenicity tests, adverse event (AE) assessment, and concomitant therapies).

1.4. Study design and methods

Study LAL-CL01 was a Phase 1/2 multi-center, open-label, repeat-dose, dose escalation study to evaluate the safety, tolerability, and pharmacokinetics (PK) of 3 dose levels of SBC-102.

Subjects

A total of 9 adult patients with liver dysfunction due to LAL deficiency (aged 19 to 45 years) were enrolled and allocated to one of the 3 dose cohorts (3 subjects per cohort). All 9 (100%) subjects completed the study. Each dose cohort comprised 3 subjects with each subject received 4 once-weekly (qw) IV infusions of SBC-102.

Study products

SBC-102 was supplied in single-dose 10 mL glass vials, each containing approximately 10.(b)(4) mL (including (b)(4)% overfill) of a (b)(4) solution at a concentration of 2 mg/mL. The lot numbers of SBC-102 used in this study were 102-09-006, 102-09-007, and 102-09-008.

Dose administration

Subjects were treated in 3 sequential dose cohorts: 0.35 mg/kg (Cohort 1), 1 mg/kg (Cohort 2), and 3 mg/kg (Cohort 3). In each cohort, subjects were administered IV infusions of SBC-102 over approximately 2 hours on Day 0, Day 7, Day 14, and Day 21.

PK sampling and measurement

Blood samples for determination of SBC-102 serum concentrations were collected on Day 0 (first infusion) and Day 21 (fourth infusion) at the following time points: pre-dose, 10, 15, 20, 40, 60, 90 minutes during the infusion, at the end of the infusion (approximately 120 minutes), and at 5, 10, 20, 30, 40, 60 and 120 minutes after the infusion.

An enzyme activity-based quantitative assay was used for the measurement of SBC-102 activity in human serum. The LLOQ was 9.375 ng/mL (assay concentration at 3.125 ng/mL after dilution with assay buffer at 1/3).

Pharmacodynamic (PD) assessments

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Blood samples for serum lipids (total cholesterol, triglycerides, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]) were collected at Pre-treatment (Day -28 to Day -7), Days 0 (pre-dose), 28, 35 (optional study visit), and 52 (Cohorts 2 and 3 only).

Blood samples for liver enzymes (Alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyl transferase [GGT]) were collected at Pre-treatment (Day -28 to Day -7), Days 0, 1, 7, 14, 21, 28, 35 and 52.

Blood samples for acute phase reactants (serum ferritin and high-sensitivity C-reactive protein [hsCRP]) were collected at Pre-treatment (Day -28 to Day -7), Days 0 (predose), 28 and 52.

Immunogenicity

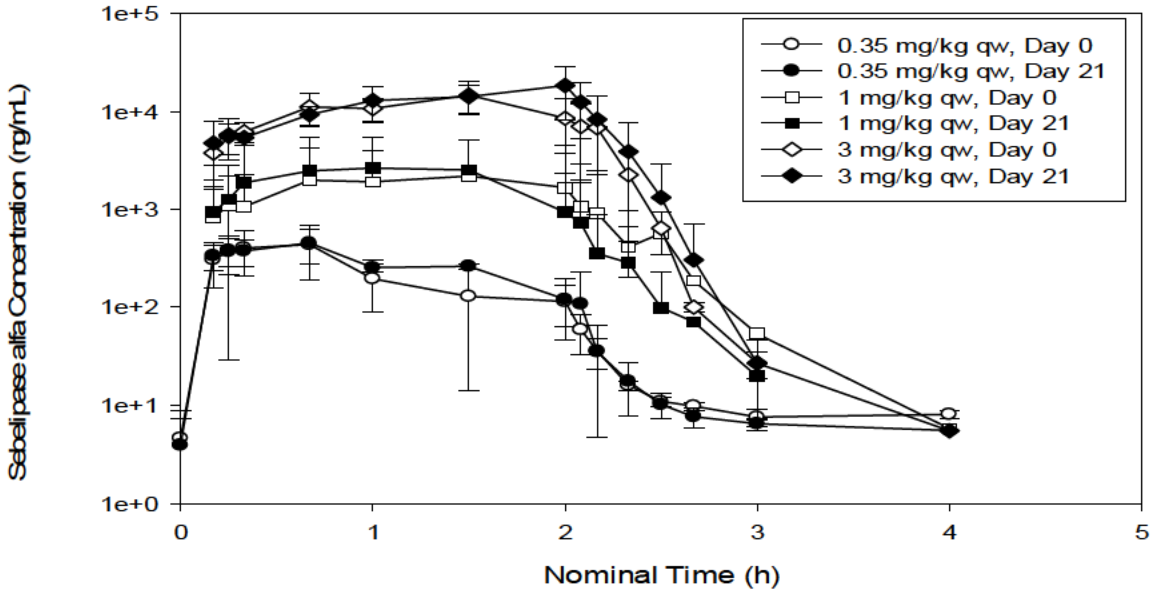
Blood samples for immunogenicity testing (anti-SBC-102 antibodies) were collected at Screening (Day -28 to Day -7), Days 0 (pre-dose), 28 and 52.

1.5. Results

PK results

The mean serum concentration time profiles of SBC-102 by doses of 0.35, 1 and 3 mg/kg are shown in Figure 1.5. At each dose level, the respective Visit 2 (Day 0) and Visit 6 (Day 21) post-infusion serum concentrations of SBC-102 declined in a parallel fashion.

Figure 1.5. **Mean (+SD) sebelipase alfa plasma concentration over time in Adults from Study LAL-CL01 (**Data source: plot by the reviewer).



The PK parameters are summarized in Table 1.5.1. Following IV infusion over 2 h, SBC-102 was rapidly eliminated from the systemic circulation with the median $t_{1/2}$ values range from 0.11 – 0.78 hours across dose cohorts at Day 21. After both the first and fourth infusions, there was a reasonably dose-proportional increase in exposure between the 0.35 and 1 mg/kg doses, and there was a greater than dose-proportional increase in exposure between the 1 and 3 mg/kg doses.

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Compared to data in Day 0, the median $AUC_{0\text{-last}}$ was slightly higher (approximately 15%), but the pre-infusion sample had similar concentration at Day 0 and at Day 21.

Table 1.5.1 The PK parameters After Single-Dose (Day 0) and Multiple-Dose (Day 21) Administration (qw) in Study LAL-CL01. Data source: LAL-CL01CSR, Table 7, Page 64.

	Median (Range)					
	Day 0			Day 21		
	0.35 mg/kg (N=3)	1 mg/kg (N=3)	3 mg/kg (N=3)	0.35 mg/kg (N=3)	1 mg/kg (N=3)	3 mg/kg (N=3)
C_{max} (ng/mL)	370 (262-718)	836 (561-5484)	15027 (9080-19904)	379 (330-655)	1212 (814-5991)	16080 (9616-29613)
$AUC_{0\text{-last}}$ (ng h/mL)	449 (441-663)	1091 (846-8254)	22030 (12796-27029)	509.9 (494-757)	1687 (1026-9198)	22137 (16661-31437)
T_{max} (h)	0.67 (0.33-1.58)	1.00 (1.00-1.50)	1.50 (1.50-1.50)	0.67 (0.67-0.67)	1.25 (1.00-1.50)	1.80 (1.75-2.08)
$t_{1/2}$ (h)	1.37 (0.60-3.51)	0.11 (0.11-0.28)	0.13 (0.10-0.24)	0.78 (0.07-2.05)	0.11 (0.08-0.14)	0.13 (0.09-0.16)
V_Z (mL/kg)	1489 (455-3653)	151.9 (48.1-183)	25.8 (16.1-78.1)	788 (48.0-1964)	70.0 (21.7-118)	22.1 (18.3-35.0)
CL (mL/h/kg)	722 (524-755)	916 (121-1180)	136 (111-229)	665 (462-700)	541 (109-974)	136 (95.4-180)

C_{max}: maximum observed serum concentration; T_{max}: time of maximum observed serum concentration; $AUC_{(0\text{-last})}$, area under the serum concentration-time curve (AUC) from the start of the infusion to the time of the last quantifiable concentration; $t_{1/2}$: apparent terminal half-life; CL: total body clearance , and V_z: the volume of distribution during the terminal phase.

PD results

The mean serum lipids concentration changes from baseline are summarized in Table 1.5.2. At all three dose cohorts, increases from baseline (Day 0) in total cholesterol, triglycerides, and LDL were observed at the first assessment performed 1 week after the fourth infusion (Day 28). On average, the magnitude of the increases in total cholesterol, triglycerides, and LDL was comparable in the 2 lowest dose cohorts (0.35 and 1 mg/kg), and appeared to be more pronounced in Cohort 3 (3 mg/kg). With available assessments performed at Day 52 (approximately 30 days of discontinuation of SBC-102 therapy), normal or near-normal lipids levels were observed in all subjects of cohorts 2 and 3.

Table 1.5.2 Mean (SD) Changes from Baseline in Serum Lipid Parameters, by Dose Cohort, in Study LAL-CL01. Data source: LAL-CL01CSR, Table 8, Page 71.

	Cohort 1: 0.35 mg/kg N=3		Cohort 2: 1 mg/kg N=3		Cohort 3: 3 mg/kg N=3	
	Day 28	Day 52	Day 28	Day 52	Day 28	Day 52
LDL, mg/dL	32.7 (41.2)	ND[a]	68.7 (94.5)	-32.0 (8.72)	239.0 (258.8)	-16.0 (38.2)
HDL, mg/dL	2.3 (6.11)	ND[a]	-1.7 (4.62)	0.3 (1.53)	-3.3 (5.03)	13.0 (0)
Total Cholesterol, mg/dL	95.7 (23.6)	ND[a]	58.3 (85.6)	-30.0 (0)	264.7 (263.0)	-22.3 (43.3)
Triglycerides, mg/dL	57.3 (32.9)	ND[a]	32.7 (46.5)	-18.0 (11.8)	156.3 (131.4)	-83.3 (88.7)

ND = not determined; [a] Serum lipids were not measured at Day 52 due to an oversight in the protocol schedule of assessments.

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Immunogenicity results

None of the 9 subjects tested positive for anti-SBC-102 antibodies (ADAs) in serum at any time during the study.

2. STUDY LAL-CL04

2.1. Title

- An Open Label Multicentre Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of Sebelipase Alfa in Adult Subjects with Liver Dysfunction Due to Lysosomal Acid Lipase Deficiency Who Previously Received Treatment in Study LAL-CL01

2.2. Study period

- 12 December 2011 (study initiation date) to 05 February 2014 (clinical cut-off date at which 7 of the 8 subjects enrolled had completed the Week 104 visit), the study is still ongoing.

2.3. Primary Objective

- To evaluate the long-term safety and tolerability of sebelipase alfa in subjects with liver dysfunction due to LAL Deficiency.

2.4. Study design and methods

Study LAL-CL04 was a Phase 2, open-label, extension study evaluated the long-term safety, tolerability, PK, and efficacy of SBC-102 in adult subjects who previously received 4 weekly doses of SBC-102 in the Phase 1/2 Study LAL-CL01. This is an ongoing study; a follow-up visit will be conducted for all subjects at 30 days after the last dose of investigational medicinal product (IMP).

Subjects

Eight of 9 subjects who completed LAL-CL01 initiated treatment in the extension study LAL-CL04. The interval between completion of dosing in LAL-CL01 and initiation of dosing in LAL-CL04 ranged from 9 to 28 weeks.

Study products

SBC-102 was supplied in single-dose 10 mL glass vials, each containing approximately 10 (b) (4) mL (including (b) (4) % overfill) of a (b) (4) solution at a concentration of 2 mg/mL. The lot numbers of SBC-102 used in this study were 102-09-006, 102-09-007, 102-09-009, 102-09-010, 102-09-011, 102-09-012, 102-09-013, 102-09-014, 102-09-018, 102-09-019, 102-09-020, P49703A, P49704A, P49705A and P49707A.

Dose administration

Each subject initiated treatment in the extension study at the same qw dose of sebelipase alfa that he/she received in study LAL-CL01, i.e., 0.35 mg/kg qw, 1 mg/kg qw, or 3 mg/kg qw for 4 weeks. After the initial 4 weekly doses, all subjects moved to dosing at 1 mg/kg qow (subjects who initiated dosing at 0.35 or 1 mg/kg qw) or 3 mg/kg qow (subjects who initiated dosing at 3 mg/kg qw) at Week 6. SBC-102 was administered by IV infusion over approximately 2 hours. After Week 12, modifications to the dose and dosing frequency were allowed for individual subjects based on observed safety, tolerability and clinical response to treatment.

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PK sampling and measurement

Blood samples for determination of SBC-102 serum concentrations were collected at Weeks 24, 52, and 104 at the following time points: pre-dose, 10, 15, 20, 40, 60, 90 minutes during the infusion, at the end of the infusion (approximately 120 minutes), and at 5, 10, 20, 30, 40, 60 and 120 minutes after the infusion.

An enzyme activity-based quantitative assay was used for the measurement of SBC-102 activity in human serum. The LLOQ was 9.375 ng/mL (assay concentration at 3.125 ng/mL after dilution with assay buffer at 1/3).

PD assessments

Blood samples for serum lipids and liver enzymes (Alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyl transferase [GGT]) were collected at Screening (Day -14 to Day -1), Weeks 1, 4, 8, 12, 16, 20, 24, 25, 32, 38, 52, 66, 78, 90 and Week 104 or End of Study (30 days after the last dose).

Blood samples for acute phase reactants (serum ferritin and high-sensitivity C-reactive protein [hsCRP]) were collected at Pre-treatment (Day -28 to Day -7), Days 0 (predose), 28 and 52.

Immunogenicity

Blood samples for immunogenicity testing were collected at Screening (Day -14 to Day -1), Weeks 4, 8, 12, 16, 20, 24, 32, 38, 52, 66, 78, 90 and Week 104 or End of Study (30 days after the last dose).

Immunogenicity (anti-SBC-102 antibodies) in human serum was assessed by the ELISA method. Samples from subjects with positive ADA titers were also tested for the presence of neutralizing antibodies (NAbs) that inhibit LAL enzyme activity (an enzymatic activity-based neutralizing assay) and inhibit cellular uptake of LAL in a rat macrophage cell line (a cell-based assay).

2.5. Results

PK results

The PK parameters at Weeks 24, 52 and 104 for both dose groups are summarized in Table 2.5. SBC-102 was rapidly eliminated from the systemic circulation. Within each dose group, the median $t_{1/2}$ was consistent at Weeks 24, 52, and 104. Based on median values for $AUC_{0\text{-last}}$, area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-inf}}$), and C_{max}, the difference in exposure to sebelipase alfa between the 1 and 3 mg/kg groups was consistently more than dose proportional at Weeks 24, 52, and 104.

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Table 2.5. The PK parameters After Multiple-Dose Administration (qow) in Study LAL-CL04 *(Data source: LAL-CL04 CSR, Table 21, Page 136).*

Parameter	Median (Range)					
	1 mg/kg			3 mg/kg		
	Week 24 (N=5)	Week 52 (N=4)	Week 104 (N=5)	Week 24 (N=3)	Week 52 (N=3)	Week 104 (N=1)
C_{max} (ng/mL)	1110 (815-1780)	1095 (628-1280)	595 (498-1050)	15600 (10800-32300)	14600 (9730-29100)	12700 (12700-12700)
$AUC_{0\text{-last}}$ (ng.h/mL)	1683 (1310-2433)	1600 (1089-1873)	1108 (991-1585)	27757 (19122-50785)	21671 (17173-43768)	18208 (18208-18208)
T_{max} (h)	1.00 (0.38-1.00)	0.50 (0.33-1.03)	1.50 (0.67-2.70)	2.00 (1.50-2.25)	1.50 (1.00-2.25)	2.17 (2.17-2.17)
$t_{1/2}$ (h)	0.258 (0.15-0.46)	0.147 (0.09-0.22)	0.212 (0.14-0.25)	0.197 (0.20-0.25)	0.106 (0.10-0.21)	0.212 (0.21-0.21)
V_z (mL/kg)	164 (115-393)	147 (89.4-173)	229 (164-343)	30.6 (21.6-44.6)	21.1 (20.5-26.3)	50.4 (50.4-50.4)
CL (mL/h/kg)	592 (410-762)	627 (533-916)	900 (630-1003)	108 (59.1-157)	138 (68.5-175)	165 (165-165)

PD results

The mean serum lipids concentration changes from baseline are summarized in Table 2.5.2. At all two dose cohorts, increases from baseline (Day 0) in total cholesterol, triglycerides, and LDL were observed at Week 4. On average, the magnitude of this effect on serum lipids appeared to be more pronounced in Cohort 2. With continued treatment with sebelipase alfa, the mean LDL, total cholesterol and TGs decreased to below original baseline levels at Week 8 and remained so through Week 104 on the qow dosing regimens. The mean HDL increased from baseline (Day 0) at Week 4 and remained so through Week 104.

Table 2.5.2 Mean (SD) Changes from Baseline in Serum Lipid Parameters, by Dose Cohort, in Study LAL-CL04. Data source: LAL-CL04-tables-figures, Table 14.4.3.3.1, Page 2791.

	Cohort 1: 1 mg/kg N=5							Cohort 2: 3 mg/kg N=3						
	W1	W4	W8	W12	W24	W52	W104	W1	W4	W8	W1	W2	W5	W104
LDL, mg/dL	7.8 (25.2)	97.2 (93.8)	-8.8 (44.4)	-17.4 (28.3)	-58.8 (40.7)	-73.5 (37.4)	-55.0 (29.9)	-1.7 (38.3)	217.0 (157.4)	-45.7 (15.9)	50.3 (17.6)	-73.3 (24.0)	-72.7 (27.3)	-85.0 (24.0)
HDL, mg/dL	0.2 (3.8)	0.2 (1.6)	1.8 (2.9)	5.2 (1.3)	3.6 (5.6)	6.3 (4.1)	4.3 (3.1)	-1.0 (5.2)	3.0 (15.7)	3.3 (6.0)	3.7 (3.1)	8.3 (6.0)	13.0 (6.6)	6.0 (11.3)
Total Cholesterol, mg/dL	-12.6 (46.1)	114.6 (101.5)	-22.6 (58.9)	-35.8 (44.5)	-67.0 (62.2)	-72.0 (32.2)	-49.8 (32.4)	0.3 (33.1)	229.0 (171.9)	-42.7 (47.3)	-53.0 (29.1)	-66.7 (21.1)	-70.0 (37.2)	-99.0 (28.3)
TGs, mg/dL	-30.4 (26.0)	25.2 (49.3)	-26.4 (62.1)	-34.6 (27.2)	-29.8 (53.4)	-69.5 (63.3)	-31.5 (33.8)	-20.0 (109.4)	58.0 (100.2)	-62.7 (85.5)	-62.0 (55.5)	-67.3 (85.5)	-74.7 (84.6)	-139.5 (40.3)

Immunogenicity results

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With the exception of a single isolated ADA-positive sample at Week 4 in one subject (ADA titer estimated at 1/8 and sample was negative for NAbs), all of the samples from the 8 subjects in this study were negative for ADAs. The Applicant considered this single result a spurious finding based on the very low titer and all subsequent ADA results from this subject were negative.

3. STUDY LAL-CL02

3.1. Title

- A Multicenter, Randomized, Placebo-controlled Study of SBC-102 in Patients with Lysosomal Acid Lipase Deficiency

3.2. Study period

- 22 January, 2013 (Study initiation date) to 30 May 2014 (Study completion and data cut-off date for the double-blind period), the open-label period is still ongoing.

3.3. Primary objective

- To demonstrate efficacy of sebelipase alfa relative to placebo, based on normalization of alanine aminotransferase (ALT) in patients with LAL Deficiency.

3.4. Study design and methods

This was a multicenter, randomized, placebo-controlled study was designed to evaluate the safety and efficacy of sebelipase alfa in patients with LAL Deficiency. The study consisted of a 20-week double-blind treatment period (Week 0 to Week 20), and an open-label period of up to 130 weeks (beginning at Week 22). Subjects in the placebo group crossover to receive sebelipase alfa upon entry into the open-label period.

Subjects

A total of 66 subjects with LAL Deficiency (aged 4 to 58 years) were enrolled, of whom 36 were randomly assigned to sebelipase alfa (13 subjects aged ≥ 18 years) and 30 were randomly assigned to placebo (6 subjects aged ≥ 18 years). As of the data cutoff date (30 May 2014), 65 subjects had completed and 1 had discontinued from the double-blind period of the study (due to a related adverse event following the second infusion). Furthermore, 65 subjects, 35 in the sebelipase alfa group and 30 in the placebo group, had entered the open-label period and continued/started treatment with sebelipase alfa.

Study products

The study drug was provided in a single-dose 10 mL glass vial containing approximately 10.(b)(4)mL (including (b)(4)% overfill) of a (b)(4) solution of sebelipase alfa at a concentration of 2 mg/mL (active treatment) or approximately 10 (b)(4)mL of a (b)(4) solution identical in composition to the formulation (b)(4) for sebelipase alfa (placebo). The lot numbers of sebelipase alfa used in this study were as follows: P49701A, P49705A, P49702A, P49704A, P49703A, P49706A.

Dose administration

- Double-blind treatment period (Week 0 to Week 20): Active treatment group received every-other-week (qow) IV infusions of sebelipase alfa at a dose of 1 mg/kg, for a total of 11 infusions over this 20-week period.

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- Open-label period (beginning at Week 22 and up to 130 weeks): all subjects received qow IV infusions of sebelipase alfa at a dose of 1 mg/kg, regardless of their treatment allocation during the double-blind period.

PK sample collection and measurement

Blood samples for PK assessments were collected at the following time points for pediatric subjects (< 18 years of age at randomization) in Table 3.5.1 and for adult subjects (≥ 18 years of age at randomization) in Table 3.5.2.

Table 3.5.1 PK Sampling in Pediatric Subjects. *(Data source: Table 8, LAL-CL02 Clinical Study Report, Page 97).*

	Week 0	Week 22	Week 56
	± 2 days	± 7 days	± 7 days
During Infusion			
0 hour to End of Infusion[1]	X	X	X
After Completion of Infusion			
0 to 15 minutes	X[2]	X[2]	X
15 to 30 minutes			
30 to 45 minutes	X[2]	X[2]	X
45 minutes to 1 hour			
1 to 2 hours	X	X	X

[1] A sample was obtained any time after the start of the infusion up until the end of the infusion (i.e., after the infusion bag was emptied, but prior to the sodium chloride flush).
[2] One sample was obtained during this time window.

Table 3.5.2 PK Sampling in Adult Subjects. *(Data source: Table 9, LAL-CL02 Clinical Study Report, Page 97).*

	Week 0	Week 22	Week 56
	± 2 days	± 7 days	± 7 days
Pre-infusion (within 30 minutes)	X	X	
During Infusion[1]			
15 minutes (±5 minutes)	X		
30 minutes (±5 minutes)	X	X	
1hour (±5 minutes)	X		
End of Infusion[2](±5 minutes)	X	X	X
After Completion of Infusion			
5 minutes (±2 minutes)	X	X	
10 minutes (±2 minutes)	X	X	
15 minutes (±2 minutes)	X	X	
30 minutes (±5 minutes)	X	X	
45 minutes (±5 minutes)	X	X	
1 hour (±5 minutes)	X	X	
2 hour (±5 minutes)	X	X	
0 to 1 hour			X
1 to 2 hour			X

[1] Sampling times were relative to the start of the infusion.
[2] After the infusion bag was emptied, but prior to the sodium chloride flush.

An enzyme activity-based quantitative assay was used for the measurement of SBC-102 activity in human serum. The LLOQ was 9.375 ng/mL (assay concentration at 3.125 ng/mL after dilution with assay buffer at 1/3).

PD assessments

Blood samples for serum lipids and liver enzymes were collected during Screening and at Weeks 0, 2, 4, 6, 10, 14, 18, and 20 during the double-blind period and Weeks 22, 24, 26, 28, 32, 36, 40, 42, 46,

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and 50 during the open-label period. After Week 52, blood samples for serum lipids and liver enzymes are to be collected every 12 weeks through study completion and at the End of Study visit.

Immunogenicity

Blood samples for immunogenicity testing were collected at Weeks 0, 4, 8, 12, and 20 during the double-blind treatment period. During the open label period, blood samples for immunogenicity testing were collected at Weeks 22, 28, 32, 36, 42, 52. After Week 52, blood samples for immunogenicity testing are to be collected at Week 56, every 12 weeks thereafter and at the End of Study Visit (Early Withdrawal).

Immunogenicity (anti-SBC-102 antibodies) in human serum was assessed by an bridging enzyme linked immunosorbent assay (ELISA) method. Samples from subjects with positive anti-drug antibody (ADA) titers were also tested for the presence of neutralizing antibodies (Nabs) that inhibit LAL enzyme activity (an enzymatic activity-based neutralizing assay) and inhibit cellular uptake of LAL in a rat macrophage cell line (a cell-based assay).

3.5. Results

PK results

PK data were sparse for subjects < 18 years of age, which were not amenable for the non-compartmental analysis (NCA). Concentration-time profiles showed that sebelipase alfa concentration rose quickly within the first hour after the start of infusion; C_{max} was reached close to or at the end of infusion (Figure 3.5.). Thereafter, concentrations rapidly declined. The PK parameters for adult subjects with rich PK sampling scheme using NCA method are summarized in Table 3.5.3. In general, the PK parameter results from this study are consistent with previously conducted studies in adults treated with sebelipase alfa (Study LAL-CL04).

Figure 3.5. **Mean (+SD) sebelipase alfa plasma concentration over time in Adults from Study LAL-CL02 (**Data source: plot by the reviewer).

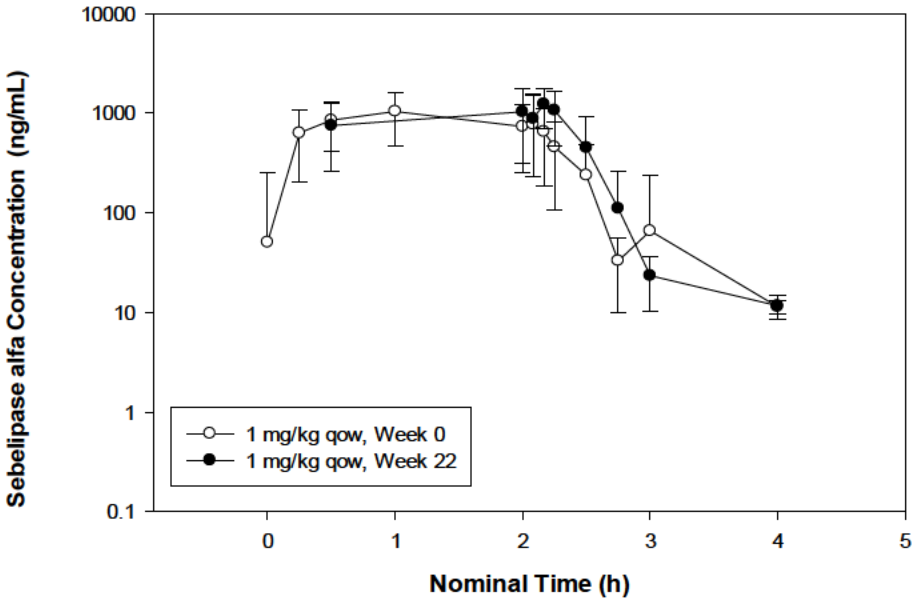

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Table 3.5.3 PK Parameters Summary for Adult Subjects. *(Data source: Table 7 & 8, Clinical Pharmacology Report Study LAL-CL02 version 1.0, Page 8).*

Pharmacokinetic Parameter	Week 0 (N=17) Median (Range)	Week 22 (N=11) Median (Range)
AUC_{last} (ng*hr/mL)	1713.5 (690.2 – 3362.7)	1706.8 (638.7- 3439.7)
AUC_{inf} (ng*hr/mL)	1798.6 (1147.2 – 3365.4)	1768.8 (645.2 – 3447.5)
C_{max} (ng/mL)	1113.9 (672.3 - 2555)	1285.7 (501.0 – 2167.1)
T_{max} (hr)	1.1 (0.5 – 2.45)	1.8 (0.5 – 2.3)
CL (mL/hr/kg)	556.4 (297.1 – 871.7)	570.4 (290.1 – 1549.9)
V_z (mL/kg)	392.9 (53.9 – 1952.8)	100.2 (50.9 -991.7)
$T_{1/2}$ (hr)	0.5 (0.1 – 2.3)	0.13 (0.09 – 0.9)

Reviewer's Comments: *Because rich pharmacokinetic (PK) sampling was performed in patients ≥18 years of age at Weeks 0 and 22, we requested and the Applicant performed the NCA for all subjects who are ≥18 years of age in Study LAL-CL02 (See IR dated 19 December 2014 and the response to IR dated 9 January 2015). Data were included in Table 7 of the QBR.*

Sparse PK data for sebelipase alfa in pediatric subjects were analyzed using population PK modeling and model-based simulations were subsequently conducted to generate PK parameters for each study subjects. A summary table for sebelipase alfa PK parameters in pediatric subjects was included in Table 8 of the QBR.

Efficacy results:

The results for the primary efficacy endpoint that the Applicant proposed in the study (normalization of ALT) are summarized in Table 3.5.2. There are a greater proportion of subjects in the SA group (31%) than in the placebo group (7%) achieved normalization in ALT by the last time point in the double-blind period. The 24% difference between groups was statistically significant (p=0.0271).

Table 3.5.2 Summary of Per Protocol Primary Efficacy Endpoint by Treatment Group. *(Data source: Table 29, LAL-Cl02 Clinical Study Report, Page 182).*

ALT normalisation [n (%)]	Sebelipase Alfa (N=36)	Placebo (N=30)	Statistically significant in fixed sequence test
N	36	30	Yes
Yes	11 (31)	2 (7)	
Difference	24%		
p-value	0.0271		

Reviewer's Comments: *The Agency was concerned that the primary efficacy endpoint, normalization of ALT did not reliably reflect improvement in liver disease related to LAL deficiency. Subsequently, the Agency has concluded that LDL is the most suitable endpoint to assess efficacy in patients with late-onset LAL deficiency (See Mid-Cycle Communication dated 24 April 2015).*

The serum lipids concentration percentage changes from baseline are summarized in Table 3.5.3. At the last time point in the double-blind period, a greater mean percent decrease from baseline in LDL-c (-28.42% versus -6.25%, respectively), and triglyceride (-25.45% versus -11.14%, respectively), was seen in the sebelipase alfa treatment group than in the placebo group; the difference between groups

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was statistically significant. Similarly, a greater mean percent increase in HDL-c was seen in the sebelipase alfa treatment group than in the placebo group (19.57% versus -0.29%, respectively); the difference between groups was statistically significant.

Table 3.5.3 Serum Lipids Percent Change from Baseline Over Time by Treatment Group at the last time point in the double-blind period. *(Data source: Table 29, LAL-Cl02 Clinical Study Report, Page 182-184).*

Parameter/Statistic	SA (N=36)	Placebo (N=30)
LDL-c % change from baseline Mean ± SD Median Range	-28.42 ± 22.304 -28.89 -59.41- 45.87	-6.25 ± 13.02 4.82 -32.80 - 15.88
Difference p-value	-22.17 < 0.0001	
HDL-c % change from baseline Mean ± SD Median Range	19.57 ± 16.833 19.13 -24.11- 66.07	-0.29 ± 12.360 1.20 -25.37 – 20.65
Difference p-value	19.86 < 0.0001	
Triglyceride % change from baseline Mean ± SD Median Range	-25.45 ± 29.411 -32.41 -66.89- 58.99	-11.14 ± 28.827 -14.90 -50.56- 55.96
Difference p-value	-14.30 0.0375	

Immunogenicity results:

A total of 35 subjects in the sebelipase alfa treatment group during the double-blind treatment period were evaluated for the development of antibodies to sebelipase alfa. Overall, 5 of these subjects (5/35, 14%) were determined to be ADA-positive at some point during the double-blind period and only 2 (2/35, 6%) were ADA positive at more than one time point; none of these 5 subjects developed neutralizing antibodies at any time.

None of the 30 subjects with data in the placebo group had positive ADA titers during the double-blind period or after initiating sebelipase alfa treatment in the open-label period.

4. STUDY LAL-CL03

4.1. Title

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

4.2. Study period

Reference ID: 3776330

- 04 May 2011 (Study initiation date) to 10 Jun 2014 (data cut-off date), the study is still ongoing.

4.3. Primary objectives

- To evaluate the effect of sebelipase alfa therapy on survival at 12 months of age in children with growth failure due to LAL Deficiency.

4.4. Study design and methods

This was a multicenter center, open label, repeat-dose, intra-subject dose escalation study designed to evaluate the efficacy and safety of enzyme replacement therapy (ERT) with sebelipase alfa in subjects with LAL Deficiency who presented as infants and were considered to have rapidly progressive disease based primarily on the presence of growth failure within the first 6 months of life. The study consisted of a treatment period of up to 4 years, and a follow-up visit at least 30 days after the last dose of IMP.

Subjects

Nine subjects were enrolled, treated, and analyzed. Median age at initiation of treatment with sebelipase alfa was 3.0 months (range = 1.1 to 5.8 months). As of the data cut-off (10 Jun 2014), 6 subjects continue to receive treatment in the study and 3 subjects are considered early terminated due to death prior to 12 months of age.

Study products

SBC-102 was supplied in single-dose 10 mL glass vials, as a clear liquid solution with a concentration of 2 mg/mL. The lot numbers of SBC-102 used in this study were 102-09-006, 102-09-007, 102-09-008, 102-09-009, 102-09-010, 102-09-011, 102-09-012, 102-09-013, 102-09-018, P49702A, P49703A, P49705A, P49707A and P49710A.

Dose administration

Six subjects initiated treatment at a dose of 0.35 mg/kg weekly (qw), and were escalated to a dose of 1 mg/kg qw after 2 infusions of 0.35 mg/kg qw dosing. One subject initially received emergency therapy at a lower starting dose of 0.2 mg/kg with a more gradual dose escalation to 1 mg/kg over a period of 4 weeks, and thereafter continued on a dose of 1 mg/kg qw. Two subjects died after receiving a single infusion dose of 0.35 mg/kg. One subject died after 2 infusions at a dose of 1 mg/kg.

As shown in Table 4.4, the 6 subjects surviving beyond Week 4 were dose escalated to 1 mg/kg and remained at this dose for varying duration before escalating to 3 mg/kg or further to 5 mg/kg.

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Table 4.4. Dose Escalations to 3 mg/kg or 5 mg/kg due to Suboptimal Clinical Response. (*Data source: LAL-CL03 CSR, Table 15, page 170*)

Subject ID	No. of infusions at ≤0.35 mg/kg qw	No. of infusions at 1 mg/kg qw	First Infusion at 3 mg/kg qw	Infusion at 3 mg/kg qow	First Infusion at 5 mg/kg qw	Criterion Not Met (Dose escalation to 3 mg/kg)
(b) (6)	2	21	Week 23		Week 88[c]	WFA plateaued; also hepatomegaly
	2	10	Week 14			WFA plateaued
	4[a]	86	Week 91	Weeks 122 to 154[b]		Mesenteric lymphadenopathy
	2	10	Week 12			Failure to gain an average of 5 g /kg body weight per day, and WHO LFA/HFA Z-score < -2
	2	4	Week 6			Failure to gain an average of 5 g /kg body weight per day, and WHO LFA/HFA Z-score < -2
	2	8	Week 10			Failure to gain an average of 5 g /kg body weight per day, and WHO LFA/HFA Z-score < -2

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

a - Early and late suboptimal response criteria are defined in Section 8.4.5.1 of LAL-CL03 CSR

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

PK sample collection and measurement

Limited PK sampling was performed, as blood volume permitted, to measure sebelipase alfa concentrations within critical time windows. Blood samples for determination of SBC-102 serum concentrations were collected at Weeks 0, 22, and 48 within the following time windows: 0 to 1 hours after the start of the infusion, between 1 hour after the start of the infusion and the end of the infusion, 0 to 0.5 hours after completion of the infusion, 0.5 to 1 hour after completion of the infusion, 1 to 2 hours after completion of the infusion.

All 6 surviving subjects provided drug concentration data for at least one time point. Data were unavailable for the 3 deceased subjects due to blood volume restrictions or loss of samples.

An enzyme activity-based quantitative assay was used for the measurement of SBC-102 activity in human serum. The LLOQ was 9.375 ng/mL (assay concentration at 3.125 ng/mL after dilution with assay buffer at 1/3).

Immunogenicity

Blood samples for immunogenicity testing were collected at Weeks 0, 2, 8, 12, 16, 20, 24, every 24 weeks thereafter and at the follow-up / early withdrawal visit (30 days after the last dose of IMP).

Immunogenicity (anti-SBC-102 antibodies) in human serum was assessed by the ELISA method. Samples from subjects with positive ADA titers were also tested for the presence of NAbs that inhibit LAL enzyme activity (an enzymatic activity-based neutralizing assay) and inhibit cellular uptake of LAL in a rat macrophage cell line (a cell-based assay).

4.5. Results

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PK results

Due to sparse PK sampling, the PK of sebelipase alfa were not analyzed by the NCA method.

The sebelipase alfa concentrations were included in the population PK analysis with a model that was developed using all available data from Studies LAL-CL01, LAL-CL04, LAL-CL03, and LAL-CL02. Individual PK parameters for subjects in Study LAL-CL03 were then derived using individual model-predicted concentration values.

Efficacy results:

The primary efficacy endpoint is the proportion of subjects surviving at 12 months of age. The Figure 4.5. presents the Kaplan-Meier plots of survival to 12 months of age from birth for all subjects in Study LAL-CL03 versus those of a historical control study (LAL-1-NH01) from 21 infants who had confirmed growth failure and were untreated (i.e., no hematopoietic stem cell transplant, liver transplant or ERT). The proportion (exact 95% CI) of subjects in Study LAL-CL03 surviving to 12 months of age was 67% (29.93%, 92.51%). In contrast, the proportion (exact 95% CI) of patients surviving to 12 months of age in Study LAL-1-NH01 was 0% (0%, 16.11%).

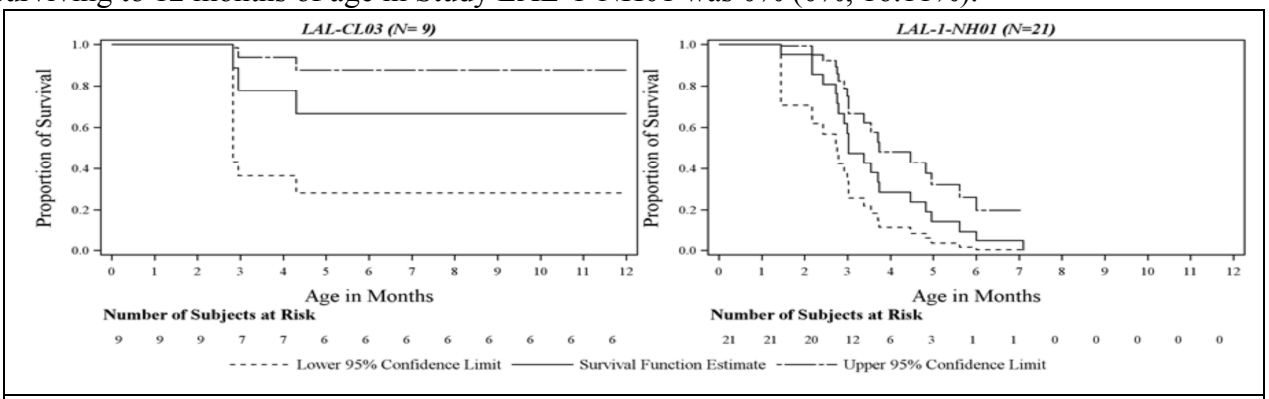

Figure 4.5. Kaplan-Meier Plot of Survival from Birth to 12 Months of Age for Sebelipase alfa-Treated Subjects in LAL-CL03 (PES) vs. Untreated Patients in LAL-1-NH01 (Patients with Early Growth Failure Only). *(Data source: Figure 3, LAL-CL03 Clinical Study Report, Page 111).*

Immunogenicity results

Four of the seven evaluable subjects (57%) with post-treatment immunogenicity data were ADA positive during at least one assessment. At the time of initial ADA positivity, 3 subjects were receiving a dose of 1 mg/kg qw, and 1 subject was receiving a dose of 3 mg/kg qw. The ADA titers decreased to undetectable levels during continued treatment in 3 of the 4 subjects.

Two out of 4 subjects with positive ADA titers were tested positive for NAbs that inhibited LAL enzyme activity and cellular uptake of LAL. In these 2 subjects, inhibition of LAL enzyme activity was detected concurrent with the first report of positive ADA titer. One subject had a comparatively low level of inhibition (18.9%) when first tested at Week 5, and thereafter had a high level of inhibition (70.9% to 90.3%). This subject also tested positive for neutralizing antibody that inhibits cellular uptake at Week 72. The other subject had a high level of inhibition when first tested at Week 8 (83.2%) and continued to have a high level of inhibition through Week 48 (82.1% to 89.8%); the subject was ADA negative at the last assessment at Week 58 (an unscheduled visit), and thus neutralizing antibody activity was not evaluated for this time point. At unscheduled assessments at approximately Week 23 and at Week 25, this subject tested positive for neutralizing antibody that inhibits cellular uptake.

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/s/

JING FANG
06/08/2015

YOW-MING C WANG
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General Information About the Submission

	Information		Information
NDA/BLA Number	**125561**	**Brand Name**	**Kanuma (proposed)**
OCP Division (I, II, III, IV, V)	**DCP III**	**Generic Name**	**Sebelipase alfa (proposed)**
Medical Division	**DGIEP**	**Drug Class**	**Lysosomal enzyme – recombinant human lysosomal acid lipase**
OCP Reviewer	**Jing Fang, Ph.D.**	**Indication(s)**	**Lysosomal Acid Lipase Deficiency**
OCP Team Leader	**Yow-Ming Wang, Ph.D.**	**Dosage Form**	**Concentrated solution for IV infusion after dilution**
Pharmacometrics Reviewer		**Dosing Regimen**	**1) 1 mg/kg once every other week as an IV infusion** **2) In infants presenting with rapidly progressive disease, starting dose is 1 mg/kg once weekly as an IV infusion, dose escalation to 3 mg/kg once weekly based on clinical response**
Date of Submission	**11/21/14**	**Route of Administration**	**IV**
Estimated Due Date of OCP Review	**4/21/15**	**Sponsor**	**Synageva BioPharma Corp.**
Medical Division Due Date		**Priority Classification**	**Priority**
PDUFA Due Date	**7/21/15**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**X**	**1**		

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multiple dose:	X	4		
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:	X	2		
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	X	2		
Phase 3:	X	2		
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	2		
Phase 3 clinical trial:	X	2		
Population Analyses -				
Data rich:	X	2		
Data sparse:	X	2		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	X	3		
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	1		
Total Number of Studies		4		

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The to-be-marketed formulation was used in the clinical trials.
2	Did the applicant provide metabolism and drug-drug interaction			X	

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	information? (Note: RTF only if there is complete lack of information)				
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

	Content Parameter	**Yes**	**No**	**N/A**	**Comment**
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or	X			

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	pharmacodynamics?				
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			(b) (4) [redacted] in the proposed labeling
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____X____

Please convey the below IR to the sponsor:

1. Table 9 of the LAL-CL02 Clinical Study Report suggests that rich pharmacokinetic (PK) sampling was performed in patients ≥18 years of age at Weeks 0 and 22. These data would allow a non-compartmental analysis (NCA) that could determine PK parameters for each subject. We request that you perform the NCA for all subjects who are ≥18 years of age in Study LAL-CL02 and provide the following:

- All datasets for the NCA PK analyses, including the original PK data, PK analysis dataset, and PK parameter dataset. All data files should be submitted in the sas transport file (.xpt) format. If you have already submitted the requested analysis and the datasets, clarify the location within the eCTD where they are located.

- A tabular summary of the PK parameters of sebelipase alfa from Day 0 (single dose) and Week 22 (multiple-Dose) for Study LAL-CL02

- Updated assessment of dose proportionality after single dose administration using combined NCA results from Study LAL-CL01 and LAL-CL02.

2. Section 6.5.5.2 in LAL-CL01 Report Body (eCTD 5.3.3.2) states that "Results of any such pharmacogenetic analysis will be presented in a separate report". We recommend that you submit available pharmacogenetic study results from Study LAL-CL01 including patient-level LIPA genotype data as well as provide information on the assay(s) used. In addition, we recommend that you evaluate the impact of LIPA genotype on the safety, efficacy, PK, PD, and immunogenicity of SBC-102 for subjects in Studies LAL-CL01 and LAL-CL04. If you have already submitted the requested analysis and the datasets, clarify the location within the eCTD where they are located.

Note: The first IR was sent out to the sponsor on 12/19/14 and the response was received on 01/09/15. The second IR was sent out to the sponsor on 01/09/14 and the response was received on 01/12/15.

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Review Summary

SBC-102 is a recombinant human lysosomal acid lipase (rhLAL) with a molecular weight of 55,000 Daltons, and is purified from egg white of transgenic hens (Gallus) with the same amino acid sequence as the native human LAL. It received Orphan Drug designation in July 2010 and Fast Track designation in June 14, 2011 for the treatment of LAL deficiency, and Breakthrough Therapy designation for the treatment of LAL deficiency presenting in infants in May 13, 2013.

SBC-102 is proposed for [redacted] (b) (4)) for patients with Lysosomal Acid Lipase (LAL) Deficiency which is an autosomal recessive lysosomal storage disease characterized by a genetic defect resulting in a marked decrease in activity of LAL enzyme. There are two phenotypes of LAL deficiency: infantile- and late-onset LAL deficiency. LAL deficiency in infants, historically called Wolman disease, is the most aggressive presentation of LAL deficiency. LAL deficiency in children and adults, historically called Cholesteryl Ester Storage Disease (CESD), is more heterogeneous with respect to age of diagnosis and onset.

Proposed dosing regimens

- 1 mg/kg administered as an intravenous (IV) infusion once every other week.
- In patients presenting with rapidly progressive disease in infancy, the recommended starting dose is 1 mg/kg administered as an IV infusion once weekly. In clinical studies, these patients were dose escalated to 3 mg/kg once weekly.

Proposed dosage forms and strengths

- Concentrated solution for IV administration after dilution
- 20 mg/10 mL vial (2 mg/mL) in single-use vials

To support the proposed indication, the applicant submitted this BLA containing 4 clinical studies that contributed information on the clinical pharmacology of SBC-102. One study was completed (LAL-CL01) and 3 studies are in the ongoing extension study or follow-up period. A total of 84 subjects with LAL deficiency received SBC-102 treatment in 2 open-label Phase 1/2 studies in adults (Study LAL-CL01, and its ongoing extension study, Study LAL-CL04), 1 Phase 3 study (Study LAL-CL02, double-blind, placebo-controlled period for 20 weeks followed by an open label extension period) in children (≥ 4 years old) and adults, and 1 dose escalation Phase 2/3 study in infants (Study LAL-CL03). The pivotal studies to demonstrate the efficacy of SB-102 in LAL deficient patients are Study LAL-CL02 in adults and children >4 years old and Study LAL-CL03 in infants. The dose regimens investigated in all of the 4 studies ranged from 0.35 mg once every week (qw) to 3 mg/kg qw and once every other week (qow) with the maximum treatment duration ranging between 3 and 4 years. Additionally, Study LAL-CL03 evaluated 0.2 mg/kg as the starting dose in one subject and dose escalated to 5 mg/kg in another subject.

The clinical development program of SBC-102 contains additional 5 studies which were included in the Clinical Overview (eCTD 2.5) and not included in the clinical pharmacology summary (eCTD 2.7.2). The natural history study LAL-1-NH01 served as a historical control for the pivotal Phase 2/3 study in infants (Study LAL-CL03). An observational Study LAL-2-NH01 of children and adults with LAL deficiency and its associated Substudy (assess hepatic and splenic volume and fat content in a subset of subjects in Study LAL-2-NH01) provided case record review of patients with LAL deficiency in order to improve the understanding of the clinical phenotype. Two open-label Phase 2 clinical studies LAL-CL06 in pediatric (> 8 months) and adults and LAL-CL08 in infants (< 8 months) were initiated in 2014 and no data was submitted.

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A summary of four key SBC-102 clinical studies in this BLA submission is presented in **Error! Reference source not found.**1.

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Table 1: Table 1. Summary of four Key SBC-102 Clinical Studies in the BLA Submission

Study Identifier	Study Design	Regimen (Duration of treatment)	Study Population	Number of Subjects Treated[a] / PK[b]	PK Assessment	PD Assessment	PG Assessment	Immunogenicity Assessment
LAL-CL01 (completed)	Phase 1/2, open-label study	0.35, 1, or 3 mg/kg qw for 4 weeks, IV	Adults (≥18 and ≤65 years of age) with liver dysfunction due to LAL deficiency	9/9	Day 0 (single-dose) and Day 21 (multiple-dose)	ALT, Serum lipids (total cholesterol, TGs, HDL-c, LDL-c)	Yes	ADA
LAL-CL04 (ongoing)	Single-arm, open-label, extension study	0.35, 1, or 3 mg/kg qw for 4 weeks, then 1 or 3 mg/kg qow, for up to 3 years, IV	Subjects who completed LAL-CL01	8/8	Weeks 24, 52, and 104	ALT, Serum lipids (LDL-c, TGs, HDL-c, and total cholesterol), and liver fat content	No	ADA
LAL-CL02 (Double-blind period complete, open-label period ongoing)	Phase 3, randomized, double-blind, placebo-controlled study	Double-blind period: 1 mg/kg or placebo qow for 20 weeks, IV; Open-label period: 1 mg/kg qow (irrespective of treatment in double-blind period) for up to 130 weeks	Pediatric (≥ 4 years old) and adult subjects with LAL deficiency	66/65[d]	Day 0 and at Weeks 22 and 56	ALT, Serum lipids (LDL-c, TGs, HDL-c, non-HDL-c), and liver fat content	Yes	ADA, NAb
LAL-CL03 (Primary analysis complete, subject follow-up ongoing)	Phase 2/3, Single-arm, open-label, dose escalation study	0.35 mg/kg qw for 2 infusions, IV, then 1 mg/kg qw, then 3 mg/kg qw if a suboptimal clinical response, and to 5 mg/kg qw if a continued suboptimal clinical response. Maximum treatment up to 4 years. Subjects treated for at least 96 weeks and with a stable dose for at least 6 months could transition to a qow regimen at same dose as qw regimen.	Infants with LAL deficiency who developed growth failure or other clinical evidence of a rapidly progressive disease course before 6 months of age	9/5[c]	Day 0 and Weeks 22 and 52	No	Yes	ADA, NAb

[a] Number of subjects includes only those subjects who received at least 1 infusion of sebelipase alfa. The number of subjects included in the PK, PD/efficacy, and exposure-response analyses may have been less, and may have varied over time or between parameters, depending on data availability.
[b] Analysed for PK.
[c] Population PK analysis.

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SBC-102 Drug Product (DP)

The to-be-marketed formulation for SBC-102 was used in the 4 aforementioned clinical studies.

Pharmacokinetic (PK) Assessment

The submission contains SBC-102 single dose and multiple-dose PK data collected with a rich sampling design and a sparse sampling design (see Table 2 below). The applicant performed non-compartmental analysis (NCA) with SBC-102 concentration data from adult subjects in 2 clinical studies (N=9 in LAL-CL01 and N=8 in LAL-CL04). PK data were sparse for all infant subjects in study LAL-CL03 and for subjects < 18 years of age in study LAL-CL02, which are not amenable for the NCA analysis.

In study LAL-CL02, a rich PK sampling scheme was employed with up to 12 samples being collected at each study visit for 19 subjects who are ≥18 years of age. However, NCA PK analysis was not performed for these subjects in Study LAL-CL02.

Table 2. PK Sampling Scheme and Data Analysis Method

Study no.	Age group	Rich PK sampling (Yes/No)	Doses (mg/kg) studied; dosing frequency	PK Analysis Method	N
LAL-CL01	Adults	Yes (Day 1 and Day 21)	0.35, 1 or 3; qw x4	NCA	9
LAL-CL04 (extension of LAL-CL01)	Adults	Yes (Weeks 24, 52, 104)	0.35, 1, or 3; qw x4 followed by 1 or 3; qow	NCA	8
LAL-CL02	Adults	Yes (Day 0, Week 22) No (Week 56)	1; qow	NCA* Population PK	19 (Day 0) 13 (Week 22)
LAL-CL02	Ages 4-17	No (Day 0, Weeks 22 and 56)	1; qow	Population PK	46
LAL-CL03	Infants	No (Day 0, Weeks 22, 52)	0.2 – 5; qw	Population PK	5

* To be requested

A population PK model with full covariate analysis was developed to describe SBC-102 concentration-time data collected in adult and pediatric subjects. The model was developed using all available data from studies LAL-CL01, LAL-CL04, LAL-CL03, and LAL-CL02, with a total of 987 SBC-102 concentrations datapoints from 79 subjects. In addition, the model was used to identify and quantify covariate effects that described variability in the PK of SBC-102, and then to estimate PK parameters in subjects participated in pivotal studies LAL- CL02 and LAL-CL03.

Reviewer's comment

The current submission contains NCA data in only 8-9 adult subjects. Given an additional 19 adult subjects in study LAL-CL02 had rich PK sampling, their NCA PK data can potentially strengthen the overall understanding of the adult PK and to support the labeling. We will request NCA results for these subjects from the applicant.

Based on the initial review of the population PK analysis report, the model development utilized the data from all subjects. The applicant did not set aside a subset of data to perform an external validation of the model. Further evaluation of the population PK analysis will be a review focus.

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Effect of renal impairment on PK

The applicant did not conduct a dedicated study to evaluate the effect of renal impairment on the PK of SBC-102. The potential effect of renal impairment was assessed in the population PK model by testing the creatinine clearance as a covariate and the results did not show any potential positive relationship with the variability random effects parameter for CL and V_c. (b) (4) The appropriateness of this conclusion will be a review issue.

Efficacy/Safety/Pharmacodynamics (PD) Assessment
The pivotal efficacy data are from Study LAL-CL02 for adults and children >4 years old and from Study LAL-CL03 for infants. Studies LAL-CL01 and LAL-CL04 contributed to additional PD assessments. A summary of study endpoints are described below:

Efficacy Endpoints for adults and children ≥4 years of age (LAL-CL02)

The primary efficacy endpoint is the proportion of subjects who achieved ALT normalization (i.e., ALT below the age- and gender-specific upper limit of normal [ULN] provided by the central laboratory performing the assay) at the end of the double-blind period at Week 20.

Efficacy Endpoints for infants (Study LAL-CL03)

The primary efficacy endpoint is the proportion of subjects surviving at 12 months of age. The proportion of subjects surviving to 12 months of age as well as the Kaplan-Meier plots of survival to 12 months of age from birth were compared with those of a historical control study (LAL-1-NH01) in subjects who had confirmed growth failure and were untreated (i.e., no hematopoietic stem cell transplant or liver transplant).

Efficacy Endpoints for adults (Study LAL-CL04)

To assess the long-term efficacy (the secondary objective), the efficacy endpoints include liver and spleen volumes and fat content by magnetic resonance imaging (MRI) or ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) and liver biopsy (ongoing). The primary objective of the study was to evaluate the long-term safety and tolerability of SBC-102 in subjects with liver dysfunction due to LAL deficiency.

Safety Endpoints

The safety assessment was conducted in all 4 clinical studies, which includes the infusion-associated reactions (IARs) data.

PD Endpoints used in the E-R analyses

Liver enzymes include Alanine aminotransferase (ALT); serum lipids include total cholesterol, triglycerides (TGs), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and liver fat content.

Evaluation of Exposure-Response (E-R) Relationship

The applicant has conducted graphical exposure-response analyses to assess potential relationships between exposure to SBC-102 and the PD endpoints (for studies LAL-CL01, LAL-CL04, and LAL-

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CL02) and safety endpoints (all 4 studies combined). For Study LAL-CL03, due to the limited data, the applicant did not perform graphical exposure-response analyses. Additionally, the applicant did not conduct a statistical analysis of the dose-response relationship for Study LAL-CL03 either because subjects received variable doses and dosing frequencies of SBC-102 and were dose-escalated at different times.

For the E-R analyses on PD responses, the response parameters were absolute, change from baseline, and percent change from baseline values of the PD endpoints mentioned above. The exposure parameters were the area under the concentration-time curve (AUC), the cumulative area under the plasma concentration-time curve (AUC_{cum}), and the maximum concentration (C_{max}); which were derived from the population PK model.

For the E-R analyses with the safety data from all 4 clinical studies, the response parameter was IAR and the exposure parameter was AUC_{cum}. In addition, potential relationships between the occurrence of IARs were assessed and SBC-102 dose or rate of infusion, together with potential relationships between subject age and the occurrence of IARs.

The E-R analyses were submitted in a population PK-PD report. The applicant claimed that the E-R relationships supported the dose and dosing regimen selection and the rationale was summarized in the Summary of Clinical Efficacy. The appropriateness of the proposed dose and dosing regimen in patients with LAL deficiency and in infants presenting with rapidly progressive disease will be a review issue.

Pharmacogenetic (PG) Assessment

The assessment of genetic mutations for allelic variants of the LIPA gene was performed and submitted for subjects in Studies LAL-CL02 (adults and children > 4 years old) and LAL-CL03 (infants). The applicant also assessed the potential impact of the genetic mutation on the PK exposure to SB-102 and the efficacy as well as PD parameters at baseline. Blood samples for pharmacogenetic analyses were collected from subjects in Study LAL-CL01/LAL-CL-04; however, the results of any such pharmacogenetic analysis were not submitted.

The c.849G>A mutation is the most commonly found mutation in children and adults with LAL deficiency. Subjects who have the common mutation are further divided into two groups (homozygous and confirmed or presumed compound heterozygous for the mutation)

In Study LAL-CL03, the genetic mutation was reported in two categories as either "common" or "other". All 6 subjects who had LIPA genetic testing were classified as "other" mutations. Distinct mutations were identified in each of the 6 subjects.

In Study LAL-CL02, three categories were used: Group 1: homozygous c.849G>A mutation, Group 2: heterozygous c.849G>A mutation, and Group 3: “other”. Of 66 subjects in Study LAL-CL02, 32% (21/66) were homozygotes, i.e., in Group 1, 53% (35/66) were heterozygotes, i.e., Group 2, and 15% (10/66) were “other”, i.e., in Group 3.

The applicant evaluated the impact of genetic mutation on baseline parameters of disease activity as well as on the efficacy endpoints in Study LAL-CL02 at the end of the double blind period (Week 20). For the baseline parameters, serum transaminases appeared to be higher in Group 3 compared to Groups 1 or 2. No differences or trends were observed among the three mutation catetories for LDL-c, non HDL-c, TG, or HDL-c. For the efficacy endpoints, the results were generally similar within each group. The

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applicant concluded that these data suggest that SBC-102 was effective regardless of genetic mutation category.

In addition, to evaluate the potential relationship between the genotype mutation status and the systemic exposure to SBC-102 in Study LAL-CL02, the applicant conducted an analysis using boxplot to compare the population PK estimates of AUC for Week 0 among the 3 mutation categories as described above. The applicant stated that there was a high degree of overlap in the observed AUC and C_{max} values observed among these 3 mutation categories, suggesting a consistency in the exposure to SBC-102 irrespective of the genotype mutation status. In Study LAL-CL03, the genotype mutation status for all 4 of the ADA-positive subjects was "other". Therefore, the applicant did not evaluate the potential relationship between genotype mutation status and exposure to SBC-102.

The conclusions regarding the impact of genetic mutation status on PK, PD and efficacy will be further reviewed.

Immunogenicity Assessment

The applicant has included SBC-102 immunogenicity results for all 4 clinical studies. Samples were tested for the presence of anti- SBC-102 antibodies (ADA). Samples from subjects with positive ADA titers were also tested for the presence of neutralizing antibodies (NAb) that inhibit LAL enzyme activity. The incidence as well as the titer of ADA (for positive ADA status) was reported for the 4 aforementioned clinical studies. The effects of antibodies on PK, PD, efficacy, and safety were evaluated and submitted. Samples with positive ADA were tested for the presence of NAb that inhibited LAL enzyme activity and NAb that inhibited cellular uptake of LAL in a rat macrophage cell line.

Bioanalytical Assays

The applicant submitted 4 method validation reports that contain an enzymatic method to determine the activity of SBC-102 in human serum, an ELISA method to examine antibody to SBC-102 (ADA) in human serum (contains three components: screening, confirmatory and titration assay), an enzymatic activity-based neutralizing assay for the detection of the anti-SBC-102 neutralizing antibodies (NAb, inhibition of enzyme activity), and a cell-based assay for the detection of NAb (inhibition of cellular uptake) in human serum.

No ADA samples have been further characterized to date for IgE subtype analysis. The applicant has developed an IgE assay and it is undergoing validation.

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/s/

JING FANG
01/20/2015

YOW-MING C WANG
01/20/2015