A PHASE 2, OPEN LABEL, MULTICENTER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, EFFICACY, AND PHARMACOKINETICS OF SEBELIPASE ALFA IN INFANTS WITH RAPIDLY PROGRESSIVE LYSOSOMAL ACID LIPASE DEFICIENCY

Unique Protocol ID: **LAL-CL08**

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Date of Protocol: **08 December 2015**

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Protocol Number: **LAL-CL08**

Date of Protocol: **08 December 2015**

Amendment: **3.0**

Product: **Sebelipase alfa (SBC-102)**

IND No.: **108460**

EUDRACT No.: **2014-000533-22**

Sponsor: **Alexion Pharmaceuticals, Inc.**
352 Knotter Drive
Cheshire, CT 06410
USA

Amendment History	
Protocol	**Date of Approval**
Original	14 February 2014
Amendment 1 (country-specific: United Kingdom)	12 August 2014
Amendment 2	02 December 2014
Amendment 3.0	08 December 2015

PROTOCOL SIGNATURE PAGE

Protocol title:	**A Phase 2, Open Label, Multicenter Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Sebelipase Alfa in Infants with Rapidly Progressive Lysosomal Acid Lipase Deficiency**
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Sponsor:	**Alexion Pharmaceuticals, Inc.** **352 Knotter Drive** **Cheshire, CT 06410** **USA**

PPD

8 DEC 15

Date

Alexion Pharmaceuticals, Inc.

INVESTIGATOR AGREEMENT

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the Sponsor.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects. This study may be terminated by the Sponsor, with or without cause.

I agree to personally conduct or supervise this investigation at my institution and to ensure that all of my associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. The study will be conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of subjects.

I will ensure that the requirements relating to Institutional Review Boards/Independent Ethics Committees (IRB/IEC) review and approval are met. I will provide the Sponsor with any material which is provided to the IRB/IEC for ethical approval.

I agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements.

I agree to promptly report to the IRB/IEC any changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB/IEC approval, except where necessary to ensure the safety of study participants.

_____	_____
Print Name	Institution
_____	_____
Signature	Date

Protocol Synopsis

Summary of planned clinical study	
Protocol Number (study identifier)	**LAL-CL08**
Title	A Phase 2, Open Label, Multicenter Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Sebelipase Alfa in Infants with Rapidly Progressive Lysosomal Acid Lipase Deficiency
Study design features	This is an open-label, repeat-dose, study of sebelipase alfa in infants with rapidly progressive LAL Deficiency. Eligible subjects will receive once-weekly (qw) infusions of sebelipase alfa for up to 3 years. Subjects who are on treatment for at least 96 weeks and are on a stable dose for at least 24 weeks may be considered to transition to an every other week dosing schedule. All subjects will initiate treatment at a dose of 1 mg/kg qw. A dose escalation to 3 mg/kg qw may be considered, as specified in section 3.1.1, contingent upon acceptable safety and tolerability of preceding infusions and as approved by the Investigator and Sponsor. All subjects will be evaluated for safety, tolerability, and efficacy. Where feasible, given blood volume thresholds based on subject weight, blood samples will also be collected for analyses of the pharmacokinetics (PK) of sebelipase alfa and for an exploratory analysis of potential disease-related biomarkers in this patient population.
Background (rationale)	Lysosomal Acid Lipase (LAL) Deficiency is a rare autosomal recessive lipid storage disorder that is caused by a marked decrease or almost complete absence of LAL, leading to the accumulation of lipids, predominately cholesteryl esters and triglycerides, in various tissues and cell types. In the liver, accumulation of lipids leads to hepatomegaly, liver dysfunction, and hepatic failure. In the small intestine, lipid-laden macrophage accumulation in the lamina propria leads to profound malabsorption. LAL Deficiency presenting in infancy is an extremely rare form of LAL Deficiency that is usually fatal within the first 6 months of life (Assmann, 2001, *The Metabolic and Molecular Basis of Inherited Disease*). It is characterized by profound malabsorption, growth failure, and hepatic failure, and is usually fatal in the first 6 months of life. There is currently no safe or effective therapy for the treatment of LAL Deficiency.
Main objective(s)	The primary objective of the study is to evaluate the safety and tolerability of sebelipase alfa in infants with rapidly progressive LAL Deficiency. The secondary objectives are to evaluate the effect of sebelipase alfa therapy on: (1) Survival at 12 months of age (2) Survival past 12 months of age; (3) Growth parameters; (4) Hepatomegaly, splenomegaly, and liver function; (5) Hematological parameters; and (6) to characterize the PK of sebelipase alfa delivered by intravenous (IV) infusion. The exploratory objectives are (1) to determine the effects of sebelipase alfa on lipid parameters; (2) to assess the effects of sebelipase alfa on achievement of developmental milestones; and (3) to evaluate potential disease-related biomarkers.
Study population and subset definition	The study population is infants with rapidly progressive LAL Deficiency.

Summary of planned clinical study

Number of study participants (e.g. age, sex, severity)	Up to 10 subjects will be enrolled in this study
Main inclusion criteria	A subject must meet all of the following criteria to be eligible to participate in this study: 1. Subject's parent or legal guardian (if applicable) consents to participation in the study. 2. Confirmation of documented decreased LAL activity relative to the normal range of the lab performing the assay or a documented result of molecular genetic testing confirming a diagnosis of LAL Deficiency. 3. Substantial clinical concerns, in the opinion of Investigator and Sponsor, of rapid disease progression requiring urgent medical intervention including, but not restricted to, the following: a) Marked abdominal distension and hepatomegaly b) Failure to thrive as evidenced by: i) Weight for height is 2 or more SD below the mean for gender and age ii) Weight curve has crossed downward by more than 2 major percentile lines on the WHO growth curves (1^{st}, 3^{rd}, 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th}, 97^{th}, 99^{th}) after having previously achieved a stable pattern of growth c) Disturbance of coagulation (e.g., requirement for FFP; two values of PT >15 sec or PTT > 40 sec) d) Severe anemia (e.g., requirement for blood transfusion or hemoglobin < 8 g/dL) e) Sibling with rapidly progressive course of LAL Deficiency
Main exclusion criteria	A subject who meets any of the following criteria will be ineligible to participate in this study: 1. Clinically important concurrent disease or co-morbidities which, in the opinion of the Investigator and Sponsor, would interfere with study participation, including, but not restricted to': a) Additional severe congenital abnormality b) Presence of severe infection that requires treatment with parenteral anti-infective treatment within the past 14 days c) Previous history of circulatory collapse requiring inotropic support for more than 48 hours d) Congestive heart failure e) Acute or chronic renal failure f) Other extenuating circumstances such as life-threatening under nutrition or rapidly progressive liver disease 2. Subject will be > 8 months of age at the time of first dosing. 3. Subject has received an investigational medicinal product other than sebelipase alfa within 14 days prior to the first dose of sebelipase alfa in this study. 4. Myeloablative preparation, or other systemic pre-transplant conditioning, for hematopoietic stem cell or liver transplantation. 5. Previous hematopoietic stem cell or liver transplant. 6. Known hypersensitivity to eggs.

Summary of planned clinical study	
Randomization strategy	This study is open label and is not randomized.
Location (e.g. regions)	Multi-center (approximately 5 primary study centers globally). Subjects who are medically stable, as determined by the Investigator, may transfer to a local medical center for long-term treatment, contingent upon the local medical center having been approved and having secured the required regulatory, Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), and Sponsor approvals. Scheduled study assessments may also be performed at a local medical center with access to the appropriate facilities and expertise.
Study duration for participants	The duration of each subject's treatment in the study is expected to be at least 18 months, and subjects may continue to receive treatment in the study for up to 3 years.

Dosage, treatment regimen, route of administration and dose escalation strategy	Sebelipase alfa (SBC-102), a recombinant human lysosomal acid lipase (rhLAL) produced in transgenic *Gallus*, will be administered by IV infusion.
	
	All subjects will initiate treatment with sebelipase alfa at a dose 1 mg/kg qw. A dose escalation to 3 mg/kg qw may be considered, as specified in section 3.1.1, contingent upon acceptable safety and tolerability of preceding infusions and as approved by the Investigator and Sponsor.
	
	An independent Safety Review Committee (SRC) will oversee safety in this study. The SRC will review available safety data during at least semiannual periodic meetings and on an ad hoc basis as needed in the event of unanticipated safety findings.
	
	Subjects who do not tolerate a dose of 3 mg/kg qw may receive a dose reduction to 1 mg/kg qw at the discretion of the Investigator in consultation with the Sponsor and, where appropriate, the SRC. If a subject cannot tolerate a dose of 1 mg/kg qw, despite measures taken to manage any infusion-associated reactions (IARs), the subject will be discontinued from the study.
	
	Subjects who are on treatment for at least 96 weeks and have been on a stable dose for at least 24 weeks, may transition to an every other week dosing schedule at the same dose they received on the weekly dosing schedule at the discretion of the Principal Investigator (PI) with Sponsor consultation. If the subject meets the criteria for dose escalation while on the every other week dosing schedule they will either revert back to weekly dosing or if on 1 mg/kg qow increase to 3 mg/kg qow dosing.
	
	Criteria for dose escalation
	For purposes of dose escalation in this study, a subject may be considered eligible (first 3 months of treatment) if he/she meets 2 or more of the following criteria at a dose of 1 mg/kg qw:
	• Failure to gain an average of 5 g/kg body weight per day AND the presence of one of the following:
	  ○ weight-for-length (WFL) or weight-for-height (WFH) z-score < -2 based on WHO child growth standards; and/or
	  ○ length-for-age (LFA) or height-for-age (HFA) z-score <-2 based on WHO child growth standards
	  ○ weight-for-age (WFA) z-score <-2 based on World Health Organization (WHO) child growth standard
	• Albumin <3.5 g/dL

Summary of planned clinical study	
	• Alanine aminotransferase (ALT) >2x upper limit of normal (ULN) • Ongoing requirement for blood and/or platelet transfusion A subject may be considered for dose escalation (after at least 3 months of treatment) if, in addition to the criteria above, they meet the below criteria: • Any other clinically important manifestation of LAL Deficiency on either clinical examination, laboratory assessment, or imaging which has either o not improved from baseline o improved and plateaued but has not normalized (Note: The definition of a plateauing of effect requires consideration of a minimal of 3 assessments) o failed to normalize within 12 months of initiation of treatment Manifestations include but are not restricted to the following: A decrease in weight for age defined as crossing ≥2 major centile lines on standard weight for age curves, serum transaminases, albumin <3.5 g/dL, hepatomegaly, splenomegaly or lymphadenopathy If the subject continues to demonstrate evidence of the above specified criteria after at least 4 infusions at a dose of 3 mg/kg qw, the Investigator, may request of the Sponsor (in consultation with the SRC) to increase the dose up to a maximum of 5 mg/kg qw on a case by case basis. In the rare circumstance a dose escalation to 5 mg/kg may be considered prior to 4 infusions if agreed to by the Sponsor and SRC.
Controls	There is no placebo or comparator in this study.
Rescue treatment	No therapy has been shown to be safe or effective for the treatment of LAL Deficiency. Hematopoietic stem cell transplantation has been used experimentally but has a high morbidity and mortality in this patient population.
Criteria for evaluation	***Safety*** Safety endpoints will include the incidence of adverse events (AEs), serious adverse events (SAEs), and IARs; changes from baseline clinical laboratory tests; changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature) during and post-infusion relative to pre-infusion values; physical examination findings; use of concomitant medications/therapies; and characterization of ADAs, including ADA positivity rate, time to ADA positivity, median and peak ADA titer, and time to peak ADA titer. The impact of ADAs on safety endpoints will also be explored. Further characterization of ADAs, including inhibitory and/or neutralizing ADAs and measurement of specific ADA subtypes (e.g., IgE), may be performed, if appropriate. ***Efficacy*** Survival endpoints will include proportion of subjects surviving to 12, 18 and 24 months of age, and other timepoints, as data permit, and estimated median age at death. Survival rates and median age at death derived from this study will be compared to rates/times reported in the literature and previous studies. Other efficacy endpoints will include changes from baseline in percentiles and/or z-scores for WFA, WFL/WFH, and LFA/HFA and the corresponding growth status indicators of underweight, wasting, and stunting, as well as changes from baseline in z-scores for head circumference-for-age (HCFA)

Summary of planned clinical study	
	and mid-upper arm circumference-for-age (MUACFA); changes from baseline in aspartate aminotransferase (AST) and ALT; normalization of hemoglobin levels without requirement for blood transfusion; and change from baseline in serum ferritin. Exploratory efficacy endpoints will include changes and/or percent changes from baseline (or first available measurement if baseline data are unavailable) in alkaline phosphatase, gamma glutamyltransferase (GGT), albumin, and bilirubin (direct, indirect, and total); liver and spleen size/volume, as measured by ultrasound or magnetic resonance imaging (MRI); hepatomegaly and/or splenomegaly (abdominal girth, liver size, and spleen size) by physical examination; platelet levels; and serum lipid levels (total cholesterol, triglycerides, high density lipoprotein [HDL], low density lipoprotein [LDL]). Development will also be assessed using Denver II developmental screening test total score and four functional area scores (fine motor-adaptive, gross motor, personal-social, and language skills). The impact of anti-sebelipase alfa antibodies (ADAs) on efficacy endpoints will also be explored. ***Pharmacokinetics*** The PK endpoint will include maximum observed serum concentration (C_{max}), as data permit. The impact of ADAs on SBC-sebelipase alfa PK will also be explored. ***Exploratory Biomarkers*** Exploratory disease-related biomarkers, which may be identified based on emerging information from the sebelipase alfa development program and scientific literature, will be analyzed by changes or percent changes from baseline.
Sample size	Up to 10 subjects will be enrolled in this study. No formal sample size calculations were performed. No formal hypothesis testing is planned for this study.
Statistical plan (including study conduct and analysis)	**Analysis Sets** The Full Analysis Set (FAS) will include all subjects who received any amount of investigational medicinal product (IMP). The PK Analysis Set will include all available sebelipase alfa serum concentration data for subjects who received at least one complete infusion of IMP in this study. **General Considerations** All data will be presented in listings, and summary tables and/or graphs will be provided, as appropriate. Unless otherwise noted, tabulations for all efficacy endpoints will be presented for subjects in the FAS. Descriptive summary statistics (n, mean, median, standard deviation, minimum, and maximum) will be calculated for the continuous variables. Shift tables and/or frequencies and percentages will be produced for the categorical variables. As appropriate, 95% two-sided CIs will be calculated around the estimates based on the exact binomial distribution for binomial endpoints and the t-distribution for continuous endpoints. Baseline will be defined as the last measurement prior to the first infusion of sebelipase alfa. (Note: For exploratory analyses, the first available measurement after initiation of treatment may be used as baseline if a pretreatment measurement is unavailable.) In order to facilitate comparison

Summary of planned clinical study

with literature, survival analyses will be presented with subject birth date as "time 0"; analyses of other endpoints over time will consider date of first dose as "time 0".

Safety
Safety will be analyzed for the FAS.

All reported AEs will be listed from the date of written informed consent until the end of participation in this study. Separate listings of deaths, SAEs and IARs will also be provided. The numbers and percentages of subjects experiencing any AE, any SAE, any IAR, any related AE, any related SAE, and discontinuations due to an AE will be tabulated. The frequency of treatment-emergent AEs, SAEs, and IARs by SOC and PT (coded using Medical Dictionary for Regulatory Activities [MedDRA®]) will be tabulated. Frequencies will also be presented by the classifications of severity and causality. In addition, frequency of AEs, SAEs, and IARs will be presented for time periods spanning the entire course of treatment with sebelipase alfa: from the start of dosing with sebelipase alfa in this study to 3 months after the first dose, >3 to 6 months, >6 to 12 months, >12 to 18 months, >18 to 24 months and >24 months. As appropriate, additional listings, summary tables and graphics will be generated to evaluate IAR frequency and severity over time. A listing of subjects who withdraw from the study due to AEs will be presented, and the incidence of AEs leading to study discontinuation will be summarized.

Observed measurements and changes from baseline to each study timepoint in clinical laboratory data will be summarized. Clinically significant abnormal values will be listed. Frequencies of abnormal values relative to the laboratory normal range and clinically significant abnormal values will be tabulated for each study timepoint. Shift tables may also be provided.

Time to ADA positivity, median and peak antibody titer, and time to peak antibody titer; antibody titer values will be tabulated at each study visit using summary statistics appropriate to the data.

Changes in vital signs from pre-infusion values to each time point during or post-infusion will be summarized. Abnormal findings/values for physical examinations, vital signs, and ECGs will also be listed. Concomitant medication/treatment data will be coded using the WHO-DRUG dictionary. All data will be listed, and the percentages of subjects receiving each concomitant medication/treatment will be tabulated.

Pharmacokinetics
Pharmacokinetics will be analyzed for the PK Analysis Set. C_{max} will be recorded from direct observation. C_{max} parameters will be summarized by dose of sebelipase alfa, if applicable.

Efficacy
Efficacy will be analyzed for the Full Analysis Set.

Survival will be analyzed as the proportion of subjects surviving to 12, 18, and 24 months of age. As a complementary analysis, Kaplan-Meier survival curves of survival since birth and survival since first dose of IMP will be presented. Median age at death will also be calculated. A Kaplan-Meier estimate of median survival past first dose of IMP will be computed. Estimated survival rates and median age at death derived from this study will

Summary of planned clinical study	
	be compared to rates/times reported in the literature, and will be discussed in conjunction with information derived from previous studies. Anthropometric indicators of growth, standardized by age and gender in accordance with the methodology described by the WHO and using WHO growth charts, will be listed by study time point as observed values and as changes from baseline. Change from baseline in anthropometric data will be tabulated as continuous data. In addition, the percentages of subjects who meet criteria for underweight, stunting, and wasting will be tabulated for each timepoint. Change and/or percent changes from baseline in AST, ALT, and serum ferritin will be tabulated for each evaluation timepoint. The proportion of subjects with abnormal hemoglobin at baseline who achieve transfusion-free hemoglobin normalization will be summarized, as will the proportion of subjects who maintain transfusion-free normal hemoglobin. The Denver II total score and functional area scores will be derived from the questionnaire in accordance with the Technical Manual and compared to appropriate demographic norms. The total score and functional area scores will be summarized as continuous data and according to the classification as to whether the subject displays abnormal/normal development. Shift tables will be used to tabulate dietary changes, including discontinuation of low-fat/low-cholesterol diet and/or introduction of an unrestricted age-appropriate diet. Observed values and changes and/or percent changes from baseline in other exploratory efficacy endpoints will be tabulated for each evaluation timepoint. ***Exploratory Biomarkers*** Exploratory biomarkers will be analyzed for the FAS. Potential disease-related biomarkers will be listed and observed values and changes and/or percent changes from baseline will be summarized by timepoint. ***Subgroup Analyses*** The impact of ADAs on safety, efficacy, PK, and PD endpoints will be explored descriptively. As subject numbers permit, other subgroup analyses of interest may be performed including, but are not limited to, age, gender, and race.
Measures to minimize pain and distress (only if specific for this study)	Local analgesic cream (e.g., eutectic mixture of local anesthetics) will be allowed at least 20-30 minutes (or according to applicable institutional guidelines) prior to IV placement or blood sampling.
External safety review	Independent Safety Review Committee

Table of Contents

LIST OF TABLES

List of Abbreviations

ADA	Anti-drug Antibody
AE	Adverse Event
ALT/SGPT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST/SGOT	Aspartate Aminotransferase
CBC	Complete Blood Count
CESD	Cholesteryl Ester Storage Disease
CI	Confidence Interval
C_{max}	Maximum Observed Plasma Concentration
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
DBS	Dried Blood Spot
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram (ECG)
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERT	Enzyme Replacement Therapy
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma Glutamyltransferase
GI	Gastrointestinal
GlcNAc	N-acetylglucosamine
HCFA	Head circumference-for-age
HDL	High Density Lipoprotein
HFA	Height-for-Age
hs-CRP	High sensitivity C reactive protein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IAR	Infusion-Associated Reaction
IM	Intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LAL	Lysosomal Acid Lipase
LDL	Low Density Lipoprotein
LFA	Length-for-Age

LLN	Lower Limit of Normal
LSD	Lysosomal Storage Disorder
M6P	Mannose-6-Phosphate
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Macrophage Mannose Receptor
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MUACFA	Mid-upper Arm Circumference-for-Age
NCS	Not Clinically Significant
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamic
PI	Principal Investigator
PT	Preferred Term
PT (INR)	Prothrombin Time (International Normalized Ratio)
PK	Pharmacokinetics
qow	Every other week
qw	Once weekly
rhLAL	Recombinant Human Lysosomal Acid Lipase
SAE	Serious Adverse Event/Serious Adverse Experience
SRC	Safety Review Committee
SOC	System Organ Class
SOM	Study Operations Manual
TEAE	Treatment-emergent adverse event
TFHN	Transfusion-Free Hemoglobin Normalization
US	United States
WFA	Weight-for-Age
WFH	Weight-for-Height
WFL	Weight-for-Length

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to United States (US) and international standards of Good Clinical Practice (GCP) (FDA Title 21 part 312 and International Conference on Harmonization [ICH] guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

1.1.1 Lysosomal Acid Lipase Deficiency

Lysosomal Acid Lipase (LAL) Deficiency is a rare autosomal recessive lipid storage disorder that is caused by a marked decrease or almost complete absence of the lysosomal enzyme, LAL.

The marked reduction or almost complete absence of LAL in patients with LAL Deficiency leads to the accumulation of lipids, predominately cholesteryl esters and triglycerides, in various tissues and cell types, particularly the liver leading to hepatomegaly, liver dysfunction, and hepatic failure, and in the small intestinal macrophages leading to profound malabsorption. LAL Deficiency presenting in infancy is characterized by profound malabsorption, growth failure, and hepatic failure and is usually fatal within the first 6 months of life. In children and adults with LAL Deficiency, liver involvement and dyslipidemia dominate the clinical picture. All presentations of LAL Deficiency are due to mutations in the LIPA gene located on chromosome 10q23.2-q23.3. In LAL Deficiency presenting in children and adults, many cases are associated with a common mutated allele in which may result in some residual enzyme activity, whereas in LAL Deficiency presenting in infants there are a variety of private mutations that likely result in a complete loss of enzyme function (Assmann, 2001, *The Metabolic and Molecular Basis of Inherited Disease*). It has been hypothesized that there may be a correlation between enzyme activity and the severity of the disease.

1.1.2 LAL Deficiency Presenting in Infancy

LAL Deficiency presenting in infants, historically called Wolman disease or LAL Deficiency/Wolman phenotype, is a very rare form of LAL Deficiency that is usually fatal within the first 6 months of life (Assmann, 2001, *The Metabolic and Molecular Basis of Inherited Disease*). This form of the disease, named after the physician who first described it (Abramov, 1956, *AMA J Dis Child*), is the most rapidly progressive presentation of LAL Deficiency, with growth failure and severe hepatic disease, as evidenced by liver enlargement, elevation of transaminases, hyperbilirubinemia, coagulopathy, and hypoalbuminemia, as the predominant clinical features and key contributors to the early mortality (Anderson, 1999, *Mol Genet Metab*; Mayatepek, 1999, *J Inherit Metab Dis*). Fibrosis and cirrhosis develop rapidly and have been described in affected infants within the first 6 months of life (Marshall, 1969, *Arch Dis Child*; Konno, 1966, Tohoku *J Exp Med*; Crocker, 1965, *Pediatrics*).

Diagnosis of LAL Deficiency is established through both physical findings and laboratory analyses. Infants are typically hospitalized within the first 2 months of life due to diarrhea, persistent vomiting, feeding difficulty and growth failure (Wolman, 1995, *Clin Pediatr*).

Physical findings include abdominal distention with hepatomegaly and splenomegaly. Radiographic examination often reveals calcification of the adrenal glands. Laboratory evaluations typically reveal elevated levels of serum transaminases and absent or markedly reduced LAL enzyme activity (Assmann, 2001, *The Metabolic and Molecular Basis of Inherited Disease*; Mayatepek, 1999, *J Inherited Metab Dis*; Surve, 2005, *Indian J Pediatr*).

At present, there are no safe or effective therapies for the treatment of patients with LAL Deficiency. A variety of supportive therapies are used in an attempt to mitigate some of the effects of this rapidly fatal disease. Antibiotics may be prescribed to address pyrexia or documented infections. In an attempt to mitigate the complications due to lipid accumulation within the target cells and vital organs, dietary restriction of either breast milk or formulas containing triglycerides and cholesteryl esters and the use of a fatty ester free diet is recommended (Wolman, 1995, *Clin Pediatr*). Although some stabilization of the clinical condition has been described with nutritional support, these interventions do not substantially modify the outcome in affected patients (LAL-1-NH01; Hoeg, 1984, *Am J Hum Genet*; Meyers, 1985, *Nutr Res*).

Outcomes with hematopoietic stem cell transplantation in affected infants have recently been reviewed in the literature, and while there are reports that 3 transplanted patients have survived beyond 3 years, the majority of transplant attempts resulted in early death due to liver failure from progressive disease, or sinusoidal obstruction syndrome (veno-occlusive disease) or other transplant-related complications (Gramatges, 2009, *Bone Marrow Transplant*; Krivit 1992, *Bone Marrow Transplant*; Krivit, 2000, *Bone Marrow Transplant*; Tolar, 2009, *Bone Marrow Transplant*; Yanir, 2013, *Mol Gen Metab*). The toxicity of conditioning regimens and time required for engraftment create substantial risks in the setting of such a rapidly progressive disease as LAL Deficiency presenting in infants.

1.1.3 Medical Plausibility of Enzyme Replacement Therapy for LAL Deficiency

LAL Deficiency resembles other lysosomal storage disorders (LSDs) with the accumulation of substrate in a number of tissues and cell types. The successful treatment of Gaucher disease with placental glucocerebrosidase in the 1990s and, with the follow-on enzyme produced by recombinant DNA technology, established the medical value and long-term safetyof ERT for LSDs (Barton, 1990, *Proc Natl Acad Sci*; Barton, 1991, *N Engl J Med*). The scientific concepts established by these initial studies have now been extended to a broader range of disorders, including Pompe disease (Kishnani, 2007, *Neurology*; van der Ploeg, 2010, *N Engl J Med*), Fabry disease (Wilcox, 2004, *Am J Hum Genet*), Mucopolysaccharidosis I (Wraith, 2004, *J Pediatr*), and Mucopolysaccharidosis II (Muenzer, 2007, *Mol Genet Metab*) and there is now extensive clinical experience of long-term ERT in patients with LSDs.

In LAL Deficiency, substrate accumulation is most marked in cells of the reticuloendothelial system, including Kupffer cells in the liver, histiocytes in the spleen and macrophages in the lamina propria of the small intestine. Reticuloendothelial cells express the macrophage mannose/N-acetylglucosamine receptor (also known as macrophage mannose receptor or MMR, CD206), which mediates binding, cell uptake and lysosomal internalization of proteins

with N-acetylglucosamine (GlcNAc) or mannose terminated N-glycans, and provides a pathway for the potential correction of the enzyme deficiency in these key cell types (Stahl, 1978, *Proc Natl Acad Sci*). This knowledge and the precedent established for other LSDs provides plausibility that ERT with sebelipase alfa, which has the appropriate glycan characteristics for targeting macrophages and other key cells, will benefit patients with LAL Deficiency.

Biological activity of sebelipase alfa in patients with LAL Deficiency has been demonstrated in clinical study LAL-CL01 and LAL-CL04, including decreases in transaminases and evidence of early lipid mobilization and correction of dyslipidemia with longer term dosing, This information and the encouraging initial response to sebelipase alfa in LAL-CL03, including improvements in weight gain, decrease in hepatic and splenic size, resolution of vomiting and diarrhea, and improvement in biochemical markers, provides the first human evidence in support of the potential for ERT for this disease (see Section 1.4).

1.2 Investigational Agent

Sebelipase alfa (SBC-102) is a recombinant human lysosomal acid lipase (rhLAL) with the same amino acid sequence as the native enzyme. Sebelipase alfa is a highly purified recombinant form of the naturally occurring human lysosomal acid lipase enzyme responsible for the metabolism and degradation of cholesteryl esters and triglycerides that are delivered to lysosomes by a variety of routes including low density lipoprotein (LDL) receptor mediated endocytosis. Sebelipase alfa is a glycoprotein with a molecular weight of approximately 55 kD with 5 N-linked glycosylation sites.

Sebelipase alfa is produced by recombinant DNA technology in egg white using a transgenic *Gallus* expression system and contains predominantly GlcNAc and mannose terminated N-linked glycan structures, some of which contain mannose-6-phosphate (M6P). GlcNAc and mannose terminated glycans are specifically recognized and internalized via the MMR present on the surface of macrophages. These cells are one of the most important cell types that accumulate cholesteryl esters and triglycerides in patients with LAL Deficiency. In addition, the presence of M6P allows delivery to cells that display the widely expressed M6P receptor.

1.3 Preclinical Data

In in vitro studies, sebelipase alfa demonstrated uptake and localization to lysosomes, and produced a dose-dependent correction of LAL activity in human fibroblasts deficient in this enzyme.

In homozygous LAL-deficient rats, a nonclinical disease model of LAL Deficiency, intravenous (IV) administration of sebelipase alfa restored enzyme activity in the liver and other key target tissues, and was associated with a marked reduction in substrate accumulation (cholesteryl esters and triglycerides) in the liver, spleen, gut, and lymph nodes relative to placebo-treated animals. Homozygous LAL-deficient rats demonstrate liver and spleen abnormalities, which resemble the abnormalities seen in patients with LAL Deficiency including accumulation of cholesteryl esters and triglycerides, hepatosplenomegaly, transaminase elevation, Kupffer cell expansion with disruption of normal liver architecture and liver fibrosis (Leavitt, 2011, *J Hepatol*).

In addition, the LAL-deficient rats show other abnormalities that are prominent in rapidly progressing LAL Deficiency, including gastrointestinal (GI) involvement with abnormal lipid accumulation in macrophages in the lamina propria of the small intestine, markedly impaired weight gain, and early mortality (Leavitt, 2011, *J Ped Gastroenterol Nutr*; Sponsor data on file). Once weekly (qw) and every other week (qow) administration of sebelipase alfa by IV injection administered over a 4-week period led to a statistically significant improvement ($p<0.05$) in weight gain and organ size compared to placebo-treated LAL-deficient rats. Of note, the improvements in weight gain were statistically significant within 2 weeks of initiation of the first dose. Liver abnormalities were all markedly improved within 4 weeks of treatment initiation. In a subsequent study, sebelipase alfa was administered to LAL-deficient rats qw at a dose of 3 mg/kg (given by bolus tail vein injection) for 19 weeks, beginning at 8 weeks of age, to investigate the effectiveness of sebelipase alfa in the presence of more advanced disease and to determine whether restoration of growth and correction of other disease-related abnormalities with sebelipase alfa treatment was associated with extended survival. In this study, sebelipase alfa treatment resulted in substantial improvements in the phenotypic abnormalities seen in this disease model. Sebelipase alfa-treated LAL-deficient rats gained more weight than vehicle-treated animals, and survived without exception to the scheduled sacrifice time (27 weeks of age); in a separate study, untreated animals did not survive beyond 14 weeks of age. The growth rate of the sebelipase alfa-treated LAL-deficient rats was sustained through study termination in a manner comparable to wildtype rats. Favorable responses were observed with regard to organomegaly, with reductions in the size of all affected organs examined, and a concomitant reduction in hepatic levels of LAL substrates, consistent with the expected mechanism of action of sebelipase alfa. The reduction in hepatomegaly was also accompanied by a normalization of serum transaminases. Histologically, the appearance of the liver in the sebelipase alfa-treated LAL-deficient rats resembled that of the wildtype rat. These positive disease-modifying effects of sebelipase alfa were comparable to the effects observed following short-term (4 weeks) administration. Additional discussions of the dose response of the effects seen in the nonclinical model are included in Section 1.5.1.

There were no meaningful toxicological findings in 4-week repeat dose toxicology studies in the Sprague-Dawley rat and Cynomolgus monkey administered IV infusions of sebelipase alfa at doses up to 50 mg/kg qw. In a 6-month repeated dose toxicity study in juvenile Cynomolgus monkeys administered qw IV infusions of sebelipase alfa at doses of 3 mg/kg, 10 mg/kg, or 30 mg/kg (5 males and 5 females per dose group), or placebo infusions (5 males, 5 females), sebelipase alfa was well tolerated up to the highest dose level of 30 mg/kg. There were no sebelipase alfa related changes in any of the study parameters, although there was an apparent infusion reaction observed in one animal on Day 1 of dosing following administration of sebelipase alfa at a dose of 10 mg/kg. With diphenhydramine pretreatment, no additional reactions were observed during the subsequent 25 infusions in this animal. No infusion reactions were observed in a total of 754 infusions administered to the other 29 animals in this study. These results support the long-term dosing with sebelipase alfa.

Pharmacokinetic (PK) studies in Sprague-Dawley rats administered IV bolus injections of sebelipase alfa at doses of 1 mg/kg and 5 mg/kg demonstrate that sebelipase alfa is rapidly cleared from the circulation and uptake appears to be saturable. Consistent with these findings, PK data from the first clinical study of sebelipase alfa in adult subjects with LAL Deficiency (study LAL-CL01) indicate that sebelipase alfa has a short plasma half-life in humans, ranging from 0.07 to 2.04 hours at the lowest dose of 0.35 mg/kg, and from 0.09 to 0.21 hours at higher doses of 1 or 3 mg/kg. Clinical PK data for sebelipase alfa are not yet available for children and adolescents with LAL Deficiency.

1.4 Clinical Data

Clinical investigations to assess the efficacy, safety, and tolerability of sebelipase alfa in patients with LAL Deficiency are currently ongoing. One clinical study of sebelipase alfa in adults with LAL Deficiency has been completed (LAL-CL01) and 5 clinical studies of sebelipase alfa are ongoing in infants, children, or adults with LAL Deficiency (LAL-CL02, LAL-CL03, LAL-CL04, LAL-CL06, and LAL-CL08). Brief summaries can be found below for the completed study (LAL-CL01) and the 3 ongoing studies for which data have been reported through the primary completion date (LAL-CL02 and LAL-CL03) or Week 104 of treatment (LAL-CL04). Refer to the IB for further information on the clinical experience with sebelipase alfa.

1.4.1 Completed Study LAL-CL01

LAL-CL01, the first clinical study with sebelipase alfa, evaluated the safety, tolerability, and pharmacokinetics (PK) of sebelipase alfa following a 4-week regimen of once-weekly (qw) IV infusions of sebelipase alfa at doses of 0.35 mg/kg, 1 mg/kg, and 3 mg/kg in adult subjects with liver dysfunction due to LAL Deficiency. A total of 9 subjects were enrolled into 3 sequential cohorts of 3 subjects each.

All 3 doses of sebelipase alfa were well tolerated by the subjects in this study. There were no deaths or treatment-emergent serious adverse events (SAEs), and no subject experienced an infusion-associated reaction (IAR) or discontinued treatment due to a treatment-emergent adverse event (TEAE). Most (86.4%) of the 44 reported TEAEs were considered unrelated to sebelipase alfa, and all but one were assessed by the Investigator as Grade 1 (86.4%) or Grade 2 (11.4%) in severity. One subject in the 3 mg/kg dose cohort had a Grade 4 TEAE of hypercholesterolemia. Although the subject was asymptomatic, this laboratory abnormality met the definition of a Grade 4 event according to Common Terminology Criteria for Adverse Events, which was used to assess severity in this study.

All 3 doses of sebelipase alfa were biologically active, as evidenced by decreases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and increases in serum lipids (total cholesterol, triglycerides, and LDL cholesterol), which were observed within 2 and 4 weeks, respectively, and were reversible following discontinuation of sebelipase alfa therapy. Effects on serum lipids appeared more pronounced in the 3 mg/kg dose cohort, whereas effects on ALT and AST appeared to be independent of dose.

PK data in adult subjects with LAL Deficiency indicate that sebelipase alfa has a short plasma half-life, ranging from 0.07 to 2.04 hours at the lowest dose of 0.35 mg/kg and from 0.09 to 0.21 hours at higher doses of 1 or 3 mg/kg. Sebelipase alfa area under the concentration-time curve (AUC) and maximum observed concentration (C_{max}) increased proportional to dose from 0.35 to 1 mg/kg and more than proportional to dose from 1 to 3 mg/kg. Clinical PK data for sebelipase alfa are not yet available for children and adolescents with LAL Deficiency.

1.4.2 Ongoing Study LAL-CL04

Study LAL-CL04 is an ongoing open-label multicenter extension study in adults with liver dysfunction due to LAL Deficiency who completed Study LAL-CL01 (Balwani, 2013, *Hepatology;* Valayannopoulos, 2014, *J Hepatol*). This study is designed to evaluate the long-term safety, tolerability and efficacy of sebelipase alfa at 2 dose levels (1 and 3 mg/kg). After completing all follow-up assessments for Study LAL-CL01, subjects were eligible to initiate treatment in the extension study at a qw dose of sebelipase alfa equivalent to the dose administered during their fourth infusion in Study LAL-CL01. After the fourth infusion under this protocol, all subjects receive an every-other-week (qow) dosing regimen of 1 or 3 mg/kg. Safety and efficacy assessments are conducted at regular intervals throughout the extension study. In addition, blood samples are obtained at selected time points for analysis of sebelipase alfa PK and biomarkers of sebelipase alfa pharmacodynamic (PD) activity. Refer to the IB for discussion of the preliminary safety and efficacy data from this study.

1.4.3 Ongoing Study LAL-CL02

Study LAL-CL02 is an ongoing multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of sebelipase alfa in subjects ≥4 years of age with LAL Deficiency. Eligible subjects are randomly assigned in a 1:1 ratio to receive sebelipase alfa 1 mg/kg or placebo qow for 20 weeks. Efficacy, PK and safety assessments are performed at regular intervals throughout the study. After completing a 20-week double-blind treatment period, each subject can begin open-label treatment with sebelipase alfa at a dose of 1 mg/kg qow during an extension period.

1.4.4 Ongoing Study LAL-CL03

Study LAL-CL03 is an ongoing multinational study to evaluate the safety, tolerability, efficacy, PK and PD of sebelipase alfa in children who developed growth failure or other clinical evidence of a rapidly progressive course of LAL Deficiency before 6 months of age. This is an open-label, repeat-dose, dose-escalation study in which subjects receive qw doses of sebelipase alfa. All subjects initiate treatment at a dose of 0.35 mg/kg qw. Dose escalation to 1 mg/kg qw occurs in all subjects, contingent upon acceptable safety and tolerability, and a further dose escalation to 3 mg/kg qw may be permitted for subjects who have a suboptimal response to treatment. All subjects are evaluated for safety, tolerability and efficacy. Refer to the IB for discussion of the preliminary safety and efficacy data from this study.

1.5 Dose Rationale and Risk/Benefits

1.5.1 Dose Rationale

In this study, sebelipase alfa will be administered at a starting dose of 1 mg/kg qw and all subjects may receive a dose increase to 3 mg/kg (contingent on safety). These doses of sebelipase alfa were selected based on the following:

- As discussed in Section 1.4, clinical data are available from a completed study in adult subjects with LAL Deficiency (LAL-CL01) administered qw infusions of sebelipase alfa at doses of 0.35 mg/kg, 1 mg/kg, or 3 mg/kg as well as 1 mg/kg, or 3 mg/kg qow (LAL-CL04). These data show:
    - All 3 dose levels of sebelipase alfa were well tolerated.
    - Sebelipase alfa therapy produced rapid and comparable reductions in serum transaminases at all 3 dose levels.
    - Increases in serum lipids were seen at all 3 dose levels in adults within 4 weeks of treatment initiation, consistent with the known mechanism of action of sebelipase alfa. These effects were more marked with the 3 mg/kg qw dose and may therefore be dose related. Compared to a dose of 3 mg/kg qw, doses of 0.35 and 1 mg/kg qw may have less marked short-term effects on serum lipids, but a potentially comparable clinical benefit.
    - Maintenance of clinical response (reduction in ALT and AST and improvement of lipid levels) was observed in adult subjects treated with qow dosing in LAL-CL04.
- There is an adequate safety margin for sebelipase alfa based on nonclinical toxicology studies. Refer to the IB for further information.

An ongoing study in infants with rapidly progressive LAL Deficiency, LAL-CL03, was designed to confirm a survival benefit in subjects who present with growth failure prior to 6 months of age. As that was the first study in infants with rapidly progressive LAL Deficiency, dosing was initiated with 2 weekly doses at 0.35 mg/kg prior to allowing escalation to 1 mg/kg. Based on favorable safety data at 1 and 3 mg/kg in both infants and adults with LAL Deficiency, and a desire for aggressive intervention in this rapidly progressive presentation of the disease, this study is designed to initiate therapy at a 1 mg/kg weekly dose. Given the extreme rarity and immediate life-threatening nature of rapidly progressive LAL Deficiency, this study will allow within-subject dose escalation to 3 mg/kg weekly, as the pre-clinical model demonstrated dose dependent pharmacological effects. In the preclinical rat model, it was established that the pharmacodynamic (PD) effects of 3 mg/kg qw and 5 mg/kg qw are comparable. Based on this information, it is not anticipated that exploration of doses greater than 3 mg/kg qw in subjects with LAL Deficiency will be required unless there is evidence of a loss of efficacy due to the potential development of neutralizing antibodies.

1.5.2 Risk/Benefit Assessment

LAL Deficiency is a very rare disease with no safe or effective therapies. LAL Deficiency presenting in infants results in significant morbidity and death typically within 6 months of age (Assmann, 2001, *The Metabolic and Molecular Basis of Inherited Disease*).

No significant toxicities were identified in pre-clinical pharmacology and toxicology studies at doses equivalent to and substantially greater than the planned doses for the current study (Refer to IB for details).

Clinical experience with sebelipase alfa in adult subjects with LAL Deficiency treated in study LAL-CL01 and LAL-CL04 indicates that sebelipase alfa is well tolerated at doses ranging from 0.35 mg/kg qw to 3 mg/kg qw and produces rapid improvements in serum transaminases and other evidence of biological activity. Sebelipase alfa has also demonstrated an acceptable safety profile and positive treatment effects in infants receiving doses up to 3 mg/kg qw on in study LAL-CL03. See Section 1.4 and the IB for further details on the clinical experience with sebelipase alfa. Thus, there is a reasonable basis to conclude that sebelipase alfa therapy in this study will be well tolerated and associated with beneficial effects on disease activity.

In addition to clinical experience with sebelipase alfa, extensive human experience exists for ERTs in the treatment of other lysosomal storage disorders including Gaucher, Pompe, and Fabry disease. The main unfavorable effects associated with administration of approved ERTs (including but not limited to Cerezyme®, VPRIV®, Myozyme®/Lumizyme®, Fabrazyme®) are IARs, which typically occur during or within several hours following completion of the infusion and are usually mild and can be managed by changes in infusion rate and/or the administration of antipyretics and antihistamines. Severe infusion reactions including anaphylaxis, and SAEs related to ERT administration occur rarely and can require intensive medical intervention. Given the propensity for infusion reactions with ERT administration, measures have been incorporated in this protocol to minimize risk and monitor subject safety.

Anti-drug antibodies (ADAs) have been reported with approved ERTs and these may be associated with altered response to treatment and/or increased risk of infusion reactions.

Given the relatively low level of subject risk relative to the terminal nature of untreated LAL Deficiency presenting in infancy, it is concluded that the risks to subjects in this study are reasonable in relation to the anticipated benefits and/or knowledge that can be expected from the results.

2 Study Objectives

2.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of sebelipase alfa in infants with rapidly progressive LAL Deficiency.

2.2 Secondary Objectives

The secondary objectives are:

- To evaluate the effects of sebelipase alfa on:
- Survival at 12 months of age
- Survival past 12 months of age
- Growth parameters
- Hepatomegaly, splenomegaly, and liver function
- Hematological parameters
- To characterize the PK of sebelipase alfa delivered by IV infusion

2.3 Exploratory Objectives

The exploratory objectives are:

- To determine the effects of sebelipase alfa on lipid parameters
- To assess the effects of sebelipase alfa on achievement of developmental milestones
- To evaluate potential disease-related biomarkers

3 Study Design

3.1 Overview of Study Design and Flow Chart

This is an open-label, repeat-dose, study of sebelipase alfa in infants with rapidly progressive LAL Deficiency. Eligible subjects will receive once weekly (qw) IV infusions of sebelipase alfa for up to 3 years, as described below. All subjects will be evaluated for safety, tolerability, and efficacy. Where feasible, given blood volume thresholds based on subject weight, blood samples will also be collected for analyses of the PK of sebelipase alfa and for an exploratory analysis of potential disease-related biomarkers in this patient population.

All subjects will initiate treatment with sebelipase alfa at a dose 1 mg/kg qw. A dose escalation to 3 mg/kg qw may be considered for a subject who meet specified criteria, as defined below, contingent upon acceptable safety and tolerability of preceding infusions and as approved by the Investigator and Sponsor.

An independent Safety Review Committee (SRC) will oversee safety in this study. The SRC will review available safety data during at least semiannual periodic meetings and on an ad-hoc basis as needed in the event of unanticipated safety findings. Additional details about the SRC review process can be found in Section 7.5.

Subjects who do not tolerate a dose of 3 mg/kg qw may receive a dose reduction to 1 mg/kg qw at the discretion of the Investigator in consultation with the Sponsor and, where appropriate, the SRC. If a subject cannot tolerate a dose of 1 mg/kg qw, despite measures taken to manage any IARs, the subject will be discontinued from the study.

Subjects who are on treatment for at least 96 weeks and have been on a stable dose for at least 24 weeks, may transition to an every other week dosing schedule at the same dose they received on the weekly dosing schedule at the criteria of the Principal Investigator (PI) and in consultation with the Sponsor. If the subject meets the criteria for dose escalation while on the every other week dosing schedule they will either revert back to weekly dosing or if on 1 mg/kg qow increase to 3 mg/kg qow dosing.

Given the severity and life threatening nature of rapidly progressive LAL Deficiency, it is likely that these subjects will be hospitalized during the first several weeks on study. For the subjects who are stable enough to be treated on an outpatient basis, safety follow-up assessments for AEs will be conducted by telephone 24 hours following the first 2 infusions of 1 mg/kg qw and 3 mg/kg qw, as applicable.

Subjects who appear to have an acute illness (e.g., upper respiratory infection or febrile illness) should have their scheduled infusions postponed by up to 2 days (up to 5 days if subject is on a qow infusion schedule) to allow for resolution. If the illness persists for longer than 2 days (5 days if subject is on a qow infusion schedule), the infusion schedule should reset to the next scheduled infusion after the subject's recovery. The Investigator may conduct an unscheduled visit at any time during the study at his/her discretion. Assessments performed at this visit should be symptom directed. Safety laboratory testing may be performed if the Investigator considers it necessary. Repeat laboratory testing may be needed based on results from the

unscheduled laboratory testing. If the subject is discontinued from study treatment at a scheduled visit or at an unscheduled visit, the subject should return no earlier than 7 days after the last dose of IMP for an End of Study assessment.

3.1.1 Dose Escalation

The Investigator, in consultation with the Sponsor, will monitor subjects for evidence of the below specified criteria that may reflect a need for a dose increase. These considerations should include evaluation of other potential causes of any clinical manifestations that are thought to negatively impact these criteria. Other causes could include:

- missed study infusions
- initiation of a potentially hepatotoxic concomitant medication in a subject with elevated ALT
- concomitant illness in a subject with reduced weight gain such as an upper respiratory tract infections or other childhood viral infection

3.1.1.1 Dose escalation criteria during first 3 months of treatment

During this period, a subject may be considered for dose escalation if he/she meets 2 or more of the following criteria at a dose of 1 mg/kg qw:

- Failure to gain an average of 5 g/kg body weight per day AND the presence of one or more of the following:
    - weight-for-length (WFL) or weight-for-height (WFH) z-score <-2 based on World Health Organization (WHO) child growth standards; and/or
    - length-for-age (LFA) or height-for-age (HFA) z-score <-2 based on WHO child growth standards
    - weight-for-age (WFA) z-score <-2 based on World Health Organization (WHO) child growth standard
- Albumin <3.5 g/dL
- Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
- Ongoing requirement for blood and/or platelet transfusion

3.1.1.2 Dose escalation after at least 3 months of treatment

- In addition to the criteria in Section 3.1.1.1, any other clinically important manifestation of LAL Deficiency on either clinical examination, laboratory assessment, or imaging which has either
    - not improved from baseline
    - improved and plateaued but has not normalized
    - (Note: The definition of a plateauing of effect requires consideration of a minimal of 3 assessments)
    - failed to normalize within 12 months of initiation of treatment

Manifestations include but are not restricted to the following: A decrease in weight for age defined as crossing ≥2 major centile lines on standard weight for age curves, serum transaminases, albumin <3.5 g/dL, hepatomegaly, splenomegaly or lymphadenopathy.
If the subject continues to have criteria for dose escalation after at least 4 infusions at a dose of 3 mg/kg qw, the Investigator may request of the Sponsor (in consultation with the Safety Committee) to increase the dose up to a maximum of 5 mg/kg qw on a case by case basis. In rare circumstances, a dose escalation to 5 mg/kg may be considered prior to 4 infusions, if agreed to by the Sponsor and SC.

3.2 Rationale for Study Design

3.2.1 Dose Selection

Refer to Section 1.5.1 for the dose selection rationale.

3.2.2 Outcome Variable Selection

3.2.2.1 Safety

The safety and tolerability of treatment with sebelipase alfa, administered by IV infusion, will also be evaluated in this study. An ongoing study in infants with rapidly progressive LAL Deficiency, LAL-CL03, was designed to confirm a survival benefit in subjects who present with growth failure prior to 6 months of age. As that was the first study in infants with rapidly progressive LAL Deficiency, dosing was initiated with 2 once weekly doses at 0.35 mg/kg prior to allowing escalation to 1 mg/kg. Based on favorable safety data at 1 and 3 mg/kg in both infants and adults with LAL Deficiency, and the observed rapidly progressive presentation of the disease, this study is designed to initiate therapy at a 1 mg/kg weekly dose. In addition, because this study does not require confirmation of growth failure for entry, treatment may be initiated at a slightly earlier age than previously experienced in LAL-CL03. Thus, an important objective for this study is to confirm safety of initiating therapy at 1 mg/kg weekly in subjects at the earliest age at which diagnosis of rapidly progressive LAL Deficiency is confirmed.

Endpoints for safety of sebelipase alfa in children with LAL Deficiency will include:

- Incidence of AEs, SAEs, and IARs
- Changes from baseline clinical laboratory tests
- Changes in vital signs during and post-infusion, relative to pre-infusion values
- Physical examination findings
- Use of concomitant medications/therapies
- Characterization of ADAs, including ADA positivity rate, time to ADA positivity, median and peak ADA titer, and time to peak ADA titer.

Given the potential for ADAs to alter the safety profile of sebelipase alfa, the impact of ADAs on safety endpoints will be explored. Further characterization of ADAs, including inhibitory and/or neutralizing ADAs and measurement of specific ADA subtypes (e.g., IgE), may be performed, if appropriate.

3.2.2.2 Efficacy

The study is designed to confirm the efficacy of treatment with sebelipase alfa in subjects with rapidly progressive disease presenting in infancy. Survival endpoints will include proportion of subjects surviving to 12, 18, and 24 months of age, and other timepoints, as data permit, and estimated median age at death. Survival rates and median age at death derived from this study will be compared to rates/times reported in the literature and previous studies.

Subjects with LAL Deficiency presenting in infancy typically stop growing and this growth failure, in addition to being the predominant clinical feature, is also one of the main contributors to mortality. Improvement in growth is anticipated to be a prerequisite for any beneficial effects of sebelipase alfa on survival. Therefore, efficacy endpoints will include changes from baseline in the following growth parameters:

- Percentiles and/or z-scores, based on WHO child growth standards (WHO Multicentre Growth Reference Study Group, 2006 and 2007), for the following parameters:
  - Weight-for-age (WFA)
  - WFL or WFH
  - LFA or HFA
  - Head circumference-for-age (HCFA)
  - Mid-upper arm circumference-for-age (MUACFA)
- Dichotomous growth status indicators for underweight, wasting, and stunting based on WFA, WFL/WFH, and LFA/HFA, respectively (UNICEF, 2009)

Note: Given the switch at age 2 years from measurement of length to measurement of height, growth parameters include weight related to both length and height and age related to both length and height.

A successful therapy for LAL Deficiency presenting in infancy should also mitigate the liver and hematological changes associated with the disease. Therefore, the following laboratory parameters will also be included as efficacy endpoints:

- Changes from baseline in aspartate aminotransferase [AST] and ALT levels
- Normalization of hemoglobin levels without requirement for blood transfusion
- Changes from baseline in serum ferritin levels

Additional exploratory efficacy parameters will be investigated to provide supportive evidence of an improvement of LAL Deficiency with sebelipase alfa treatment, and will include changes or percent changes from baseline (or first available assessment if baseline data are unavailable) in:

- Alkaline phosphatase, gamma glutamyltransferase (GGT), albumin, and bilirubin (direct, indirect, and total)
- Liver and spleen size/volume, as measured by ultrasound or magnetic resonance imaging (MRI)

- Hepatomegaly and/or splenomegaly (abdominal girth, liver size, and spleen size) by physical examination
- Platelet levels
- Serum lipid levels (total cholesterol, triglycerides, high density lipoprotein [HDL], and LDL)

Because LAL Deficiency presenting in infancy is rapidly progressive and patients often die within 6 months of age (Assmann, 2001, *The Metabolic and Molecular Basis of Inherited Disease*), information on development is limited in this patient population. The potential extended life expectancy in subjects receiving long-term treatment with sebelipase alfa provides an opportunity to develop an understanding of the developmental process in infants with LAL Deficiency treated with sebelipase alfa. To this end, the study will include an exploratory analysis of developmental outcomes, as assessed by the total and functional area scores on the Denver II developmental screening test.

Given the potential for ADAs to alter the PD effect of sebelipase alfa, the impact of ADAs on efficacy endpoints will be explored.

3.2.2.3 Pharmacokinetics

The C_{max} of sebelipase alfa in infants with rapidly progressive LAL Deficiency will be characterized in this study, blood volume permitting. The impact of ADAs on sebelipase alfa C_{max} will also be explored, if data permit.

3.2.2.4 Exploratory Biomarkers

Blood samples will also be collected to support exploratory analyses of changes or percent changes from baseline in potential disease-related biomarkers, which may be identified based on emerging information from the sebelipase alfa development program and scientific literature.

3.2.3 Study Duration

The duration of each subject's treatment in the study is expected to be at least 18 months, and subjects may continue to receive treatment in the study for up to up to 3 years. Therefore, the overall duration of a subject's participation in the study, inclusive of a 3-week screening period and a 4-week follow-up period, may be up to 3 years and 7 weeks.

4 Study Population

4.1 Target Population

The target population for this study is infants with rapidly progressive LAL Deficiency.

4.2 Number of Subjects

In light of the extremely low prevalence of the target disease, up to 10 subjects will be enrolled in the study.

4.3 Inclusion Criteria

A subject must meet all of the following criteria to be eligible to participate in this study:

1. Subject's parent or legal guardian (if applicable) consents to participation in the study.
2. Confirmation of documented decreased LAL activity relative to the normal range of the lab performing the assay or a documented result of molecular genetic testing confirming a diagnosis of LAL Deficiency..
3. Substantial clinical concerns, in the opinion of Investigator and Sponsor, of rapid disease progression requiring urgent medical intervention including, but not restricted to, the following:
    a. Marked abdominal distension and hepatomegaly
    b. Failure to thrive as evidenced by:
        i. Weight for height is 2 or more SD below the mean for gender and age
        ii. Weight curve has crossed downward by more than 2 major percentile lines on the WHO growth curves (1st, 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th, 99th) after having previously achieved a stable pattern of growth
    c. Disturbance of coagulation (e.g., requirement for FFP; two values of PT >15 sec, or PTT > 40 sec)
    d. Severe anemia (e.g., requirement for blood transfusion or hemoglobin < 8 g/dL)
    e. Sibling with rapidly progressive course of LAL Deficiency

4.4 Exclusion Criteria

A subject who meets any of the following criteria will be ineligible to participate in the study:

1. Clinically important concurrent disease or co-morbidities which, in the opinion of the Investigator and Sponsor, would interfere with study participation, including, but not restricted to:
    a. Additional severe congenital abnormality
    b. Presence of severe infection that requires treatment with parenteral anti-infective treatment within the past 14 days
    c. Previous history of circulatory collapse requiring inotropic support for more than 48 hours

d. Congestive heart failure
e. Acute or chronic renal failure
f. Other extenuating circumstances such as life-threatening under nutrition or rapidly progressive liver disease

2. Subject will be > 8 months of age at the time of first dosing.
3. Subject has received an investigational medicinal product other than sebelipase alfa within 14 days prior to the first dose of sebelipase alfa in this study.
4. Myeloablative preparation, or other systemic pre-transplant conditioning, for hematopoietic stem cell or liver transplantation.
5. Previous hematopoietic stem cell or liver transplant.
6. Known hypersensitivity to eggs.

4.5 Concomitant Medication and Treatment

A concomitant medication is any drug or substance taken during the study after the informed consent is signed. Any concomitant medications (including over the counter medications, herbal medications, preventive vaccines, vitamins and food supplements), treatments and procedures (including parenteral feeds, surgery, or physical therapy) received by the subject through completion of the follow-up visit, approximately 30 days after the last dose of IMP, must be recorded in the electronic case report form (eCRF). A description of the type of drug or procedure, the amount, duration, reason for administration of drug and the outcome of any procedure must be documented. Adverse events related to the administration of a concomitant medication or the performance of a procedure must also be documented on the AE page of the eCRF.

4.6 Discontinuation of Subjects from Treatment or Assessment

4.6.1 Premature Withdrawal from Study Participation

In accordance with the Declaration of Helsinki, subject's parent or legal guardian have the right to withdraw their child from the study at any time for any reason. The Investigator and Sponsor also have the right to withdraw subjects from the study at any time. A subject will be considered to have completed if they withdraw from the study.

Specific reasons for discontinuation may include but are not restricted to the following:

- Intercurrent illness
- Medically significant AEs
- Protocol deviation or non-compliance
- Termination of the study by the Sponsor

4.6.2 Procedures for Discontinuation

A subject's parent or legal guardian is free to withdraw consent and/or discontinue the subject's participation in the study at any time, without prejudice to further treatment. A subject's participation in the study may also be discontinued at any time at the discretion of the Investigator or Sponsor.

Should a subject's parent or legal guardian decide to withdraw consent, all efforts will be made to complete and report the observations as thoroughly as possible. The parent or legal guardian of subjects who are discontinued from the study should be asked about the reason(s) for their discontinuation and about the presence of AEs. The date and the reason for discontinuation will be recorded in the eCRF. Subjects who discontinue prior to IMP administration will be replaced.

Subjects who are prematurely withdrawn from the study will be asked to complete all discontinuation assessments prior to withdrawal (see Appendix A), if possible. Information on the survival of discontinued subjects will be collected until completion of the study. Serious AEs will be followed according to Section 7.2.3 and reported according to Section 7.4. A subject will be considered early terminated if the subject does not complete the study after enrollment. A subject will be considered discontinued due to an AE if the subject received any infusion or partial infusion of the investigational medicinal product, but did not complete the study because of an AE, whether or not considered drug related. At the end of the subject's participation in the study, the Investigator will document the reason(s) for study discontinuation in the eCRF.

In the event that a subject dies, permission will be sought (through a separate informed consent form) from the subject's parent or legal guardian for an autopsy. Samples collected from these procedures will be used to further understand LAL Deficiency and the effect of sebelipase alfa.

When a subject fails to return for scheduled assessments, the following efforts should be made to contact his/her parent or legal guardian to determine a reason for the failure to return: 3 attempts, including the date and time, to be documented in the subject's chart. If there is no response, a certified letter should be sent. After these efforts have been exhausted, a subject should be identified as lost to follow-up in the eCRF.

4.7 Subject Replacement Policy

Subjects are not replaced in this study. If a subject who qualifies for the Full Analysis Set discontinues the trial prematurely before receiving at least 4 infusions of sebelipase alfa, an additional subject may be enrolled, at the discretion of the Sponsor.

4.8 Subject Recruitment and Screening

Subjects may be recruited into the study directly from the Investigators' or sub-investigators' clinical practices, or referred to the investigative sites from other clinics. Information about the study will be posted on the http://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ websites.

Subject screening should occur between 0 and 21 days prior to the infusion at Week 0 (Day 0). Prior to any screening procedures, a subject needs to be registered with the Sponsor.

5 Schedule of Assessments and Study Procedures

The schedule of assessments, Screening through Follow-up, is presented in Appendix A. All visits will be calculated from Week 0; consecutive infusions must be administered at least 5 days apart. Additional details regarding the visit schedule and the timing of study procedures are provided in the Study Operations Manual (SOM).

Subjects who are clinically stable enough to tolerate general anesthesia may be considered for central line placement for long-term vascular access, in accordance with institutional guidelines. Magnetic resonance imaging (MRI) should be considered for subjects receiving general anesthesia and/or sedation for central line placement or for other procedures (see Section 5.1.8).

Subjects who are medically stable, as determined by the Investigator, may transfer to a local medical center for long-term treatment, contingent upon the local medical center having been approved and having secured the required regulatory, IRB/IEC, and Sponsor approvals. Scheduled study assessments may also be performed at a local medical center with access to the appropriate facilities and expertise.

Local analgesic cream (e.g., eutectic mixture of local anesthetics) will be allowed at least 20-30 minutes (or according to applicable institutional guidelines) prior to IV placement or blood sampling.

The European Medicines Agency recommended blood volume limits should be used as guidance for blood sampling in this study: http://www.emea.europa.eu/docs/en_GB /document_library/Scientific_guideline/2009/09/WC500003754.pdf. Per individual, the study-related blood loss should not exceed 3% of the total blood volume during a 4-week period or 1% of total blood volume at any single time. The actual situation of the child (sleep/activity, severity of anemia, and hemodynamic state) must permit such blood sampling. Table 1 summarizes mean blood volume per body weight based on an individual's age. Assuming a total blood volume of 80 mL/kg body weight for an average subject in this study, 3% of total blood volume corresponds to 2.4 mL/kg body weight and 1% of total blood volume corresponds to about 0.8 mL/kg body weight.

Table 1: Mean Blood Volume, by Age

Age	Mean blood volume per weight (mL/kg)
Newborn, 24 hours	83.3
Children, 3 months	87
Children, 6 months	86
Children, 1 year	80
Children, 6 years	80
Children, 10 years	75
Children, 15 years	71

Source: Geigy Scientific Tables, 7th Ed.

5.1 Study Assessments

5.1.1 Informed Consent

The parent or legal guardian of a potential subject will be given a verbal explanation of the study and the procedures involved and will have all questions addressed. The subject's parent or legal guardian must sign and date a consent form that has been approved by the appropriate IRB/IEC before the screening procedures are initiated. The subject's parent or legal guardian will be given a copy of the signed and dated informed consent form.

5.1.2 Subject Eligibility

All subjects will be assessed for eligibility against the inclusion and exclusion criteria described in Section 4.3 and Section 4.4 and background clinical information collected.

5.1.3 Medical History

Complete medical history, including prenatal, birth history, family history and disease history will be recorded at Screening.

5.1.4 Demographic Information

The following demographic information will be collected at Screening: date of birth, birth weight, gender, race and ethnicity.

5.1.5 Anthropometrics

Anthropometrics, including weight, recumbent length (subjects ≤2 years of age at the time of examination) or height (subjects >2 years of age at the time of examination), head circumference, mid-upper arm circumference, and abdominal circumference will be measured at the timepoints specified in Appendix A. Refer to the SOM for a detailed description of the procedure for each anthropometric measurement.

Percentiles and/or z-scores for WFA, WFL/WFH, LFA/HFA, HCFA, and MUACFA will be determined based on WHO child growth standards (WHO Multicentre Growth Reference Study Group, 2006 and 2007). Growth status will also be classified according to 3 dichotomous indicators: underweight (<-2 standard deviations [SD] from the median for WFA), wasting (<-2 SD from the median for WFL/WFH), and stunting (<-2 SD from the median for LFA/HFA).

5.1.6 Physical Examination

A physical examination will be performed by the Investigator or qualified designee at the timepoints specified in Appendix A. The examination will include an assessment of the subject's general appearance, skin, head, eyes, ears, nose, and throat, heart, lungs, abdomen, extremities/joints, and neurological status. Whenever possible, the same person should perform the physical examination at each study visit. Abnormal findings will be captured in the eCRF.

Every physical examination will also include the following:

- **Liver size:** A clinical assessment of liver size (palpable/non palpable and centimeters below costal margin), regularity (smooth/nodular) and sensitivity (tender/non tender) will be made.
- **Spleen size:** A clinical assessment of spleen size (palpable/non palpable and centimeters below costal margin), regularity (smooth/nodular) and sensitivity (tender/non-tender) will be made.
- **Lymphadenopathy:** An assessment of the size, location, and character of any palpable lymph nodes will be made. Areas to be examined include: cephalic (occipital, preauricular, postauricular, submental, submandibular), cervical, clavicular, axillary, and inguinal. Any enlarged nodes will be characterized as tender or non-tender.

Information about a subject's diet prior to initiation of treatment with sebelipase alfa in this study and any changes in a subject's diet during treatment in this study (e.g., discontinuation of a low-fat/low-cholesterol diet and/or introduction of an unrestricted age-appropriate diet) will be recorded in the eCRF.

A digital photographic image of the subject in a supine position (full length and abdominal close up) will obtained during selected physical examinations, as specified in Appendix A.

5.1.7 Abdominal Ultrasound

Abdominal ultrasonography will be performed at the timepoints specified in Appendix A to measure the liver and spleen size.

Abdominal ultrasonography will be performed by a qualified person, and results will be interpreted by a radiologist trained in ultrasonography.

5.1.8 Abdominal MRI

Abdominal MRIs should be considered at the timepoints specified in Appendix A to provide a more accurate quantification of liver and spleen volume.

Abdominal MRIs are considered optional in this study. Investigators are encouraged to obtain abdominal MRIs in subjects receiving general anesthesia and/or sedation for other procedures at a scheduled imaging timepoint. To allow flexibility in scheduling MRIs, a broad time window is given for each MRI assessment in Appendix A. For example, the baseline MRI may be obtained at any time from Screening through the Week 0 study visit.

Because MRI can provide important information on liver and spleen volume that can be related to expected normal values abdominal MRIs should be obtained during the treatment phase, where feasible, even if a subject did not provide a baseline MRI.

All imaging scans will be acquired and the results interpreted by a magnetic resonance technician or other qualified individual using standardized imaging protocols.

Refer to the Imaging Manual for instructions on image acquisition and analysis.

5.1.9 Vital Signs

Vital signs will include pulse rate, respiratory rate, systolic and diastolic blood pressure and core body temperature (rectal or oral). Assessment of pulse rate and blood pressure will be taken after the subject has been in a supine position.

Vital signs will be measured at the timepoints specified in Appendix A. On dosing days, vital signs will initially be recorded pre-infusion, every 15 (±5) minutes during infusion and every 30 (±10) minutes from 0 to 4 hours after completion of the infusion. After a subject has successfully completed at least 1 year of treatment with no occurrence of moderate-to-severe IARs, the post-infusion period for vital sign monitoring may be shortened from 4 hours to 2 hours.

Additional readings may be taken at the discretion of the Investigator and in the event of an IAR.

5.1.10 Electrocardiogram

An age-appropriate 12-lead electrocardiogram (ECG) will be obtained at Screening and reviewed by a qualified clinician. Additional age-appropriate 12-lead ECGs may be obtained at subsequent study visits, if clinically indicated. Any abnormalities identified by the clinician will be specified as clinically significant (CS) or not clinically significant (NCS).

5.1.11 Laboratory Assessments

5.1.11.1 Clinical Laboratory Tests

Blood and urine samples for laboratory tests will be collected at the timepoints specified in Appendix A.

Due to the limitations on the volume of blood collection that is considered to be acceptable in young children with very small total circulating blood volumes (see Section 5), the laboratory samples will be ranked in the order corresponding to the study objectives, as shown in Table 2. Only Tier 1 assessments are considered mandatory and all efforts should be made to collect these in all subjects. Samples for the Tier 2 and Tier 3 assessments will only be collected if the blood volume threshold for subject's weight, as well as the subject's clinical status, permit (see Section 5 for further details).

Table 2: Clinical Laboratory Tests, By Tier

Tier 1 (Mandatory)	
Complete Blood Count (CBC)/ Hematology:	White blood cell count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, neutrophil, lymphocytes, monocytes, eosinophils, basophils, peripheral smear for examination of cell morphology
Chemistry:	Glucose, urea nitrogen, creatinine, sodium, potassium, chloride, calcium, magnesium, inorganic phosphorus, total protein, lactate dehydrogenase
Liver Function Tests:	AST/SGOT, ALT/SGPT, alkaline phosphatase, GGT, albumin, bilirubin (direct, indirect, total)
Anti-drug Antibody:	Anti-sebelipase alfa antibody
Urinalysis:	pH, glucose, ketones, blood, protein, nitrite, and leukocytes (microscopic examination will only be done if blood, nitrite and/or leukocytes are abnormal)
Coagulation Studies:	PT (INR), aPTT Fecal occult blood (*(screening; thereafter only if the preceding assessment was abnormal or if clinically indicated)*
DNA Sample (screening):	See Section 5.1.15
LAL Enzyme Activity (screening)**:**	See Section 5.1.16
Tier 2 (Optional, based on blood volume thresholds)	
Lipid Panel:	Total cholesterol, triglyceride, HDL, LDL
Other Chemistry:	Ferritin, high sensitivity C reactive protein (hs-CRF)
Tier 3 (Optional, based on blood volume thresholds)	
Pharmacokinetic Assessments	See Section 5.1.14
Exploratory Biomarkers	See Section 5.1.13

5.1.11.2 Clinical Laboratory Collection for Changes in Dose or Lipid Lowering Medications

Subjects who undergo a dose modification or changes in lipid-lowering medications will have the following additional laboratory monitoring schedule of selected analytes:

- Prior to the first infusion of new dose/schedule or change in lipid-lowering medication: serum lipid panel, liver panel, hematology, serum chemistry, ferritin, hs-CRP

- 4 weeks after starting new dose/schedule or change in lipid-lowering medication: serum lipid panel, liver panel
- 8 weeks after starting new dose/schedule or change in lipid-lowering medication: serum lipid panel, liver panel
- 12 weeks after starting new dose/schedule or change in lipid-lowering medication: serum lipid panel, liver panel, hematology, serum chemistry

In the event that any of the above additional laboratory monitoring time points coincides with the standard protocol scheduled laboratory assessment, the standard laboratory assessment will supersede the additional laboratory monitoring (see Appendix B).

If a subject's blood volume threshold for weight or clinical status limit collection of samples on the scheduled visit date, the Sponsor or medical monitor should be consulted for guidance with regard to a modified sample collection schedule for that visit.

5.1.11.3 Clinical Laboratory Collection and Analysis

Refer to the SOM and/or laboratory manual for further details regarding the collection, processing, and storage of these samples.

Laboratory reports will be reviewed by the Investigator, or designee, and any abnormalities will be specified as clinically significant (CS) or not clinically significant (NCS). In the event of unexplained clinically significant abnormal laboratory test values, the tests should be repeated as soon as possible (preferably within 24 hours) and followed up until they have returned to within the normal range and/or an adequate explanation has been identified.

5.1.12 Denver II Developmental Screening Test

The Denver II will be administered at the timepoints specified in Appendix A.

The Denver II is a standardized measure to assess development in children from 1 month to 6 years of age (Frankenberg, 1992, *Pediatr*). The Denver II includes performance-based and parent-reported items in 4 functional areas: fine motor-adaptive, gross motor, personal-social, and language skills. The test was normed on a diverse sample of children who were full term and had no obvious developmental disabilities; the norms indicate when 25%, 50%, 75%, and 90% of children passed each item. The Denver II has good inter-rater and test-retest reliability (correlations ≥ 0.90 for most tests).

The Denver II must be administered by a trained clinician. Administration and scoring of the Denver II is based upon the child's age. (Note that for premature infants, the number of months premature is subtracted from the infant's chronological age.) For each test item administered, the clinician determines if the child's response falls within or outside of the normal expected range of success on that item for the child's age. The interpretation of the individual test items is then used to classify the child's development in each functional area and for the overall test.

Refer to the SOM for further information on administration and scoring of the Denver II.

5.1.13 Exploratory Biomarkers

Whenever feasible, based on the blood volume threshold for the subject's weight, a blood sample for serum isolation will be obtained at the timepoints specified in Appendix A. The

serum sample will be used to identify baseline disease and dynamic markers that will help better understand the pathogenesis of LAL Deficiency, related comorbidities and response to treatment. Given the rarity of LAL Deficiency and the paucity of information on disease characteristics, the definitive list of analytes remains to be determined.

Refer to the SOM and/or laboratory manual for further details regarding the collection, processing, and storage of these samples.

5.1.14 Pharmacokinetic Assessments

Sampling for measurement of sebelipase alfa serum levels will be performed during the study visits indicated in Appendix A. A sparse sampling scheme will be employed for to reduce the risk of iatrogenic anemia. Up to 3 blood samples will be collected at each study visit requiring a PK assessment. These samples will be collected within broad time windows, rather than at discrete time points, to allow more flexibility in the management of PK sampling for these subjects and to provide opportunities for measurement of drug concentrations across a broader time period with limited sampling:

In all subjects:

- Between 0 hour to end of infusion (i.e. when the infusion bag has been emptied, but prior to the sodium chloride flush)

In those subjects for whom the thresholds for allowed blood collection volumes have not been exceeded: One sample will be obtained during the following time windows:

- 0 to 30 minutes after completion of the infusion
- 0.5 to 1 hour after completion of the infusion

PK samples should not be taken from the same extremity where the infusion catheter is in place. All PK samples, at time points that coincide with a vital sign assessment, will be taken before cuff inflation for blood pressure assessment on the non-infusion arm. PK samples at other time points will be taken at least 5 minutes after cuff deflation.

Refer to the SOM and/or laboratory manual for further details regarding the collection, processing, and storage of these samples.

5.1.15 DNA Sample

The Sponsor intends to apply pharmacogenetics to the sebelipase alfa program in order to explore how genetic variations may affect clinical parameters associated with sebelipase alfa use and acid lipase biology. DNA sequences, including both the protein coding sequence and sequences that regulate gene transcription, messenger ribonucleic acid (mRNA) stability and the efficiency of protein translation that may be investigated include:

1. LAL (LIPA)
2. Genes coding for other proteins involved in lipid biology that may contribute to and/or modify the disease presentation of LAL Deficiency, e.g. ABCA1
3. Genes that may modify susceptibility to any sebelipase alfa related AEs

Where possible and in compliance with local regulations, a blood sample for DNA extraction will be collected from the subject at Screening or as soon as practically possible thereafter based on blood volume collection threshold, unless a stored DNA sample is already available for the subject. The DNA will be stored and used as part of a later pooled analysis. This will include determining the spectrum of LAL mutations in subjects with rapidly progressive LAL Deficiency and the relationship between gene mutation, safety, efficacy and susceptibility to anti-sebelipase alfa antibody development.

If feasible, a blood sample for DNA extraction and testing of the LAL gene mutations will be collected from the subjects' biological parents after a separate consent has been obtained.

The Sponsor will only analyze DNA sequences within genes relevant to the mode of action and response to sebelipase alfa, including variants important in understanding AEs, and candidate genes with a potential role in the etiology, pathogenesis, and progression of LAL Deficiency.

Samples will be stored by the Sponsor, or designee, in a secure, monitored, and controlled environment. No additional testing will be performed on the samples collected in the study.

Refer to the SOM and/or laboratory manual for further details regarding the collection, processing, and storage of these samples.

5.1.16 LAL Enzyme Activity

Study inclusion will be contingent on documented decreased LAL activity relative to the normal range of the lab performing the assay or a documented result of molecular genetic testing confirming a diagnosis of LAL Deficiency.

Blood samples will be collected at Screening to measure LAL activity in peripheral blood mononuclear cells (PBMCs) and in a dried blood spot (DBS) collected on filter paper to ensure consistency of LAL activity measurement in all subjects. In the unlikely event of a discrepancy between the diagnosis of LAL Deficiency based on baseline LAL activity in PBMCs and/or DBS and the previously documented diagnosis, a subject may be discontinued from the study and may be replaced.

Refer to the SOM and/or laboratory manual for further details regarding the collection, processing, and storage of this sample.

5.1.17 Liver Biopsy

Liver biopsies will be obtained for evaluation of hepatic histology at the timepoints specified in Appendix A. If a subject had a liver biopsy prior to Week 48 as part of clinical standard of care, this information should be captured.

Biopsies will be performed only with consent from the subject's parent/guardian and where local regulations permit, and are subject to discretionary approval from each center's IRB/IEC.

Liver biopsy procedures should be performed according to the local institutional practices by a qualified professional.

All biopsies collected in this study will be centrally evaluated by a pathologist with the appropriate expertise. This evaluation will include an assessment of the overall disease activity as well as a description of specific histopathological features of the disease.

Refer to the Histopathology Manual for further details on the collection and processing of liver biopsies.

6 Investigational Medicinal Product

6.1 Description of IMP

Study kits containing sebelipase alfa will be supplied by the Sponsor or designee. The study drug will be delivered in a 10 mL glass vial containing approximately 10.5 mL (including 5% overfill) of a buffered solution of sebelipase alfa at an approximate concentration of 2 mg/mL. The study drug contains no preservatives and is designed for single use only.

Sodium Chloride (0.9%) for injection USP, for use in preparation of diluted solutions for infusion, will be sourced locally by the study center.

6.2 Method for Assigning Subjects to Treatment Groups

No randomization schemes will be employed; all subjects will receive the same starting dose of sebelipase alfa in this study.

Each subject will be assigned an enrollment number after informed consent has been obtained from the subject's parent or legal guardian. This enrollment number will be used to identify the subject throughout his/her participation in the study.

A subject who does not meet all study eligibility criteria due to a potentially transient condition observed at screening (e.g., discontinuation of another investigational medicinal product within 14 days) will be allowed to return for re-screening.

6.3 Storage and Disposition of IMP

6.3.1 Receipt of IMP

Upon receipt of the IMP, an inventory must be performed and verified. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable IMP in a given shipment will be documented in the study files. The Investigator must notify study Sponsor of any damaged or unusable IMP that was supplied to the Investigator's site.

6.3.2 Storage

Vials of sebelipase alfa must be stored under controlled refrigerated conditions at 2°C to 8°C (36°F to 46°F). Vials should not be frozen and will be protected from light during storage. Temperature monitoring must be performed by the investigational site to ensure proper storage of sebelipase alfa throughout the study. Refer to the IMP manual for instructions on how to handle temperature excursions.

The infusion bag (or syringe) containing sebelipase alfa will be prepared just prior to infusion administration. The prepared infusion, diluted in 0.9% Sodium Chloride Injection, may be stored at room temperature (20°C to 25°C) for no more than 12 hours, although it is preferable that prepared solution be used within 4 hours of dilution. Shaking or other forms of agitation must be avoided.

6.3.3 Disposition

The Investigator or designated person (e.g. a licensed pharmacist) will be responsible for maintaining accurate records for all IMP used. Opened sebelipase alfa vials still containing any residual volume may be stored at room temperature for IMP accountability. Following IMP accountability, the Sponsor or designee will give written authorization to the Investigator to return or destroy any remaining IMP as instructed.

6.4 Preparation and Administration of IMP

6.4.1 Preparation of IMP

The infusion bag (or syringe) containing sebelipase alfa will be prepared just prior to the start of infusion administration. Prior to preparation of the infusion, the vials of study drug will be visually inspected. The solution should not be used if it contains foreign particulate matter or is discolored. The solution may be used if a small number of visible translucent to opalescent or white amorphous or threadlike particles are present in the vial. The contents should NOT be warmed using a microwave or other heat source. Sebelipase alfa is a protein and will be handled and mixed gently to prevent foaming.

If subject's weight cannot reliably be obtained on the morning of the infusion then the subject's most recent weight measurement within 7 days, rounded to the nearest 0.1 kg, will be used for calculating the volume of study drug to be withdrawn from the vial(s) to prepare the infusion.

Sebelipase alfa should be diluted to a concentration of 0.1 to 1.5 mg/ml for infusion. Refer to the IMP manual for detailed instructions regarding preparation

6.4.2 Administration of IMP

Study drug should not be infused with other products in the same infusion tubing as the compatibility of sebelipase alfa in solution with other products has not been evaluated.

It is required that all infusions of study drug be administered using in-line filtration with a low-protein binding 0.2-µ filter. Occlusion of the in-line filter may occur, which is not uncommon with IV infused proteins. Studies of sebelipase alfa with several commercially available 0.2-µ filters have shown that the IV line occlusion is primarily attributed to the surface area of the filter. Since several 0.2-µ filters are available at both 0.45 cm^2 and 10 cm^2, it is recommended to contact the filter manufacturer to determine the surface area of the 0.2-µ filter that is being used if occlusion of the in-line filter occurs. In this situation, a larger surface area 0.2-µ filters will be used.

The IMP infusion will be administered at an infusion rate depending on the subject's weight, and must be administered under close supervision of the Investigator, or designee. Sebelipase alfa should not be administered at an infusion rate exceeding 4 ml/kg/hr. Refer to the IMP manual for detailed instructions regarding administration.

6.5 Blinding of IMP

This is an open label study with no requirement for blinding.

6.6 Destruction of IMP

Following IMP accountability and written permission from the Sponsor to destroy IMP, documentation of destruction must contain, at a minimum, the following:

1. Identity, lot number or subject number
2. Quantity
3. Date of destruction
4. Method of destruction
5. Name and signature of person or company responsible for destruction

7 Assessment of Safety

The methods for collecting safety data are described below. All personnel involved with the study must ensure they are familiar with the content of this section.

7.1 Adverse Events and Laboratory Abnormalities

7.1.1 Clinical Adverse Events

An ***Adverse Event*** is any untoward medical occurrence in a subject, which does not necessarily have to have a causal relationship with the administration of a study drug. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the medicinal product. Pre-existing conditions that worsen in severity during the course of the study are to be reported as AEs.

All AEs occurring during the clinical study will be reported on the AE page of the CRF as described in Section 7.3.

The Investigator will assess the severity, causality (relationship to study drug), and seriousness of each AE.

Severity: The Investigator will assess the severity of all AEs/SAEs as mild, moderate, or severe based on the following definitions (developed from Clinical Data Interchange Standards Consortium Study Data Tabulation Model standard terminology v3.1.1).

- **Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- **Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Causality: AEs will be assessed as not related, unlikely related, possibly related, or related to study drug. Table 3 provides general guidance on the assessment of causality. For data reporting purposes, AEs assessed as not related or unlikely related will be classified as unrelated to study drug, and AEs assessed as possibly related or related will be classified as related to study drug. Assessment of causality should be based on the Investigator's medical judgment and the observed symptoms associated with the event.

Table 3: Assessment of Causality

Relationship to IMP	Criteria for Judgment
Related	Reasonable temporal relationship of the clinical event to study drug administration AND cannot be reasonably explained by other factors (such as the subject's clinical state, concomitant therapy, and / or other interventions).
Possibly Related	The temporal relationship of the clinical event to study drug administration makes causal relationship possible but not unlikely AND other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.
Unlikely Related	The temporal relationship of the clinical event to study drug administration makes causal relationship unlikely but not impossible AND other drugs, therapeutic interventions or underlying conditions provide a plausible explanation for the observed event.
Not Related	Data are available to clearly identify an alternative cause for the reaction.

Seriousness: AEs will be classified as serious or non-serious according to the definitions provided below.

A ***serious adverse event*** is any AE that results in any of the following outcomes:

- Death
- Immediately life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in congenital anomaly/birth defect
- Persistent or significant disability or incapacity
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed

All AEs that do not meet any of the criteria for serious, should be regarded as ***non-serious adverse events***. Given the severity and life threatening nature of LAL Deficiency in infants, it is plausible that some pediatric subjects will be hospitalized during the first several weeks on study. Continuation of this initial hospitalization for participation in the trial is not considered an SAE. Also, a hospitalization to accommodate a study procedure is not considered an SAE. However, during the hospitalization, adverse events will be collected and assessed for seriousness & reported appropriately (i.e., Important medical event or prolonged hospitalization).

All SAEs and IARs must be reported to the Sponsor as described in Section 7.4.

7.1.2 Laboratory Test Abnormality

Laboratory test results will be recorded, or appear on the laboratory reports submitted directly from the central laboratory. Out of range laboratory test values should not be reported as AEs UNLESS they are considered to be clinically significant abnormalities by the Investigator.

7.1.3 Adverse Events of Special Interest (Infusion-Associated Reactions)

Infusion-associated reactions (IARs) will be considered AEs of special interest. Any AE that occurs during the infusion or within 4 hours after the infusion is completed and is assessed by the Investigator as at least possibly related to study drug will be designated as an IAR. In addition, if, at any time during the study, the Investigator observes symptoms that he/she considers to be consistent with an IAR or hypersensitivity reaction related to administration of study drug, the symptoms should be recorded as an AE(s) and designated as an IAR(s). Individual adverse event terms should be recorded rather than the terms, IAR or Infusion Associated Reaction.

As with any ERT, medications and equipment for the treatment of hypersensitivity reactions must be available for immediate use in case of unexpected, severe hypersensitivity reaction. These supplies include, but are not limited to, oxygen, acetaminophen, antihistamines (e.g., diphenhydramine, parenteral and oral), corticosteroids, epinephrine, and cardiopulmonary resuscitation devices.

General guidelines for classifying the severity of a reaction are provided in Appendix B.

For similar biological products, most acute IARs occur within 2 hours of the infusion. Signs of a possible acute IAR may include:

- Hyperemia, flushing, fever and/or chills, nausea, pruritus, urticaria, gastro-intestinal symptoms (vomiting, diarrhea, abdominal cramping), cardiopulmonary reactions, including chest pain, dyspnea, wheezing, stridor, hypotension or hypertension

If any of the above signs and symptoms are observed during the infusion and the subject remains hemodynamically stable:

- The infusion rate must be slowed (reduced to half the rate being given at the onset of the event, e.g., from 10 mL/hr to 5 mL/hr) and the infusion time extended in accordance with the institutional standard of care. The infusion rate may be decreased further by 25% if symptoms persist.Once the event has resolved, the infusion should continue for a minimum of 30 minutes at the reduced rate before the rate is increased to 75% of the original rate on the infusion schedule. . If the subject tolerates the infusion at 75% of the original rate for at least 30 minutes the original rate may be restored for the remainder of the infusion.
- In accordance with institutional standard of care for the subject's age, treatment with an antihistamine and antipyretic should be considered.

In subjects who experience severe infusion reactions with clinically significant cardiovascular effects (eg, hypertension or hypotension defined as a decline approaching 20-30% of their pre-infusion value without alternative etiology, agitation, pain, fluid overload, dehydration), respiratory symptoms (significant shortness of breath, stridor, wheezing, laryngeal edema or swelling of tongue), cardiac arrhythmias, or anaphylactic/anaphylicatoid shock with hypotension and circulatory collapse::

a) The infusion should be stopped.
b) The subject should be treated for an anaphylactic reaction with IV antihistamines, corticosteroids, and epinephrine, if necessary, in accordance with institutional standard of care for the subject's age.
c) Dosing of the subject will be suspended until the Safety Review Committee has completed review of the IAR, and any other relevant safety data.
d) Subjects who experience a moderate or severe IAR should have a serum sample collected for tryptase 1-3 hours after the IAR onset and another serum sample for tryptase and ADA during the next study visit prior to the infusion. Skin testing may be considered.

Additional details on the management of subjects with infusion reactions are outlined in the table in Appendix B.

7.2 Handling of Safety Parameters

7.2.1 Serious Adverse Events (Immediately Reportable to the Sponsor)

All SAEs **and** all IARs (serious and non-serious), irrespective of the treatment received by the subject, must be reported to the Sponsor or designee immediately and no later than 24 hours of the Investigator's first knowledge of the event (expedited reporting).

7.2.2 Adverse Event Reporting Period

The study period during which AEs must be reported is defined as the period from signature of the informed consent to the end of the study treatment follow-up. Adverse events occurring after signing the informed consent but prior to the first dose of study medication will only be recorded if assessed as related to protocol procedures or requirements. For this study, the study treatment follow-up is defined as a minimum of 30 days following the last administration of study treatment. If a subject experiences an SAE that is considered to be related to study treatment at any time after the study, it must be reported to the Sponsor.

7.2.3 Treatment and Follow-up of Adverse Events

During the study, all AEs and SAEs will be followed up until they have returned to baseline status or stabilized or until the Investigator and Sponsor or designee agree that follow-up is no longer necessary. If a clear explanation is established, it should be documented.

Treatment of AEs is at the discretion of the Investigator and should follow the standards of medical care at the Investigator's institution.

7.2.4 Follow-up of Abnormal Laboratory Test Values

In the event of unexplained clinically significant abnormal laboratory values, the tests should be repeated immediately and followed up until they have returned to baseline values and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be documented.

7.2.5 Pregnancy

Subjects in this study will be of non-reproductive potential.

7.3 Recording of Adverse Events

At each contact with the subject (and the subject's parent or legal guardian), the Investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source documentation and in the eCRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded under one diagnosis.

AEs will be recorded from the time of signing of the informed consent until completion of the last scheduled visit, i.e., the follow-up visit. Adverse events occurring after signing the informed consent but prior to the first dose of study medication will only be recorded if assessed as related to protocol procedures or requirements. Any AEs remaining unresolved at the completion of the last visit should be recorded as ongoing. Ongoing AEs/SAEs should continue to be followed up for the period specified in Section 7.2.2 but without further recording in the eCRF. However, follow-up information on SAEs must be reported to the Sponsor or designee as described in Section 7.4.1. Any SAE that occurs after the study period and is considered to be related to the study treatment or study participation should be recorded and reported immediately.

Any AE that occurs within 24 hours of the infusion will be recorded by time and date, AEs occurring 24 hours after the infusion will be recorded by date only. The date and time, or the date when the AE started and stopped, as well as the intensity, seriousness, action taken with regard to the study treatment, causality assessment and outcome of the event will be recorded for each AE.

7.4 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the Sponsor must conform to the AE reporting timelines, formats, and requirements of the various entities to which they are responsible. (§13 GCP-V; Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ['CT-3']; US CFR Title 21, §312.32, Investigational New Drug [IND] safety reporting). The Sponsor or designee will report all reportable events to all regulatory authorities, and Investigators as required by local regulations.

All SAEs and IARs, and other reportable events (see Section 7.4.3) must be reported to the Sponsor or designee in an expedited manner according to timelines described in Section 7.4.3. Periodic Safety reporting to regulatory authorities will be done by the Sponsor according to national and local regulations.

7.4.1 Investigator Reporting: Notifying the Study Sponsor

Any SAE, IAR, or unanticipated problem posing risk of harm to subjects, must be reported to the Sponsor, or designee immediately and no later than 24 hours of the Investigator's first knowledge of the event. To report such events, an SAE/IAR form must be completed by the Investigator and sent within 24 hours. The Investigator will keep a copy of this SAE or IAR form on file at the study site.

The Investigator must promptly provide further information on the SAE, IAR, or the unanticipated problem. This should include a copy of the completed SAE or IAR form, and any other information that will assist the understanding of the event. Significant new information on ongoing SAEs or IARs must be reported to the Sponsor or designee immediately and no later than 24 hours of the Investigator's knowledge. Report SAEs and IARs by phone, fax, or email to:

SAE Reporting:

Europe and Asia Pacific
24-Hour Hotline: PPD
SAE Fax: PPD
Email: PPD

North, Central and South America:
Hotline (Urgent Calls Only) PPD
24-Hour Hotline: PPD
Fax: PPD

7.4.2 Investigator Reporting: Notifying the IRB/IEC

Unanticipated problems posing risks to subjects or others as noted above will be reported to the IRB/IEC according to local regulations. Copies of each report and documentation of IRB/IEC notification and receipt will be kept in the Investigator's study file.

7.4.3 Sponsor Reporting: Notifying the FDA and all Regulatory Authorities

The Sponsor is required to report certain study events in an expedited manner to the FDA, the European Medicine Authority, and to all country Regulatory Authorities where the study is being conducted. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- Immediately and within 7 calendar days
  - Any suspected adverse reaction that is associated with the use of the study drug, unexpected, and fatal or life threatening
  - Follow-up information must be reported in the following 8 days

- Immediately and within 15 calendar days
    - Any suspected adverse reaction that is associated with the use of the study drug, unexpected, and serious, but not fatal or life threatening
    - Any finding from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity
    - Any event in connection with the conduct of the study or the development of the IMP which may affect the safety of the trial subjects
    - Follow-up information must be reported within 15 calendar days

The Sponsor will comply with all additional local safety requirements, as applicable. Periodic safety reporting to competent authorities will be done by the Sponsor or designee according to national and local regulations.

7.4.4 Sponsor Reporting: Notifying Participating Investigators

It is the responsibility of the study Sponsor or designee to immediately notify all participating Investigators of any suspected AE associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects.

7.5 Independent Safety Review Committee (SRC)

It will be the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. Additional oversight of the subject safety in the study will be provided by an independent SRC composed of individuals with pertinent medical expertise, who will serve in advisory capacity to the Sponsor to provide an additional level of scrutiny to minimize the chance that clinical trial participants are exposed to unreasonable or unnecessary risks. The activities and composition of the SRC will be outlined in the SRC Charter which will be ratified during the initial meeting, prior to commencement of dosing of the study subjects. The SRC will be tasked with ongoing review of safety data in order to advise the Sponsor regarding continued dosing and dose escalation decisions for the study. These safety monitoring functions and the oversight of such activities will be distinct from the requirement for study review and IRB/IEC approvals.

Core members of the SRC will not participate in the trial as investigators or sub-investigators, as members of any team otherwise participating in the trial, or in any other capacity that may compromise their privileged activities on the SRC. Neither members of the SRC nor their immediate families will have a direct financial interest in the sponsor or an interest that is dependent of the outcome of the trial. To be considered for SRC membership, all candidates must disclose all actual or potential conflict of interest, including any financial interest in, or research activity on a competing product. SRC members will be compensated at an appropriate market rate for time spent reviewing, discussing, and attending the meetings. The sponsor will also reimburse SRC members for any out-of-pocket travel expenses required for attendance at the meetings. Aside from the above, SRC members will receive no additional compensation for their membership on the committee as outlined in the SRC Charter.

8 Statistical Plan

The Sponsor or its designee will be responsible for data collection and editing, reviewing and validating all the information in the eCRFs, statistical analysis, and generation of the clinical study reports.

An analysis will be performed after all treated subjects have reached 12 months of age or have died or withdrawn from the study.

Final analyses will be performed after all subjects have completed treatment in the study (up to 3 years) or have died or withdrawn from the study.

8.1 General Considerations

All data will be presented in listings; summary tables and graphs will be provided, as appropriate. Unless otherwise noted, tabulations for efficacy endpoints will be presented for subjects in the Full Analysis Set (FAS). Descriptive summary statistics (n, mean, median, standard deviation, minimum and maximum) will be calculated for the continuous variables. Shift tables and/or frequencies and percentages will be produced for the categorical variables. When percentages are reported, the number of treated subjects will be used as the denominator, unless otherwise noted. As appropriate, 95% two-sided confidence intervals (CIs) will be calculated around the estimates based on the exact binomial distribution for binomial endpoints and the t-distribution for continuous endpoints.

Baseline will be defined as the last measurement prior to the first infusion of sebelipase alfa. (Note: For exploratory analyses, the first available measurement after initiation of treatment may be used as baseline if a pretreatment measurement is unavailable.) In order to facilitate comparison with literature, survival analyses will be presented with subject birth date as “time 0”; analyses of other endpoints over time will consider date of first dose as “time 0”.

Details of the planned analyses and statistical methodologies will be provided in a separate Statistical Analysis Plan.

8.2 Determination of Sample Size

Up to 10 subjects who meet the requirements for inclusion will be enrolled in this study. No formal hypothesis testing is proposed in this study; all summary measures, including p-values, are considered descriptive.

8.3 Analysis Sets

The following analysis sets will be defined:

Full Analysis Set

The FAS will include all subjects who received any amount of IMP.

PK Analysis Set

The PK Analysis Set will include all available sebelipase alfa serum concentration data for subjects who received at least one complete infusion of IMP in this study.

8.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be listed for each subject and tabulated.

8.5 Subject Disposition

Data from all subjects who are consented will be included in the summary of subject disposition. The frequency and percentage of subjects who are consented for, treated in, discontinued from, and complete the study, along with reasons for discontinuation, will be summarized.

8.6 Study Treatment Usage and Compliance

Number of weeks in the study and number of study infusions received by subjects will be summarized. The number (percent) of subjects who receive all study infusions 'per protocol' up until the time of last dose (i.e., subjects without missed infusions, infusion interruptions, or rate changes) will be provided. A listing of sebelipase alfa exposure by subject will be provided, including date of first dose and total number of doses (by dose level).

8.7 Efficacy Analysis

Efficacy will be analyzed for the Full Analysis Set.

Survival will be analyzed as the proportion of subjects surviving to 12, 18, and 24 months of age. As a complementary analysis, Kaplan-Meier survival curves of survival since birth and survival since first dose of IMP will be presented. Median age at death will also be calculated. A Kaplan Meier estimate of median survival past first dose of IMP will be computed.

Estimated survival rates and median age at death derived from this study will be compared to rates/times reported in the literature, and will be discussed in conjunction with information derived from previous studies.

Anthropometric indicators of growth, standardized by age and gender in accordance with the methodology described by the WHO and using WHO growth charts will be listed by study time point as observed values and as changes from baseline. Change from baseline in anthropometric data will be provided as graphs, and also tabulated as continuous data. In addition, the percentages of subjects who meet criteria for underweight, stunting, and wasting will be tabulated for each timepoint.

Change and/or percent changes from baseline in AST, ALT, and serum ferritin will be presented graphically (and tabulated) for each evaluation timepoint.

A subject will be considered to have achieved transfusion-free hemoglobin normalization (TFHN) if the subject meets all of the following criteria:

1. Has two post-baseline measurements of hemoglobin at least 4 weeks apart that are both above the age-adjusted lower limit of normal (LLN)
2. Has no known additional measurements of hemoglobin that are below the age-adjusted LLN during the (minimum) 4-week period; and
3. Had no transfusions during the (minimum) 4-week period, and also no transfusions for 2 weeks prior to the first hemoglobin measurement in the (minimum) 4-week period

If all 3 criteria are met, the subject will be considered to have achieved TFHN on the date of the first hemoglobin assessment in the 4-week period. The proportion of subjects who achieve TFHN will be summarized and, if sufficient data are available, a summary of time to TFHN will be created.

A subject who is transfusion-free beginning at Week 6 will be considered to have maintained transfusion-free normal hemoglobin if, regardless of baseline hemoglobin value, the subject has no abnormally low hemoglobin values beginning at Week 8 of the study and continuing for at least 13 weeks (3 months). The proportion of subjects who have maintained transfusion-free normal hemoglobin will be summarized.

The Denver II screens children's performance in four developmental domains: personal-social, fine motor-adaptive, language, and gross motor with respect to the age-matched population. DDST II results are expressed as Normal, Abnormal, Questionable, and Untestable. Denver II results will be listed.

8.8 Safety Analysis

Safety will be analyzed for the FAS.

8.8.1 Adverse Events

All reported AEs will be listed from the date of written informed consent until the end of participation in this study. Separate listings of deaths, SAEs and IARs will also be provided. The numbers and percentages of subjects experiencing any AE, any SAE, any IAR, any related AE, any related SAE, and discontinuations due to an AE will be tabulated.

The frequency of subjects with treatment-emergent AEs, SAEs, and IARs by system organ class (SOC) and preferred term (PT) (coded using Medical Dictionary for Regulatory Activities [MedDRA®] version 14 or higher) will be tabulated. Frequencies will also be presented by the classifications of severity and causality. In addition, frequency of subjects with AEs, SAEs, and IARs will be presented for time periods spanning the entire course of treatment with sebelipase alfa: from the start of dosing with sebelipase alfa in this study to 3 months after the first dose, >3 to 6 months, >6 to 12 months, >12 to 18 months, >18 to 24 months and >24 months. As appropriate, additional listings, summary tables and graphics will be generated to evaluate IAR frequency and severity over time. A listing of subjects who withdraw from the study due to AEs will be presented, and the incidence of AEs leading to study discontinuation will be summarized.

8.8.2 Clinical Laboratory Tests

Observed measurements and changes from baseline to each study timepoint in clinical laboratory data will be summarized. Clinically significant abnormal values will be listed. Frequencies of abnormal values relative to the laboratory normal range and clinically significant abnormal values will be tabulated for each study timepoint. Shift tables may also be provided.

Time to ADA positivity, median and peak antibody titer, and time to peak antibody titer; antibody titer values will be tabulated at each study visit using summary statistics appropriate to the data.

8.8.3 Other Safety Data

Changes in vital signs from pre-infusion values to each time point during or post-infusion will be summarized. Abnormal findings/values for physical examinations, vital signs, and ECGs will also be listed.

Concomitant medication/treatment data will be coded using the WHO-DRUG dictionary. All data will be listed, and the percentages of subjects receiving each concomitant medication/treatment will be tabulated.

Dietary changes will be provided in listings, and, depending on the observed results, may be summarized in tables.

8.9 Pharmacokinetics

Pharmacokinetics will be analyzed for the PK Analysis Set. C_{max} will be recorded from direct observation. C_{max} will be summarized by dose of sebelipase alfa, if applicable.

8.10 Exploratory Biomarker Analysis

Potential disease-related biomarkers will be listed and observed values and changes and/or percent changes from baseline will be summarized at available timepoints.

8.11 Other Statistical Issues

8.11.1 Significance Levels

No formal hypothesis tests are planned. P-values, when presented, will be based on a 2-sided alpha of 0.05 and are intended to guide clinical judgment and interpretation of the data.

8.12 Subgroup Analyses

The impact of ADAs on safety, efficacy, PK, and PD endpoints will be explored descriptively. As subject numbers permit, other subgroup analyses of interest may be performed. These may include, but are not limited to age, gender, and race.

8.13 Missing or Invalid Data

All data will be analyzed as they were collected in the database.

8.14 Interim Analysis

No formal statistical hypothesis is planned to be tested in this protocol; therefore, no formal interim analyses are planned. Interim assessments of accumulating safety data will be performed as discussed in Section 7.5.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of applicable local regulations.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

Required data for this study will be captured on eCRFs via electronic data capture (EDC) unless otherwise specified in this document. Except for data points for which the protocol or SOM indicates that the eCRF may serve as source documentation, data are to be obtained from the subject's source documents and then entered into the eCRF by authorized site personnel. Clinical data that are not recorded on the eCRF will be captured and transferred to the Sponsor or its designee.

9.4 Records Retention

It is the Investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the Sponsor. In such an instance, it is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the study monitoring plan. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The Investigator will permit study-related monitoring, audits, and inspections by the IRB/IEC, the Sponsor, government regulatory authorities, and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of GCP (FDA Title 21 part 312 and ICH guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted IRB/IEC, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/IEC concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the Sponsor before commencement of this study. The Investigator should provide a list of IRB/IEC members and their affiliate to the Sponsor.

Each subject's parent or legal guardian for this study will be provided a consent form describing this study and providing sufficient information for the subject's parent or legal guardian to make an informed decision about their child's participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB/IEC for the study. The formal consent of a subject, using the IRB/IEC-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject's parent or legal guardian, and the Investigator-designated research professional obtaining the consent.

Any changes in the study protocol, such as changes in the study design, objectives or endpoints, inclusion and exclusion criteria, and/or procedures (except to eliminate an immediate hazard) will be implemented only after the mutual agreement of the Investigator and the Sponsor or designee. All protocol changes must be documented in protocol amendment(s). Protocol amendment(s) must be signed by the Investigator and approved by the IRB/IEC prior to implementation. Any changes in study conduct that result from a pending amendment will be considered protocol deviations until IRB/IEC approval is granted. Documentation of IRB/IEC approval must be returned to the Sponsor or designee.

12 Clinical Study Report and Publication Plan

A clinical study report will be produced after all subjects have reached 12 months of age or have died or withdrawn from the study, and will include all available subject data through 12 months of age or the date of death or early withdrawal. A final clinical study report will be produced after study completion, and will include cumulative subject data for the entire period of treatment in the study. A coordinating Investigator will be designated to review and sign the completed clinical study reports.

It is intended that the results from this research will be submitted to a peer-reviewed medical publication, once the study is completed, regardless of the outcome.

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14 Appendices

Appendix A: Schedule of Assessments

Assessments	Screening	Treatment Phase*															
	Day -21 to Day -1	W 0[10]	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16
		± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days
Informed Consent	X																	
Inclusion/Exclusion	X	X																
Medical/Family History	X																	
Physical Exam[2]	X				X						X						X	
Anthropometrics[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	If clinically indicated																
Denver II	X																	
Abdominal Ultrasound		X												X				
Abdominal MRI[5]	X															X		
Clinical LabTests[6, 7]	X	X[P]	X[P]	X[P]	X[P]	X[P]		X[P]		X[P]		X[P]		X[P]				X[P]
Exploratory Biomarkers[7]	X			X						X				X				X
DNA Sample (subject)[7, 8]	X																	
DNA Sample (parents)	X																	
PK Sample[7, 9]		X[7]																
DBS LAL Activity[7]	X																	
Sebelipase Alfa Dosing[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-drug Antibody[7]	X			X		X				X				X				X
Adverse Events	CONTINUOUS																	
Concomitant Therapies	CONTINUOUS																	

* All visits will be calculated from Week 0; consecutive infusions must be administered at least 5 days apart. Day 0 assessments do not need to be repeated if they have been conducted within the 3 days prior to Screening

P Pre-dose

1 For the subjects who are stable enough to be treated on an outpatient basis, safety follow-up assessments for AEs will be conducted by telephone 24 hours following the first 2 infusions of 1 mg/kg qw, and 3 mg/kg qw.

2 All physical examinations will include liver, spleen, and lymph node assessments and digital photographs (full length and abdominal close up) (see Section 5.1.6).

3 Weight, recumbent length or height, and abdominal circumference will be measured at all visits; head and mid-upper arm circumference will be measured at Screening, Weeks 0, 4, 8, 12, and 16.

4 During infusion visits, vital signs will be measured pre-dose, every 15 (±5) minutes during the infusion, and every 30 (±10) minutes from 0 to 4 hours post-infusion (see Section 5.1.9).

5 Abdominal MRI should be considered in subjects receiving general anesthesia and/or sedation for other procedures at the indicated timepoints. The Screening MRI may be obtained up to 8 weeks of treatment. There should be at least 3 months between each MRI. (Either a MRI or Ultrasound should be performed at a given timepoint.)

6 CBC/hematology, chemistry liver function tests, lipid panel, ferritin, urinalysis and coagulation studies (see Section 5.1.11). *Prior to any dose change, serum lipid, serum liver, hematology, chemistry, ferritin, and hs-CRP shall be obtained. Serum lipid and serum liver assessments should be taken 4, 8, and 12 weeks following any study drug or lipid lowering medication change.*

7 If blood volume is limited, refer to Section 5.1.11 for tiered assessments.

8 DNA sample should be collected at Screening or at the earliest possible visit thereafter based on blood volume threshold, unless a stored DNA sample is already available for the subject.

9 Refer to Section 5.1.14 for PK sampling timepoints

10 If the screening labs were performed within 2 days of Week 0 then the Week 0 labs do not need to be performed.

Schedule of Assessments: Week 17 through Study Completion*

	W 17	W 18	W 19	W 20	W 21	W 22	W 23	W 24	Repeating Assessments until end of study	Repeating Assessments Relative to Week 24					Annually (Week 48, Week 96, Week 144)	Follow-up/ Early Withdrawal
										Every Week	Every Month	Every 2 Months (8 weeks)	Every 3 Months (12 weeks)	Every 6 Months (24 weeks)		
	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days		± 2 days	± 2 days	± 2 days	± 5 days	±15 days	±15 days	30 (+7) days
Physical Exam[1]				X				X					X			X
Anthropometrics				X				X			X[6]		X[6]			X
Vital Signs[2]	X	X	X	X	X	X	X	X		X						
12-lead ECG	If clinically indicated										If clinically indicated					
Denver II								X						X		X
Abdominal Ultrasound								X							X	
Abdominal MRI								X[7]							X[7]	
Liver Biopsy															X	
Clinical Laboratory Assessments[3, 4]				X[P]				X[P]				X[8,P]	X[8,P]			X
Exploratory Biomarkers[3]								X						X		X
PK Sample[3, 5]						X									X[9]	
Sebelipase Alfa Infusion[10]	X	X	X	X	X	X	X	X		X						
Anti-drug Antibody				X				X					X			X
Adverse Events	CONTINUOUS															
Concomitant Medications/ Therapies	CONTINUOUS															

* All visits will be calculated from Week 0; consecutive infusions must be administered at least 5 days apart.

P Pre-dose

1 All physical examinations will include liver, spleen, and lymph node assessments. In addition, digital photographs (full length and abdominal close up) will be obtained at Weeks 20 and 24 and annually thereafter.

2 During infusion visits, vital signs will initially be measured pre-dose, every 15 (±5) minutes during the infusion, and every 30 (±10) minutes from 0 to 4 hours post-infusion (see Section 5.1.9). After a year of treatment with no IARs, the post-infusion monitoring period may be shortened from 4 hours to 2 hours.

3 If blood volume is limited, refer to Section 5.1.11 for tiered assessments.

4 CBC/hematology, chemistry, liver function tests, lipid panel, ferritin, urinalysis and coagulation studies, (see Section 5.1.11). *Prior to any dose change, serum lipid, serum liver, hematology, chemistry, ferritin and hs-CRP shall be obtained. Serum lipid and serum liver assessments should be taken 4, 8, and 12 weeks following any study drug or lipid lowering medication dose change.*

5 Refer to Section 5.1.14 for PK sampling timepoints.

6 Weight will be measured at all visits; Recumbent length or height, and abdominal circumference will be measured at every 3 month visits; head and mid-upper arm circumference will also be measured at all every 3 month visits through Week 96

7 Abdominal MRI should be considered in subjects receiving general anesthesia and/or sedation for other procedures. The MRI may be conducted at any time from Week 24 through Week 32, and then annually, and should be scheduled at least 3 months after the preceding MRI assessment.

8 Repeating assessments will be performed every 2 months through Week 48 and every 3 months thereafter until study completion.

9 PK samples will be collected only at the first annual assessment (Week 48).

10 Subjects who are on treatment for at least 96 weeks and have been on a stable dose for at least 24 weeks, may transition to an every other week dosing schedule at the same dose they received on the weekly dosing schedule at the discretion of the PI with Sponsor consultation.

Appendix B: Diagnosis and Guidelines for Management of Infusion Associated Reactions

General guidelines for the diagnosis and management of infusion-associated reactions (IARs) are provided below. These guidelines are not intended to be comprehensive. The Investigator should use his/her clinical judgment in the management of IARs in individual subjects participating in this study. In the case of a severe life-threatening reaction, current medical standards for emergency treatment are to be followed.

Symptoms	**Action**
Mild *Common* • Hyperemia (Flushing) • Lightheadedness • Nausea • Mild chest discomfort (tightness) *Less Common* • Fever and/or shivering • Palpitations • Headache • Irritability (especially in young children)	• Slow infusion rate by 50% • Administer oral anti-pyretic and/or anti-histamine • Decrease infusion rate by a further 25% if symptoms persist • If the event resolves, the infusion should continue at reduced rate for a minimum of 30 minutes before infusion is increased to 75% of original rate. If subject tolerates infusion at 75% of the original rate for at least 30 minutes the original rate may be restored for the remainder of the infusion • If symptoms continue despite rate reduction stop infusion • Pre-treat with oral antihistamine and antipyretic prior (approximately 1.5h) to next infusion ○ e.g., diphenhydramine (1 mg/kg orally) and acetaminophen (15 mg/kg orally)
Moderate Reaction • Hyperemia (flushing) • Chest discomfort • Itching and/or raised urticarial rash • Severe headache • Gastro intestinal symptoms, vomiting, diarrhoea, abdominal cramping.	• Stop infusion • Give antihistamine IV and consider IV steroids • Consider giving a beta-adrenergic inhaler treatment if appropriate • If the event resolves, the infusion may continue at a reduced rate of 50% of the original for a minimum of 30 minutes before the infusion is increased to 75% of the original rate. If the patient tolerates the infusion at 75% of the original rate for at least 30 minutes the original rate may be restored for the remainder of the infusion. • If reaction persists despite rate reduction stop infusion • • Pre-treat with oral antihistamine and antipyretic prior to next infusion

	• Collect serum sample for tryptase 1-3 hours after the IAR onset and another serum sample for tryptase and anti-drug antibody (ADA) during the next study visit (≥4 days after the IAR) prior to the infusion. • Skin testing may be considered.
<u>Severe Anaphylactic Reaction</u> • Clinically significant cardiovascular effects: eg, hypo/hypertension defined as a decline approaching 20-30% of their preinfusion value without alternative etiology (agitation, pain, fluid overload, dehydration) • Respiratory symptoms: significant shortness of breath, stridor, wheezing, laryngeal oedema, swelling of tongue. • Cardiac Arrhythmias • Anaphylactic/Anaphylactoid shock with hypotension and circulatory collapse.	• Stop Infusion • Give oxygen, if available • Give epinephrine (adrenaline) IM or inhaled • Give antihistamines IV and steroids IV • Consider giving a beta-adrenergic inhaler treatment, if appropriate • Complete SAE form • Collect serum sample for tryptase 1-3 hours after the IAR onset and another serum sample for tryptase and ADA during the next study visit (≥ 4 days after the IAR) prior to the infusion. • Skin testing may be considered • Dosing of the subject will be suspended until the Safety Committee has completed the review of the IAR and any other relevant safety data • In the event patient is approved by Safety Committee for resumption of dosing: o Pre-treat with oral antihistamine and antipyretic prior to next infusion o Slowly up-titrate the infusion rate during the subsequent infusion: e.g. if previous rate was 50 mL/hr, begin at 0.25 x previous rate (12.5 mL/hr) x 15min, then increase to 0.5 x rate (25 mL/hr) x 15min, then increase to 0.75 x rate (37.5 mL/hr) x 15min, then increase to full rate (50 mL/hr) for the remainder of the infusion