AN OPEN LABEL MULTICENTER EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF SBC-102 IN ADULT SUBJECTS WITH LIVER DYSFUNCTION DUE TO LYSOSOMAL ACID LIPASE DEFICIENCY WHO PREVIOUSLY RECEIVED TREATMENT IN STUDY LAL-CL01

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Protocol Number: **LAL-CL04**

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

IND No.: **108460**

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

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PROTOCOL SIGNATURE PAGE

Protocol title:	**An Open Label Multicenter Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of SBC-102 in Adult Subjects with Liver Dysfunction Due to Lysosomal Acid Lipase Deficiency Who Previously Received Treatment in Study LAL-CL01**
Protocol Number:	**LAL-CL04**
Date of Protocol:	**05 January 2016**
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IND No.:	**108460**
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Sponsor:	**Alexion Pharmaceuticals, Inc.** **352 Knotter Drive** **Cheshire, CT 06410** **USA**

PPD

15 JAN 16
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 at any time by the Sponsor, with or without cause.

I agree to personally conduct or supervise this investigation and to ensure that all 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

Title	An Open Label Multicenter Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of SBC-102 in Adult Subjects with Liver Dysfunction Due to Lysosomal Acid Lipase Deficiency Who Previously Received Treatment in Study LAL-CL01
Protocol Number	LAL-CL04
Phase	Phase 2
Methodology	This Phase 2, open-label, extension study will evaluate the long-term safety, tolerability, and efficacy of sebelipase alfa (SBC-102) in adult subjects with liver dysfunction due to Lysosomal Acid Lipase (LAL) Deficiency who previously received 4 doses of sebelipase alfa in the Phase 1/2 repeat-dose, dose escalation study (Study LAL-CL01). After completing all follow-up assessments for study LAL-CL01 (and no sooner than 4 weeks after the last dose in that study), eligible subjects will initiate treatment in the current extension study at a once-weekly (qw) dose of sebelipase alfa equivalent to the dose administered during their fourth infusion in study LAL-CL01. After the 4th infusion under this protocol, all subjects will move to an every other week (qow) dosing regimen of 1 or 3 mg/kg. Subsequent dose modifications may be considered for individual subjects based on observed safety and tolerability and/or clinical response to treatment after Week 12. All such decisions will be made jointly by the Investigator and Sponsor. Safety, tolerability, and efficacy assessments will be conducted at regular intervals throughout the extension study. In addition, blood samples will be obtained at selected timepoints for analysis of sebelipase alfa pharmacokinetics (PK) and biomarkers of sebelipase alfa pharmacodynamic (PD) activity. Blood and urine samples will also be collected for an exploratory analysis of potential disease-related biomarkers in this patient population, and Health-Related Quality of Life (HRQOL) will be assessed through subject questionnaires. A follow-up visit will be conducted for all subjects at 30 (+7) days after the last dose of investigational medicinal product (IMP).
Study Duration	Treatment under this protocol is expected to continue for approximately five (5) years.
Study Center(s)	Approximately 9 primary study centers will participate in this study. At any time during the extension study, a subject may choose to transfer to a local medical center to receive their IMP infusions. Scheduled study assessments may also be performed at the local medical center provided that the center has access to the appropriate facilities and expertise. Home infusions may be permitted for subjects who have been on a stable dosing regimen of sebelipase alfa for at least 12 months and have had no infusion-associated reactions (IARs) requiring medical intervention/management and no serious adverse events (SAEs) related to IMP within the prior 6 months.

Objectives	The primary objective of the study is to evaluate the long-term safety and tolerability of sebelipase alfa in subjects with liver dysfunction due to LAL Deficiency. The secondary objectives are (1) to evaluate the long-term efficacy of sebelipase alfa in subjects with liver dysfunction due to LAL Deficiency; (2) to characterize repeat-dose pharmacokinetics of sebelipase alfa delivered by intravenous (IV) infusion; and (3) to determine the effect of sebelipase alfa on pharmacodynamic biomarkers. The exploratory objectives are (1) to determine the effect of sebelipase alfa on patient HRQOL measures; (2) to evaluate the acceptability of an everyother week dosing regimen of sebelipase alfa, and (3) to evaluate liver histology.
Number of Subjects	Up to 9 subjects will be enrolled in this study after successfully completing treatment in study LAL-CL01.
Main Inclusion and Criteria for Evaluation	A subject must meet all of the following inclusion criteria to be eligible for this study: 1. Subject understands the full nature and purpose of the study, including possible risks and side effects, and is willing and able to comply with all study procedures and provide informed consent. 2. Subject received all 4 scheduled doses of sebelipase alfa in study LAL-CL01 with no life-threatening or unmanageable study drug toxicity. 3. Female subjects have a negative serum pregnancy test at screening, and are not breast-feeding. 4. Female subjects of childbearing potential are willing and able to use a highly effective and approved contraceptive method(s) from the date of informed consent until 30 days after last dose of IMP. A subject who meets any of the following exclusion criteria will be ineligible for this study: 1. Clinically significant concurrent disease, serious inter-current illness, concomitant medications, or other extenuating circumstances that, in the opinion of the Investigator, would interfere with study participation or the interpretation of the effects of sebelipase alfa. 2. Clinically significant abnormal values on screening laboratory tests, other than liver function or lipid panel tests. Subjects with an abnormal laboratory value that is of borderline significance may be allowed to undergo repeat testing once within a 30-day period.
Investigational Medicinal Product, Dose, Route, Regimen	Sebelipase alfa (SBC-102), a recombinant human lysosomal acid lipase (rhLAL) produced in the transgenic *Gallus*, will be administered by IV infusion. The following dosing regimens of sebelipase alfa may be administered in this study: 0.35 mg/kg qw, 1 mg/kg qw, 3 mg/kg qw, 1 mg/kg qow, and 3 mg/kg qow. Subjects will initiate treatment in the extension study at least 30 days after their last dose of sebelipase alfa in study LAL-CL01. Each subject will initiate treatment in the extension study at the same once-weekly dose of sebelipase alfa that he/she received during the fourth infusion in study LAL-CL01, i.e., 0.35 mg/kg qw, 1 mg/kg qw, or 3 mg/kg qw. Subsequent modifications to the dose and dosing frequency will be undertaken for individual subjects as outlined below based on observed safety and tolerability and clinical response to treatment. All such decisions will be made jointly by the Investigator and Sponsor:

	• At Week 6 (and after at least 4 infusions in the extension study), subjects receiving a starting dose of 0.35 mg/kg qw or 1 mg/kg qw will have their dose changed to 1 mg/kg qow. Similarly, subjects who were receiving a starting dose of 3 mg/kg qw for the first 4 infusions will transition to the 3 mg/kg qow regimen. • After Week 12, subjects receiving a dose of 1 mg/kg qow may have their dose increased to 3 mg/kg qow based on observed safety and tolerability and/or clinical response to treatment. • After Week 12, subjects receiving a dose of 3 mg/kg qow may be considered for a dose adjustment to 3 mg/kg qw based on observed safety and tolerability and/or clinical response to treatment. • In the event of poor tolerability at any time during the extension study, the dose may be reduced at the discretion of the Investigator. If a subject cannot tolerate the lowest starting dose (0.35 mg/kg qw) despite measures taken to manage any IARs, he/she will be discontinued from treatment.
Duration of IMP administration	The duration of each subject's treatment in the study will vary but is expected to be at least 26 weeks and approximately 5 years.
Reference therapy	No reference therapy will be administered in this study.
Criteria for Evaluation	***Safety*** The primary safety endpoints will include the incidence of adverse events (AEs) SAEs, and IARs; changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature), physical examination findings, 12-lead electrocardiogram (ECG) parameters, and clinical laboratory tests (CBC/hematology, serum chemistry and urinalysis); use of concomitant medications/therapies; and characterization of anti-sebelipase alfa anti-drug antibodies (ADAs), including ADA positive rate, time to ADA positivity, peak ADA titer, and time to peak ADA titer. The effect of ADAs on the safety of sebelipase alfa will also be explored. A further characterization of ADAs, including inhibitory ADAs, may be performed as a separate pooled analysis across studies, and will be reported separately from this protocol. ***Efficacy*** Efficacy assessments will include change and/or percent change in liver and spleen volumes by magnetic resonance imaging (MRI), liver and spleen fat content by MRI and ^{1}H-magnetic resonance spectroscopy (MRS) (if available), and liver cholesteryl ester signature by ^{13}C- MRS (in a subset of subjects receiving treatment at sites with access to this imaging technology). Histologic assessment of liver disease will be evaluated in subjects who agree to an optional liver biopsy. The effect of ADAs on the efficacy of sebelipase alfa will also be explored. ***Pharmacodynamics*** Pharmacodynamic endpoints will include change in serum transaminases, serum lipids, and acute phase reactants (e.g., serum ferritin). The effect of ADAs on the PD of sebelipase alfa will also be explored. 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.

	Health-Related Quality of Life (HRQOL) Outcomes Health-Related Quality of Life measures will include changes in scores for the 36-item Short Form Health Survey (SF-36®), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, and Chronic Liver Disease Questionnaire (CLDQ). ***Pharmacokinetics*** PK parameters will include maximum observed serum concentration (C_{max}), minimum observed serum concentration (C_{min}), area under the serum concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), terminal elimination half-life ($T_{1/2}$), apparent serum clearance (CL), and steady state volume of distribution (V_{ss}). The effect of ADAs on sebelipase alfa PK will also be explored.
Statistical Methodology	Sample size is based on the estimated total enrollment in study LAL-CL01, and assumes that all subjects treated in that study will be eligible and willing to participate in this extension study. Data collected in this study will be reported using summary tables, graphs and subject data listings. All subject data listings will be sorted by subject number. Descriptive summary statistics (n, mean, median, standard deviation, minimum and maximum) will be calculated for the continuous variables and shift tables and/or frequencies and percentages will be produced for the categorical variables. As noted, 95% two-sided confidence interval (CI) will be calculated around the estimates based on the exact binomial distribution for categorical endpoints and the t-distribution for continuous endpoints. Effect of anti-drug antibodies will be examined for efficacy, safety, PD, and PK endpoints. Numbers permitting, analyses may be conducted in other subgroups of interest. Baseline will be defined as the last measurement prior to the first infusion of sebelipase alfa in study LAL-CL04. As appropriate, a CL01 Study Baseline, defined as the last measurement prior to the first infusion in study LAL-CL01, may also be used for selected study endpoints. For endpoints that are computed as changes from baseline, a comparison between change from Baseline and change from the CL01 Study Baseline will be performed, as appropriate. Unless otherwise noted, all tabulations will present data overall and by dose and dosing frequency (qw, qow), i.e., dosing regimen. Details of the planned analyses and statistical methodologies will be provided in a separate Statistical Analysis Plan (SAP). **Safety** Safety will be analyzed using the Safety Analysis Set. As appropriate, the effect of dosing regimen and/or treatment duration on safety endpoints will also be explored. Observed measurements and changes from baseline to each study timepoint in vital signs, clinical laboratory data, and 12-lead ECG parameters will be summarized. For laboratory data, clinically significant abnormal values will be listed, and frequencies of abnormal values relative to the laboratory normal range and clinically significant abnormal values will be summarized. Abnormal findings/values for physical examinations, vital signs, and ECGs will also be listed. The number and percentages of subjects receiving each concomitant medication/treatment will be tabulated. The percentage of subjects who become ADA positive, time to ADA positivity and time to peak titer, and median and peak immunoglobulin G (IgG) antibody titer will be summarized; IgG antibody titer values will be tabulated using summary statistics at each study visit.

	All AEs, SAEs, and IARs will be listed, and the number and percent of subjects experiencing any AE, any SAE, any IAR, any related AE, any related SAE, and discontinuations due to an AE will be tabulated, Treatment-emergent AEs, SAEs, and IARs will be tabulated by system organ class and preferred term, for all events and for events by severity and causality. As appropriate, additional listings and summary statistics 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. **Efficacy, Pharmacodynamics, and Patient Health-Related Quality of Life (HRQOL) Outcomes** Efficacy, PD, and HRQOL outcomes will be analyzed using the Full Analysis Set. Observed measurements and changes or percent changes from baseline to study timepoints in liver and spleen volumes, liver and spleen fat content, liver cholesteryl ester signature, serum transaminases, plasma lipids, and acute phase reactants (e.g., serum ferritin) will be summarized overall and by dosing regimen. The percentage of subjects with abnormal transaminases at each timepoint will also be summarized overall and by dosing regimen. Scores and changes from baseline to study timepoints in the SF-36®, FACIT-Fatigue, and CLDQ will be summarized. Histologic assessments of liver disease will be described. **Pharmacokinetics** Pharmacokinetics will be characterized using the PK Analysis Set. C_{max} and C_{min} will be recorded from direct observation, and other PK parameters will be derived by non-compartmental analysis. All PK parameters will be summarized by dosing regimen.
Analysis Sets	The following populations are proposed for analysis of study endpoints: **Full Analysis Set** The Full Analysis Set (FAS) will include all subjects who received at least one complete infusion of IMP in the extension study and have at least one post-treatment measurement in the extension study. **Safety Analysis Set** The Safety Analysis Set will include all subjects who received any amount of IMP in the extension study. **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 the extension study. **Per Protocol Analysis Set** The Per Protocol Analysis Set will consist of all subjects in the FAS who have no protocol violations that could potentially confound the interpretation of serum transaminase or lipid results. The list of subjects to be included in the per-protocol analysis set will be determined before database lock. If all patients in the FAS are also in the per-protocol analysis set, then separate analyses for the per-protocol analysis set will not be performed.
Interim Analysis	A clinical study report (CSR) of interim data will be produced to support regulatory filings. A final CSR to summarize long-term efficacy, safety, and PK parameters will be produced at study completion, which will include data on all patients in the study for approximately 5 years. No inferential statistical analyses are planned.

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List of Abbreviations and Terms

ADA	Anti-drug Antibody
AE	Adverse Event
ALT/SGPT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST/SGOT	Aspartate Aminotransferase
AUC_{inf}	Area Under the Serum Concentration-time Curve from Time Zero Extrapolated to Infinity
CBC	Complete Blood Count
CESD	Cholesteryl Ester Storage Disease
CI	Confidence Interval
CL	Apparent Serum Clearance
CLDQ	Chronic Liver Disease Questionnaire
C_{max}	Maximum Observed Serum Concentration
C_{min}	Minimum Observed Serum Concentration
CRP	C- Reactive Protein
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERT	Enzyme Replacement Therapy
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GlcNAc	N-acetylglucosamine
GGTP	Gamma Glutamyl Transpeptidase
GI	Gastrointestinal
HDL	High Density Lipoprotein
HEENT	Head, Eyes, Ears, Nose, and Throat
HRQOL	Health-Related Quality of Life
IAR	Infusion Associated Reaction
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IM	Intramuscular

IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intra Uterine Device
IV	Intravenous
LAL	Lysosomal Acid Lipase
LDL	Low Density Lipoprotein
LSD	Lysosomal Storage Disorder
M6P	Mannose-6-Phosphate
MCV	Mean Corpuscular Volume
MCH(C)	Mean Corpuscular Hemoglobin (Concentration)
MCS	Mental Component Summary
MHRA	Medicines and Healthcare Products Regulatory Agency
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Macrophage Mannose Receptor
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MRS	Magnetic Resonance Spectroscopy
NCS	Not Clinically Significant
PCS	Physical Component Summary
PT	Preferred Term
PT (INR)	Prothrombin Time (International Normalized Ratio)
PHI	Protected Health Information
PD	Pharmacodynamics
PK	Pharmacokinetics
PO	By Mouth
qw	Once-weekly
qow	Every Other Week
rhLAL	Recombinant Human Lysosomal Acid Lipase
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SC	Safety Committee
SF-36®	36-item Short Form Health Survey
SOC	System Organ Class
SOM	Study Operations Manual
$T_{1/2}$	Terminal Elimination Half-life
V_{ss}	Steady State Volume of Distribution

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (GCP) (Food and Drug Administration (FDA) Title 21 part 312 and International Conference on Harmonisation (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 of the lysosomal enzyme, LAL. Although a single disease, LAL Deficiency presents as a clinical continuum with two major phenotypes: the late onset phenotype is frequently known as Cholesteryl Ester Storage Disease (CESD) and the early onset phenotype is typically referred to as Wolman Disease. For purposes of clarity in this document, CESD will hereinafter be referred to as late onset LAL Deficiency and Wolman Disease as early onset LAL Deficiency.

The marked reduction of LAL in patients with LAL Deficiency (early and late onset phenotypes) leads to the accumulation of lipids, predominately cholesteryl esters and triglycerides, in various tissues and cell types. Lipid accumulation is most evident in the liver, leading to hepatomegaly, liver dysfunction, and hepatic failure, and in the small intestinal macrophages, leading to malabsorption. Early onset LAL Deficiency is characterized by profound malabsorption, growth failure, and hepatic failure and is usually fatal within the first year of life. In late onset LAL Deficiency, liver involvement and type II hyperlipidemia dominate the clinical picture. Both the early onset and late onset phenotypes are due to mutations in the LAL gene located on chromosome 10q23.2-q23.3. In the late onset LAL Deficiency, many cases are associated with a common allele resulting in some residual enzyme activity, whereas in the early onset phenotype there are a variety of private mutations with complete loss of enzyme function (Assmann, 2001, *The Metabolic and Molecular Basis of Inherited Disease (online)*). In general, there appears to be an inverse correlation between enzyme activity and the severity of the disease.

1.1.2 Late Onset LAL Deficiency

In late onset LAL Deficiency, large amounts of lipids accumulate in cells and tissues throughout the body with predominant hepatic and cardiovascular involvement. Adrenal calcification, which is prominent in the early onset LAL Deficiency, is not typically associated with this phenotype (Assmann, 2001, *The Metabolic and Molecular Basis of Inherited Disease (online*). The liver is most severely affected with marked hepatomegaly, elevation of transaminases, and liver fibrosis, and the cardiovascular involvement is characterized by dyslipidemia (high cholesterol, high triglyceride and low high-density lipoprotein [HDL]) and accelerated atherosclerosis (Anderson, 1999, *Mol Genet Metab*; Beaudet, 1977, *J Pediatr*; Elleder, 2000, *J Hepatol*). In addition, chronic liver disease (cirrhosis) can develop. An accumulation of fatty deposits on the artery walls (atherosclerosis) is described early in life. The presentation of late onset

LAL Deficiency is highly variable with some patients going undiagnosed until complications manifest in adulthood, while others can present with liver dysfunction in early childhood. Early onset LAL Deficiency is associated with shortened lifespan and significant ill health; the life expectancy of those with late onset LAL Deficiency depends on the severity of the associated complications.

Although no approved therapies are available for treatment of LAL Deficiency, supportive therapies are used in an attempt to mitigate some of the effects of the disease. Current treatment options for late onset LAL Deficiency are focused on control of blood lipid levels through a diet that excludes foods rich in cholesterol and triglycerides and suppression of cholesterol synthesis and apolipoprotein B production through administration of statins and other lipid lowering therapies. Although some clinical improvement may be seen, the underlying disease manifestations persist and disease progression still occurs (Assmann, 2001, *The Metabolic and Molecular Basis of Inherited Disease (online);* Di Bisceglie, 1990, *Hepatol*; Gasche, 1997, *J Hepatol*; Ginsberg, 1987, J Clin Invest; Glueck, 1992, *Pediatr Res*; Tadiboyina, 2005; *Lipids Health Dis*; Tarantino, 1991, *J Pediatr*; Yokoyama, 1992, *J Inherit Met Dis*). As liver function deteriorates, liver transplantation may be required. At present there is limited information on the long-term outcomes of liver transplantation in late onset LAL Deficiency patients (Ferry, 1991, J Pediatr Gastroenterol Nutr; Hansen, 2008, *Liver Transplant*).

1.1.3 Medical Plausibility for 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 deoxyribonucleic acid (DNA) technology, established the medical value and long-term safety of enzyme replacement therapy (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 lysosomal storage disorders.

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 [MMR] or 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.

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 Nonclinical Data

Sebelipase alfa demonstrated uptake and localization to lysosomes in *in vitro* studies in macrophages. In human fibroblasts deficient in LAL enzyme activity, sebelipase alfa corrected the enzyme deficiency at a cellular level in a dose-dependent manner. In a nonclinical disease model of LAL Deficiency, intravenous (IV) administration of sebelipase alfa restored enzyme activity in key target tissues including the liver. Correction of enzyme deficiency was associated with a marked reduction in the accumulation of cholesteryl esters and triglycerides relative to a placebo treated group in the liver and spleen. In other tissues, including gut and lymph nodes, substrate reduction by sebelipase alfa was demonstrated by a decrease in oil red staining (Quinn, 2010, *American Society of Human Genetics Annual Meeting*).

Homozygous LAL deficient rats demonstrate liver abnormalities, which resemble the abnormalities seen in patients with LAL Deficiency including hepatomegaly, transaminase elevation, and hepatic accumulation of cholesteryl esters and triglycerides. In addition, the LAL-deficient rats show a marked increase in organ (liver, spleen, small intestine) size and substantial histopathological abnormalities due to substrate accumulation compared with wild type controls, as well as markedly impaired weight gain resembling that in patients with LAL Deficiency presenting in infancy. 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. Improvements in weight gain were statistically significant within 2 weeks of initiation of the first dose. Liver abnormalities were all markedly improved with sebelipase alfa treatment. Additional discussions of the dose response of the effects seen in the nonclinical model are included in Section 1.5.

There were no meaningful toxicological findings in 4-week repeat dose toxicology studies in the Sprague-Dawley rat and Cynomolgus monkey administered intravenous infusions of sebelipase alfa at doses up to 50 mg/kg once weekly. In a 6-month repeated dose toxicity study in 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 Benadryl 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.

As expected, based on the number and composition of glycan structures, 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. Based on these data, sebelipase alfa is anticipated to have a short plasma half-life in humans.

1.4 Clinical Data

The clinical development program is investigating the safety and tolerability of sebelipase alfa and its clinically meaningful effects on the medical complications of LAL Deficiency. LAL-CL01, a Phase 1/2 dose-finding study in adults with LAL Deficiency, has completed. An extension study, LAL-CL04, is ongoing in subjects who completed LAL-CL01. LAL-CL03 is an ongoing Phase 2/3 study to evaluate the safety, tolerability, efficacy, PK and pharmacodynamics of sebelipase alfa in pediatric subjects with LAL Deficiency who developed growth failure or other clinical evidence of rapidly progressive LAL Deficiency before 6 months of age. LAL-CL02 is an ongoing Phase 3 study to evaluate efficacy, safety, and PK of sebelipase alfa or placebo in pediatric and adult subjects with LAL Deficiency. LAL-CL06 is a Phase 2 study in a broad population of subjects ≥ 8 months with LAL Deficiency who may not have been eligible for other studies. LAL-CL08 is a Phase 2 study in infant subjects with rapidly progressive LAL Deficiency. Please refer to the IB for further information on the 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. While these diseases have distinct clinical manifestations and demonstrate differences in the targeting and biological effects of the ERT, there are relevant data from these studies which inform the use of investigational products of this class. Most of the AEs associated with clinical use of ERTs relate to infusion associated events which occur typically either during or within several hours following completion of the infusion. Given the propensity for infusion reactions with ERT administration, measures have been incorporated in this protocol to minimize risk and monitor subject safety.

1.5 Dose Rationale and Risk/Benefits

1.5.1 Dose Rationale

In this extension study, each individual subject will receive a starting dose of sebelipase alfa equivalent to the dose that he/she received during the fourth infusion of sebelipase alfa in study LAL-CL01. This starting dose is contingent upon that dose being deemed safe and well tolerated following evaluation of safety data for all subjects receiving that dose in study LAL-CL01.

Subjects with LAL Deficiency are expected to require long-term treatment with ERT. Reducing the frequency of infusions during maintenance therapy would lessen the burden of therapy on these patients, thereby improving quality of life and possibly patient compliance. In this study, subjects will transition to a qow dosing regimen after Week 4 (after the first 4 infusions in the extension study). Each subject will be expected to transition to a dose of 1 mg/kg qow or 3 mg/kg qow, which based on the currently available preclinical data is expected to provide a therapeutic benefit:

- In a 4-week study, the minimum effective dose of sebelipase alfa in the nonclinical model of LAL Deficiency was 0.35 mg/kg qw, and was generally comparable to the PD effects of sebelipase alfa at a dose of 1 mg/kg qow. These data suggest that a qow dose < 1 mg/kg has a decreased probability of demonstrating efficacy.
- In a nonclinical model of LAL Deficiency, the PD effects of sebelipase alfa were broadly comparable at the two highest qw dosing regimens (3 mg/kg qw and 5 mg/kg qw) and the two highest qow dosing regimens (3 mg/kg qow and 5 mg/kg qow) studied. These data indicate that 3 mg/kg is a maximally effective dose with both qw and qow administration.
- In patients with late onset LAL Deficiency, substrate accumulation and pathology are most prominent in the liver and spleen. Dose response analysis in the preclinical model demonstrates that substrate is markedly reduced in these organs with a 3 mg/kg qow regimen, and that a 1 mg/kg qow regimen is also effective, but can be differentiated from the 3 mg/kg qow regimen based on effects on growth and liver cholesteryl ester substrate content.

All planned doses of sebelipase alfa in the extension study are anticipated to be safe and well tolerated based upon the following:

- The Investigational Medicinal Product (IMP) has an amino acid sequence identical to the natural enzyme with no engineering of enhancements in biological activity.
- Knowledge of the biochemistry of LAL Deficiency and the mode of action of sebelipase alfa do not raise concerns for unexpected toxicity in humans.

- There were no meaningful toxicological findings in 4-week repeated dose toxicology studies in the Sprague-Dawley rat and Cynomolgus monkey at doses up to 50 mg/kg. Based on the human equivalent doses in rats (8.1 mg/kg) and monkeys (16.1 mg/kg), this represents a 2.7-to 5.4-fold safety margin relative to the proposed top dose in the current study (3 mg/kg).
- Sebelipase alfa was well-tolerated in a 6-month repeated dose toxicity study in Cynomolgus monkeys treated qw at doses up to 30 mg/kg, the highest dose level evaluated. Based on the human equivalent dose of 9.7 mg/kg, this represents a 3.2-fold safety margin relative to the proposed top dose in the current study. The absence of any sebelipase alfa related changes in study parameters supports the long-term dosing with sebelipase alfa.
- Safety and tolerability data from study LAL-CL01 are available to inform decisions regarding within-subject dose escalation.
- In general for LSDs, the enzymatic activities and mechanisms for lysosomal targeting are conserved across species. Toxicological studies of this class of therapy consistently demonstrate low systemic toxicity (Andrews, 2008*, Enzyme Replacement Therapies. In: Cavagnaro JA, ed. Preclinical Safety Evaluation of Biopharmaceuticals: A Science-Based Approach to Facilitating Clinical Trials.*).

As ERTs have a short plasma half-life and biological activity is primarily driven by enzyme concentrations in the target tissue and the rate of substrate accumulation, sebelipase alfa plasma concentrations are being measured only for analysis of sebelipase alfa pharmacokinetics, and will not routinely be used for decisions regarding changes in dose or dosing frequency.

1.5.2 Risk/Benefit Assessment

As discussed in Section 1.1.2, LAL Deficiency is a very rare disease with no approved therapies that leads to significant morbidity and mortality.

Nonclinical studies conducted in a relevant rodent disease model at pharmacological doses and in other nonclinical species at doses substantially in excess of those proposed in this study, revealed no significant risks.

Extensive clinical experience, with approved enzyme replacement therapies from other LSD indications, is relevant for risk evaluation of sebelipase alfa. The most common AEs associated with administration of approved ERTs (including but not restricted to Cerezyme®, VPRIV®, Myozyme®/Lumizyme®, Fabrazyme®) are infusion reactions. These 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. 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.

Based on the results from the completed study LAL-CL01, which showed good tolerability of sebelipase alfa infusions at all dosing regimens studied and no SAEs or IARs, as well as rapid improvements in serum transaminases combined with other evidence of biological activity (refer to the IB for further information), there is a reasonable basis to conclude that sebelipase alfa will continue to demonstrate beneficial effects on disease activity as these subjects resume treatment in the current long-term extension study. Irrespective of the immediate clinical value to the individual patient, the information provided from the current long-term extension study will provide benefit to patients with LAL Deficiency by guiding future clinical development.

Based on current understanding of sebelipase alfa, it was anticipated that the increases in serum lipid levels observed in study LAL-CL01 will not be sustained with continuous treatment. This has now been confirmed.

Given the relatively low level of subject risk relative to the progressive and potentially life-threatening nature of untreated LAL Deficiency, 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 long-term safety and tolerability of sebelipase alfa in patients with liver dysfunction due to LAL Deficiency.

2.2 Secondary Objective

The secondary objectives are:

- To evaluate the long-term efficacy of sebelipase alfa in patients with liver dysfunction due to LAL Deficiency;
- To characterize repeat-dose pharmacokinetics of sebelipase alfa delivered by IV infusion;
- To determine the effect of sebelipase alfa on pharmacodynamic biomarkers.

2.3 Exploratory Objective

The exploratory objectives are:

- To determine the effect of sebelipase alfa on Health-Related Quality of Life (HRQOL) outcome measures;
- To evaluate the acceptability of an every other week dosing regimen of sebelipase alfa;
- To evaluate liver histology.

3 Study Design

3.1 Overview of Study Design

This Phase 2, open-label, extension study will evaluate the long-term safety, tolerability, and efficacy of sebelipase alfa in adult patients with liver dysfunction due to LAL Deficiency who previously received 4 doses of sebelipase alfa in the Phase 1/2 repeat-dose, dose escalation study (Study LAL-CL01). The study will consist of a screening period, treatment period, and follow-up period.

Subjects who successfully receive all 4 doses of sebelipase alfa in study LAL-CL01 and wish to continue treatment with sebelipase alfa in the extension study will undergo screening assessments to determine study eligibility (Note: Assessments performed in study LAL-CL01 within a defined time period may not need to be repeated at the screening visit; see Appendix A: Schedules of Assessments for further details).

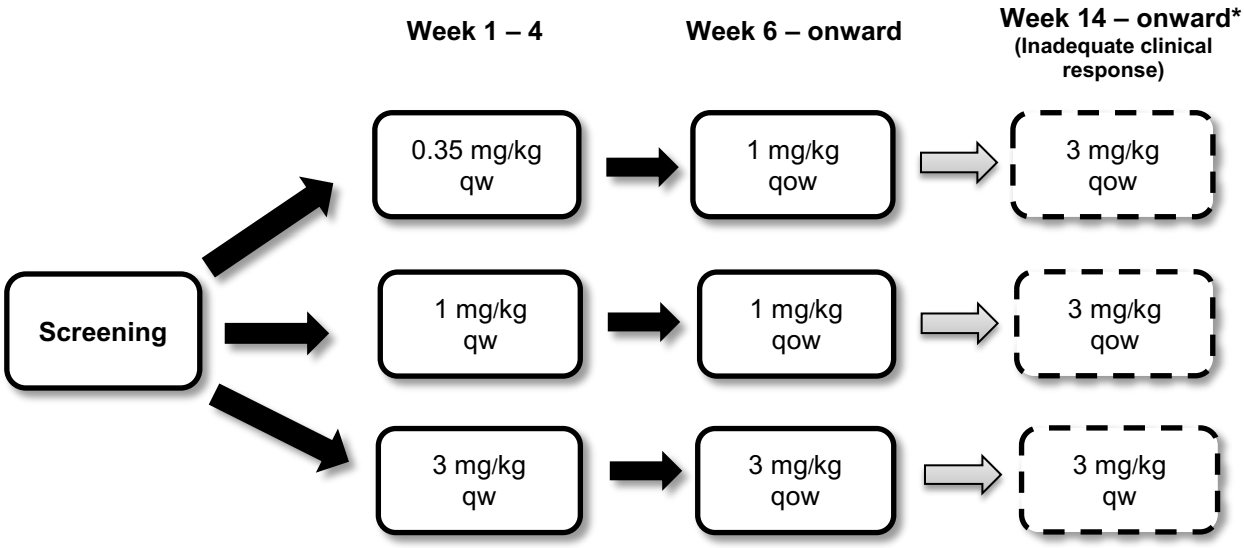
Eligible subjects will initiate treatment in the current extension study at least 4 weeks after their last dose of sebelipase alfa in study LAL-CL01. Each subject will initiate treatment in the extension study at the same once-weekly dose of sebelipase alfa that he/she received during the fourth infusion in study LAL-CL01, i.e., 0.35 mg/kg qw, 1 mg/kg qw, or 3 mg/kg qw. Subsequent modifications to the dose and dosing frequency will be undertaken for individual subjects as outlined below based on observed safety and tolerability and clinical response to treatment. All such decisions will be made jointly by the Investigator and Sponsor.

- At Week 6 (and after at least 4 infusions in the extension study), subjects receiving a starting dose of 0.35 mg/kg qw or 1 mg/kg qw will have their dose changed to 1 mg/kg qow. Similarly, subjects who were receiving a starting dose of 3 mg/kg qw for the first 4 infusions will transition to the 3 mg/kg qow regimen.
- After Week 12, subjects receiving a dose of 1 mg/kg qow may be considered for a dose increase to 3 mg/kg qow based on observed safety and tolerability and/or clinical response to treatment. Refer to Section 6.1 for additional details.
- After Week 12, subjects receiving a dose of 3 mg/kg qow may be considered for a dose adjustment to 3 mg/kg qw based on observed safety and tolerability and/or clinical response to treatment. Refer to Section 6.1 for additional details.
- In the event of poor tolerability at any time during the extension study, the dose may be reduced at the discretion of the Investigator. If a subject cannot tolerate the lowest starting dose (0.35 mg/kg qow) despite measures taken to manage any IARs, he/she will be discontinued from treatment.

Safety, tolerability, and efficacy assessments will be conducted at regular intervals throughout the extension study. In addition, blood samples will be obtained at selected timepoints for analysis of sebelipase alfa PK and biomarkers of sebelipase alfa PD activity. Blood samples will also be collected for an exploratory analysis of potential disease-related biomarkers in this patient population, and HRQOL measures will be assessed through subject questionnaires.

A follow-up visit will be conducted for all subjects at 30 (+7) days after the last dose of IMP.

Figure 1 Study Flow Diagram



*After Week 12, a dose adjustment from 1 mg/kg qow to 3 mg/kg qow, or from 3 mg/kg qow to 3 mg/kg qw, may be considered based on safety and tolerability and/or clinical response to treatment. A dose reduction is permitted at any time in the event of poor tolerability.

3.2 Rationale for Study Design

3.2.1 Dose Selection

The rationale for dose selection is described in Section 1.5.

3.2.2 Outcome Variable Selection

3.2.2.1 Safety

The study is designed to primarily evaluate the safety and tolerability of long-term treatment with sebelipase alfa, administered by weekly and biweekly IV infusions. As such, the main outcome variables in this study will assess safety and tolerability of sebelipase alfa in adult patients with liver dysfunction due to LAL Deficiency, and will include:

- *Changes from baseline in vital signs, physical examination findings, clinical laboratory tests, and 12-lead electrocardiogram (ECG) parameters.*
- *The incidence of AEs, SAEs, and IARs.*
- *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, a subgroup analysis will be conducted comparing safety endpoints in ADA-positive and ADA-negative subjects.*
- *A further characterization of ADAs, including inhibitory ADAs, may be performed as a separate pooled analysis across studies, and will be reported separately from this protocol.*

3.2.2.2 Efficacy

The biological effects of ERT for LAL Deficiency have not been fully established. However, any successful therapy for late onset LAL Deficiency must be able to mitigate the progressive liver deterioration that is a predominant clinical feature of this disorder. The following efficacy measures will be utilized to investigate the effect of sebelipase alfa on hepatic dysfunction in LAL Deficiency:

- *Liver and spleen volume by magnetic resonance imaging (MRI).*
- *Liver and spleen fat content by multi-echo gradient-echo MRI and ^{1}H magnetic resonance spectroscopy (MRS) (if available).*
- *Liver cholesteryl ester signature (as measured by ^{13}C MRS) in a subset of subjects receiving treatment at sites with access to this imaging technology.*
- *An assessment of hepatic histopathology will also be conducted in those subjects who agree to an optional liver biopsy.*

3.2.2.3 Pharmacodynamics

Based on a review of the literature, input from experts in the field, and insights from the nonclinical disease model (Section 1.3), the following biomarkers will also be investigated for their potential utility in describing pharmacodynamic responses to sebelipase alfa:

- *Serum transaminases*
- *Serum lipids*
- *Acute phase reactants (e.g., serum ferritin)*

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

Given the potential for ADAs to alter the PD effect of sebelipase alfa, a subgroup analysis will be conducted for the efficacy and PD endpoints comparing ADA-positive and ADA-negative subjects.

3.2.2.4 Health-Related Quality of Life (HRQOL) Outcomes

Based on the effects of ERT in other diseases, significant health benefits are anticipated with sebelipase alfa treatment. As there are currently no validated tool(s) to assess HRQOL in LAL Deficiency, HRQOL will be assessed using tools developed for other diseases. Changes in

scores for the 36-item Short Form (SF 36®) Health Survey, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale, and Chronic Liver Disease Questionnaire (CLDQ) will be determined. Positive treatment effects on HRQOL will provide supporting evidence of sebelipase alfa treatment benefit.

3.2.2.5 Pharmacokinetics

The preliminary clinical pharmacokinetics of seblipase alfa will be characterized in study LAL-CL01. Clinical pharmacokinetic data will continue to be collected in this extension study to permit a more robust assessment of sebelipase alfa pharmacokinetics. This will include the steady state pharmacokinetic profile of the qow dosing regimen and an assessment of the impact of ADAs (if any) on sebelipase alfa pharmacokinetics. PK parameters will include maximum observed serum concentration (C_{max}), minimum observed serum concentration (C_{min}), area under the serum concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), terminal elimination half-life ($T_{1/2}$), apparent serum clearance (CL), and steady state volume of distribution (V_{ss}).

3.2.3 Study Duration

Given the progressive and potentially life-threatening nature of untreated LAL Deficiency, and the low likelihood that beneficial effects of sebelipase alfa therapy will be maintained after discontinuation of treatment, subjects enrolled in this extension study will be given the option to continue to receive treatment under this protocol. Each patient may receive up to 5 years of treatment under this protocol.

4 Study Population

4.1 Target Population

The target population for this study is male and female subjects (≥ 18 years of age) with liver dysfunction due to LAL Deficiency who received treatment with sebelipase alfa in study LAL-CL01.

4.2 Number of Subjects

Up to 9 subjects will be enrolled in this study after successfully completing treatment in study LAL-CL01.

4.3 Inclusion Criteria

A subject must meet all of the following inclusion criteria to be eligible for this study:

1. Subject understands the full nature and purpose of the study, including possible risks and side effects, and is willing and able to comply with all study procedures and provide informed consent.
2. Subject received all 4 scheduled doses of sebelipase alfa in study LAL-CL01 with no life-threatening or unmanageable study drug toxicity.

3. Female subjects have a negative serum pregnancy test at screening, and are not breast-feeding.
4. Female subjects of childbearing potential are willing and able to use a highly effective and approved contraceptive method(s) from the date of informed consent until 30 days after last dose of IMP. A highly effective method of contraception is defined as fulfilling at least one of the following:

    a. Strict abstinence;
    b. Bilateral tubal ligation;
    c. Combined oral contraceptives (estrogens and progesterone), inserted, applied, implanted or injectable contraceptives on a stable dose for at least 1 month prior to the screening visit;
    d. Hormonal intra-uterine device (IUD) inserted at least 1 month prior to the screening visit;
    e. Vasectomized partner for at least 3 months prior to the screening visit;
    f. Condom with spermicide.

    Women may be considered of non-childbearing potential if they are surgically sterile (i.e., total hysterectomy or bilateral salpingo-oophorectomy) or post-menopausal (defined as a complete cessation of menstruation for at least one year after the age of 45 years).

4.4 Exclusion Criteria

A subject who meets any of the following exclusion criteria will be ineligible for this study:

1. Clinically significant concurrent disease, serious inter-current illness, concomitant medications, or other extenuating circumstances that, in the opinion of the Investigator, would either interfere with study participation or the interpretation of the effects of sebelipase alfa.
2. Clinically significant abnormal values on laboratory screening tests, other than liver function or lipid panel tests. Subjects with an abnormal laboratory value that is of borderline significance may be allowed to undergo repeat testing once within a 30-day period.

4.5 Concomitant Medications and Treatments

Reasonable efforts will be made to ascertain all concomitant medications and treatments (pharmacological and non-pharmacological) received by the subject from the last assessment in study LAL-CL01 until completion of the follow-up visit approximately 30 days after the last dose of IMP. Concomitant medications include prescription and over-the-counter medications, herbal medications, prophylactic and therapeutic vaccines, vitamins, and dietary supplements. Concomitant treatments include diagnostic, palliative, or interventional procedures (e.g., surgery, physical therapy).

All concomitant medications and treatments will be recorded in the electronic case report form (eCRF). The following information will be recorded: name of the medication (brand or generic) or therapy, reason for use, start date, stop date, dose and route of administration (if applicable), and frequency of administration.

Dose adjustments or discontinuation of lipid-lowering medications may be considered in consultation with the Sponsor for medical reasons including reconsideration of the need for lipid lowering therapy based on longer-term effects of sebelipase alfa on lipid levels.

Information about any major changes in diet (e.g., initiation or termination of a low-cholesterol diet) should be documented in the electronic case report form (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, subjects have the right to withdraw from the study at any time for any reason, without prejudice to further treatment.

The Investigator and Sponsor also have the right to withdraw subjects from the study at any time. Specific reasons for discontinuation may include but are not restricted to the following:

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

Unnecessary withdrawals should be avoided as an excessive rate of withdrawal can render the study uninterpretable.

4.6.2 Procedures for Discontinuation

All subjects who discontinue 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.

A subject will be considered early terminated if he/she discontinues treatment in the study prior to the Sponsor notifying the Investigators that the study will end. A subject will be considered discontinued due to an AE if the subject received any infusion or partial infusion of the IMP, but did not complete the study because of an AE, whether or not considered drug related.

Subjects who prematurely discontinue treatment in the study will also be asked to complete all discontinuation assessments prior to withdrawal, if possible. Post-study SAEs will be reported according to Section 7.4 for all subjects prematurely discontinuing treatment in the study.

When a subject fails to return for scheduled assessments, the following efforts should be made to contact him/her to determine a reason for the failure to return: three phone attempts, including the date and time, to be documented in the subject's chart. If there is no response to the phone calls, 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.

In the event that a subject dies, permission for an autopsy may be sought (through a separate informed consent form) from the subject's next of kin. Samples collected from these procedures will be used to further understand LAL Deficiency and the effect of ERT.

4.7 Subject Replacement Policy

Subjects who discontinue the study for any reason will not be replaced.

4.8 Subject Recruitment and Screening

Each Investigator (or designee) responsible for the clinical management of a subject in study LAL-CL01 will notify that subject of the potential to continue to receive treatment with sebelipase alfa in the current extension study.

Information about this study will be posted on the http://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ websites.

5 Schedule of Assessments and Study Procedures

The following Schedules of Assessments are presented in Appendix A:

- Screening through Week 24;
- Week 26 through Week 52;
- 52-week schedule of repeating assessments.

The Investigator may also perform an unscheduled visit at any time during the study at his/her discretion. Assessments performed at an unscheduled visit should be symptom directed, and will be recorded in the eCRF if the Investigator determines the subject may remain on IMP.

5.1 Study Assessments

5.1.1 Informed Consent

Subjects will be given a verbal explanation of the study and the procedures involved and will have all questions addressed. The subject must sign and date a consent form that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) before the screening procedures are initiated. All subjects 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 Sections 4.3 and 4.4 and background clinical information collected.

5.1.3 Medical History

Medical history will be collected for the time period between a subject's completion of the final follow-up visit in study LAL-CL01 and the subject's first screening assessment in the extension study.

5.1.4 Demographic Information

Demographic information will not be recorded during screening for the extension study, as this information was previously recorded during screening for study LAL-CL01.

5.1.5 Physical Examination

A general physical examination will be performed by the Investigator or qualified designee. A complete physical examination will be conducted 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 (HEENT), 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 recorded in the eCRF. Height will be measured at the screening examination, and weight will be measured at all physical examinations.

The physical examinations 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.
- **Arterial disease:** Right and left Posterior Tibialis and Dorsalis Pedis pulses will be assessed clinically.

5.1.6 Health-Related Quality of Life (HRQOL) Outcomes

Subjects will be instructed to complete the following HRQOL questionnaires at the timepoints specified in Appendix A:

- SF-36® (refer to Appendix B for details)
- FACIT-Fatigue (refer to Appendix C for details)
- CLDQ (refer to Appendix D for details)

Questionnaires should be administered in the same sequence at each study visit, and prior to any other study procedures being conducted at that visit. Detailed instructions on administration of HRQOL questionnaires are provided in the Study Operations Manual (SOM). The SF-36 was developed during the Medical Outcomes Study to measure generic physical and mental health concepts relevant across age, disease, and treatment groups. A total of 21 items within the 4 subscales of physical functioning, role-physical (i.e., role limitations due to physical problems), bodily pain, and general health compose the Physical Health summary measure and a total of 14 items within the 4 subscales of vitality, social functioning, role-emotional (i.e., role limitations due to emotional problems), and mental health compose the Mental Health summary measure

(one item, self-reported health transition, is not included in a summary measure). In addition to the scores for each subscale, higher-order summary scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS), are derived using standard scoring algorithms based on the correlation of each of the 8 subscales with physical and mental health, respectively. The SF-36 can be administered in approximately 5-10 minutes. In this study, the SF-36 version 2 will be self-administered. A sample questionnaire is provided in Appendix B.

The 13-item FACIT-Fatigue scale was developed to measure levels of fatigue in people living with a chronic disease. In this study, the FACIT-Fatigue scale version 4 will be self-administered. A sample questionnaire is provided in Appendix C.

The CLDQ is a disease-specific instrument designed to assess health-related quality of life in subjects with chronic liver disease. In this study, the CLDQ will be self-administered. A sample questionnaire is provided in Appendix D.

5.1.7 Abdominal MRI/MRS

Abdominal MRI and ^{1}H-MRS will be performed at the timepoints specified in Appendix A to quantify the organ volume and fat content of both the liver and spleen. Whenever feasible, additional abdominal imaging scans will be obtained at the same timepoints using ^{13}C-MRS to permit an exploratory analysis of the liver cholesteryl ester signature. All MR imaging and spectroscopy will be performed by an MR technician or other qualified individual.

Detailed instructions on image acquisition and analysis will be provided in the Imaging Manual.

5.1.8 Vital Signs

Vital signs, including pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature, will be measured at the timepoints specified in Appendix A. On dosing days, vital signs will be recorded pre-infusion and every 30 (±10) minutes during infusion and from 0 to 4 hours after completion of the infusion. Additional readings may be taken at the discretion of the Investigator in the event of an IAR. For each subject, the duration of post-infusion vital sign monitoring may be shortened to 2 hours after 6 months of treatment with no occurrence of IARs, and to 1 hour after 12 months of treatment with no occurrence of IARs, contingent upon approval by the Sponsor.

5.1.9 Electrocardiogram

12-lead ECGs will be obtained at the timepoints specified in Appendix A. In addition, unscheduled ECG(s) should be obtained in any subject exhibiting cardiovascular symptoms (e.g., palpitations, chest pain or tightness, tachypnea) or clinically significant changes in resting heart rate. ECGs will be reviewed by the Investigator, or designee, and any abnormalities will be specified as clinically significant (CS) or not clinically significant (NCS). If deemed to be clinically significant, these abnormalities must be recorded as Adverse Events in the electronic case report form (eCRF). In the event of any unexpected findings, subjects should be appropriately evaluated in accordance with local procedures.

5.1.10 Laboratory Assessments

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

The following clinical laboratory tests will be performed in this study:

CBC/Hematology:	White blood cell count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, neutrophil, lymphocytes, monocytes, eosinophils, basophils
Serum Chemistry:	Glucose, urea nitrogen, creatinine, sodium, potassium, chloride, calcium, magnesium, inorganic phosphorus, total protein, lactate dehydrogenase, uric acid
Liver Panel:	AST/SGOT, ALT/SGPT, alkaline phosphatase, GGT, albumin, bilirubin (direct, total)
Lipid Panel:	Total cholesterol, triglyceride, HDL, LDL
Coagulation:	PT (INR), aPTT

(if screening results are abnormal, repeat at subsequent visits until results return to normal)

Urinalysis:	Glucose, ketones, blood, pH, protein, nitrite, and leukocytes (microscopic examination will be done if urinalysis is positive for blood, protein (only if > 1+), nitrite, and/or leukocytes)
Anti-drug Antibody:	Anti-sebelipase alfa antibody
Acute Phase Reactants:	High sensitivity CRP and serum ferritin
Pregnancy:	Pregnancy testing will be performed for all female subjects. A serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed at all other scheduled visits. If a positive result is recorded at any time the procedure detailed in Section 7.2.5 should be followed.
Exploratory Biomarkers:	See Section 5.1.11

Subjects will fast for at least 9 hours (no more than 12 hours is required) and refrain from ingestion of alcohol for 24 hours prior to collection of blood samples for the lipid and liver panels. Subjects will only be permitted to drink water during this time. Whenever possible, lab samples for these visits should be drawn in the morning.

All laboratory tests will be performed by a central laboratory with the exception of PT (INR), aPTT, urinalysis, and urine pregnancy tests.

NOTE: Any subject who undergoes a dose modification, as described in Section 6.1, or changes in lipid-lowering therapies, as described in Section 4.5, will have the following additional laboratory monitoring schedule of selected analytes (all collected pre-dose):

- Prior to 1st 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 laboratory assessment, the standard laboratory assessment will supersede the additional laboratory monitoring.

Laboratory reports will be reviewed by the Investigator, or designee, and any abnormalities will be specified as 'CS' or 'NCS'. In the event of unexplained clinically significant abnormal laboratory test results, 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.

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

5.1.11 Exploratory Biomarkers

Blood samples for serum isolation (2 aliquots) will be obtained at the timepoints specified in the Schedule of Assessments (Appendix A) for exploratory biomarker analysis, as blood volume threshold permits. A urine sample will also be obtained at these same timepoints for exploratory biomarker analysis. These serum and urine samples will be used to identify baseline disease and dynamic markers that will help the Sponsor to better understand the pathogenesis of LAL Deficiency and 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. Samples will be stored by the Sponsor, or designee, in a secure and controlled environment until analysis.

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

Collection of samples, for storage as described above, will be subject to discretionary approval from each center's IRB/IEC and the subject's specific written consent. This section of the protocol only applies if approval for collection of these additional samples has been granted. If the IRB/IEC does not approve the collection of additional samples, this must be stated in the approval letter.

5.1.12 Pharmacokinetic Assessments

Blood samples for determination of sebelipase alfa serum concentrations will be collected during the study visits indicated in Appendix A. On each PK visit, samples will be collected at the following timepoints relative to infusion of IMP:

- Immediately pre-dose (within 30 minutes of dosing)

- At 10(±1), 15(±1), 20(±1), 40(±5), 60(±5) and 90(±5) minutes during the infusion and at the end of the infusion
- At 5(±1), 10(±1), 20(±1), 30(±5), 40(±5), 60(±5) and 120(±5) minutes after completion of the infusion

All PK samples will be taken from the arm opposite the infusion cannula. PK samples scheduled for the same nominal timepoint as a vital sign assessment will be taken prior to cuff inflation for the blood pressure measurement. All other PK samples 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.

5.1.13 Liver Biopsy

As is the case with many rare metabolic chronic liver diseases, there is paucity of available information regarding the histopathological features of LAL Deficiency. Long term dosing in the pre-clinical disease model is associated with marked improvement in liver pathology. At present there is no information on the long term effects of sebelipase alfa on liver pathology in humans. Although baseline assessment of liver histology was not performed, information on liver histology after longer term dosing may provide useful information about the effects of sebelipase alfa in patients with late onset LAL Deficiency.

Optional liver biopsies will be obtained for evaluation of hepatic histology between Week 52 and Week 104. If a subject had a liver biopsy within 3 years prior to screening as part of clinical standard of care and the results of that biopsy are available, these results should be recorded in the eCRF. In addition, slides or scanned images from these biopsies should be submitted for evaluation by a central pathologist, if possible. Biopsies will be performed only with consent from the subject 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 Treatments

6.1 Treatments Administered

Subjects will receive repeat IV infusions of sebelipase alfa, beginning at least 4 weeks after their last dose in study LAL-CL01 and continuing for approximately 5 years.

Each subject will initiate treatment at the same once-weekly dose of sebelipase alfa that he/she received during the fourth infusion in study LAL-CL01 (i.e., 0.35 mg/kg qw, 1 mg/kg qw, or 3 mg/kg qw), and will transition to a qow dosing regimen at Week 6 as described in Section 3.1.

At any time during the extension study, a subject may choose to transfer to a local medical center to receive their IMP infusions. Scheduled study assessments may also be performed at the local medical center provided that the center has access to the appropriate facilities and expertise.

6.1.1 Dose Escalation

After a minimum of 12 weeks of treatment in study LAL-CL04, a subject may be considered for a dose escalation, either from 1 mg/kg qow to 3 mg/kg qow or from 3 mg/kg qow to 3 mg/kg qw, if the subject exhibits an inadequate clinical response (see below). Prior to considering a dose increase, the subject should be evaluated for other potential causes of any clinical manifestations that are thought to reflect a suboptimal response. Other causes could include:

- missed study infusions,
- development of a new intercurrent illness, with the potential to confound the interpretation of biochemical efficacy measures, e.g.,
    - development of viral or autoimmune hepatitis or other alternative etiology of liver disease,
    - initiation of a potentially hepatotoxic concomitant medication in a subject with elevated ALT
    - initiation or modification of concomitant medication known to impact serum lipid levels.

Inadequate clinical response is defined as:

- Clinically important manifestations of LAL Deficiency on either clinical examination, laboratory assessment, liver biopsy or imaging which have either
    a. not improved from baseline,
    b. improved and plateaued but have not normalized,
    (Note: The definition of a plateauing of effect requires consideration of a minimum of 3 assessments.)
    c. failed to normalize within 12 months of initiation of treatment.

    Manifestations include but are not restricted to the following: elevated hepatic transaminases, abnormal liver function or coagulation tests, dyslipidemia, hepatomegaly, splenomegaly, significant histological abnormalities of the liver, or lymphadenopathy.

6.1.2 Dose Reduction

Subjects who do not tolerate their current dose level may receive a dose reduction to the next lowest dose level, i.e., 1 mg/kg qow or 0.35 mg/kg qow, at the discretion of the Investigator in consultation with the Sponsor and, where appropriate, the SC.

If a subject cannot tolerate a dose of 0.35 mg/kg qow, despite measures taken to manage any IARs, the subject will be discontinued from the study.

NOTE: Any subject who undergoes a dose modification, as described above, will have additional laboratory monitoring schedule of selected analytes, as detailed in Section 5.1.10.

6.1.3 Home Infusions

Subjects who are in the maintenance phase of the study may be eligible to receive infusions at home, if appropriate, where infrastructure, resources, and procedures are established and available, allowed by local regulations, and approved by the Investigator and Sponsor.

To be considered for home infusions, a subject must have been on a stable dose of sebelipase alfa for at least 12 months and must meet all of the following criteria during the prior 6 months:

- No occurrences of IARs that required medical intervention or management;
- No SAEs determined to be related to IMP.

Subjects who are approved for home infusions will continue to return to the clinical site (or local medical center) for scheduled study assessments.

6.2 Description of IMP

Sebelipase alfa is a recombinant human lysosomal acid lipase produced in transgenic G*allus*. Details of the nonclinical experience to date with sebelipase alfa, as well as IMP stability information, can be found in the current version of the Investigator Brochure (IB). Sebelipase alfa must be administered under close supervision of the Investigator, or designee.

Sebelipase alfa is provided in single dose 10 mL glass vials as a clear liquid. The solution (total 10.5 mL including 5% overfill) has an approximate concentration of 2 mg/mL.

Sebelipase alfa contains no preservatives and vials are single use only.

6.3 Method for Assigning Subjects to Treatment

No randomization schemes will be employed. All subjects will receive a starting dose equivalent to the dose of sebelipase alfa administered during their fourth infusion in study LAL-CL01. Subsequent modifications in dose and/or dosing frequency will be made in accordance with the protocol. See Section 3.1.

Subjects will retain the same subject number that they were assigned upon enrollment in study LAL-CL01. All IMP supply for the extension study will be linked to a unique active subject enrollment number.

6.4 Receipt, Storage, and Disposition of IMP

6.4.1 Receipt of IMP

Upon receipt of the IMP supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. 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 the Sponsor of any damaged or unusable IMP that was supplied to the Investigator's site.

6.4.2 Storage

Vials of IMP must be stored under controlled refrigerated conditions at 2 °C to 8 °C (36 °F to 46 °F). Vials should not be frozen and should be protected from light during storage.

The infusion bag containing sebelipase alfa should be prepared just prior to the start of infusion administration. Although the product in the infusion bag is stable at room temperature (23°C to 26°C) for up to 12 hours, the infusion should be initiated as soon as possible after preparation.

6.4.3 Disposition

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

Under no circumstances will the IMP be used other than as directed in the protocol.

6.5 Preparation and Administration of IMP

6.5.1 Preparation of IMP

The subject's most recent protocol-scheduled weight measurement, rounded to the nearest 1.0 kg, will be used for calculating sebelipase alfa volume for each infusion. If a subject has a change in body weight of more than 10% during an interval between protocol-scheduled weight assessments, the unscheduled weight measurement should be used.

Dose preparation and administration should be performed using sterile, non-pyrogenic disposable materials including, but not restricted to syringes, needles, transfer tubing, and stopcocks.

Sebelipase alfa is a protein and should be handled and mixed gently to prevent foaming, as this has been associated with post-translational modification to other therapeutic proteins.

Prior to administration, the admixture should be inspected visually for particulate matter and discoloration. The contents should NOT be heated using a microwave or other heat source.

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.

6.5.2 Administration of IMP

Sebelipase alfa should not be infused with other products in the same infusion tubing as the compatibility in solution with other products has not been evaluated. IMP infusions 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.

6.6 Blinding of IMP

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

6.7 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:

- Identity, lot number, or subject number
- Quantity of IMP destroyed
- Date of destruction
- Method of destruction
- 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 an IMP. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of the IMP, 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 eCRF.

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

Severity: The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 or higher. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the general guideline below. Detailed instructions on grading of events by MedDRA system organ class and lower level term are available online.

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily life (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily life (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE.

Note: Severity is distinct from seriousness. Thus, a Grade 4 AE is not by default an SAE. An AE will be reported as serious only if the Investigator judges the event to meet the definition of an SAE as provided below.

Causality: AEs will be assessed as not related, unlikely related, possibly related, or related to IMP. Table 1 provides general guidance on the assessment of causality. For data reporting purposes, AEs assessed as not related or unlikely related will be reported as unrelated to IMP, and AEs assessed as possibly related or related will be reported as related to IMP. Assessment of causality should be based on the Investigator's medical judgment and the observed symptoms associated with the event.

Table 1 Assessment of Causality

Relationship to IMP	Criteria for Judgment
Related	Reasonable temporal relationship of the clinical event to IMP 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 IMP 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 IMP 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 is or leads to any of the following:

- Death
- Immediately life threatening (An AE is considered "life threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- 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 above.

Planned hospitalizations to accommodate a study procedure are 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 AEs that do not meet any of the criteria for an SAE should be regarded as ***non-serious adverse events***.

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 provided 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 a clinically significant abnormality by the Investigator.

7.1.3 Infusion Associated Reactions

Infusion-associated reactions will be considered AEs of special interest. Any AE that occurs during the infusion or within 4 hours after the infusion and is assessed by the Investigator as at least possibly related to IMP 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 a hypersensitivity reaction related to the administration of IMP, the symptoms will be recorded as an AE(s) and designated as an IAR(s).

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 reactions. These supplies include, but are not restricted to, oxygen, acetaminophen, antihistamines (e.g. diphenhydramine, parenteral and oral [PO]), corticosteroids, epinephrine, and cardiopulmonary resuscitation devices.

General guidelines for classifying the severity of a reaction are provided below, and examples of mild, moderate, and severe IARs are provided in Appendix F.

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 does not show any respiratory symptoms and remains hemodynamically stable:

a) The infusion rate must be slowed (reduced to half the rate being given at the onset of the event, e.g. from 125 mL/hr to 62.5 mL/hr) and the infusion time extended. 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.
b) In accordance with institutional standard of care for the subject's age, treatment with an antihistamine should be considered.

In subjects who experience severe infusion reactions with clinically significant cardiovascular effects (hypotension defined as a decline approaching 20-30% of their pre-infusion value), respiratory effects (significant shortness of breath, stridor, laryngeal edema or swelling of tongue), or other effects:

a) The infusion should be discontinued.
b) The subject should be treated for an anaphylactic reaction with intravenous antihistamines, corticosteroids, and epinephrine, if necessary in accordance with institutional standard of care for the subject's age.
c) Dosing of the patient will be suspended until the Safety 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 to 3 hours after the IAR onset and another serum sample for tryptase and ADA at least 4 days after the IAR. Skin testing may be considered.

Additional details on the management of subjects with IARs are provided in Appendix F.

7.2 Handling of Safety Parameters

7.2.1 Serious Adverse Events (Immediately Reportable to the Sponsor)

All SAEs **and** IARs (serious and nonserious), must be reported to the Sponsor or designee immediately and no later than 24 hours after the Investigator's first knowledge of the event (expedited reporting).

The definition and reporting requirements are in accordance with ICH Guidance for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting (Topic E2, 1995).

7.2.2 Adverse Event Reporting Period

The study period during which AEs must be reported is defined as the period from the signature of written consent to the end of the study treatment follow-up. For this study, AEs will be reported from the date of written informed consent until completion of the follow-up visit at approximately 30 days after the last dose of IMP. 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

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

All AEs and SAEs will be followed until resolution, the condition stabilizes, or the Investigator and Sponsor agree that follow up is no longer necessary. SAEs that are ongoing after completion of the last scheduled visit should continue to be followed up to determine the final outcome. Non-serious AEs that are ongoing after completion of the last scheduled visit should be followed up until the event resolves or stabilizes, or for a minimum of 30 days after the last dose of IMP (whichever occurs first). Rules for AE/SAE follow-up apply to all subjects, including those withdrawn prematurely, to the extent allowed by the subject's consent.

The Investigator will ensure that AE/SAE follow-up includes further investigations consistent with appropriate medical management and subject consent to elucidate the nature and/or causality of the AE/SAE.

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 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 recorded in the eCRF.

7.2.5 Pregnancy

It is not known what effects sebelipase alfa has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients must agree to use a highly effective and approved contraceptive method(s) for the duration of the study and to continue to use for 30 days after the last dose of IMP. Highly effective methods of contraception are defined in Section 4.3. Regular pregnancy tests will be performed as defined in Section 5.1.10.

A female subject or a male subject with a female partner must immediately inform the Investigator if she becomes pregnant during the study. The female subject must not receive further sebelipase alfa infusions. Pregnancies occurring up to 90 days after the completion of the last infusion must be reported to the Investigator. The Investigator must report all pregnancies to the Sponsor within 24 hours of notification. The Investigator should counsel the subject discussing the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy.

7.3 Recording of Adverse Events

At each scheduled contact with the subject, the Investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AE should be recorded in the source document, and also in the appropriate AE module of the eCRF. All clearly related signs, symptoms, and abnormal diagnostic procedure results should be recorded in the source document, grouped under one diagnosis.

The date/time when the AE started and stopped, severity, seriousness, action taken with regard to the study drug, causality assessment, and outcome of the event will be recorded in the eCRF for each AE.

Any AEs/SAEs remaining unresolved after completion of the last scheduled visit (i.e., follow-up visit) should be recorded as ongoing in the eCRF. Ongoing AEs/SAEs should continue to be followed up for the period specified in Section 7.2.3, but without further recording in the eCRF. However, follow-up information on SAEs must be reported to the Sponsor as described in Section 7.4.

7.4 Reporting of Serious Adverse Events, Infusion Associated Reactions 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. At a minimum the events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others (see definitions, Section 7.1).

If the SAE/IAR report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Protocol number
- Investigator name and site number
- Subject number
- A description of the event
- Date of onset
- Time and amount of last IMP administration
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious (if an SAE)
- Investigator assessment of the relationship between the event and study treatment
- Severity

7.4.1 Investigator Reporting: Notifying the Sponsor

Any SAE, IAR or unanticipated problem posing risk of harm to subjects, must be reported to the Sponsor, or designee, within 24 hours of the event. To report such events, a SAE or IAR form must be completed by the Investigator and sent to the Sponsor within 24 hours. The Investigator will keep a copy of this SAE or IAR form on file at the study site. Report SAEs and IARs by phone, fax or email to:

For cases in North America	For cases in Europe
Phone: PPD Fax: PPD Email: PPD	Fax: PPD Email: PPD

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.

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 per their institutional policy. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

7.4.3 Sponsor Reporting: Notifying Regulatory Authorities

The Sponsor is required to report certain study events in an expedited manner to the FDA, the European Medicines Agency, 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:

Within 7 calendar days

Any study event that is:

associated with the use of the study drug, unexpected, fatal or life-threatening.

Within 15 calendar days

Any study event that is:

associated with the use of the study drug, unexpected, and serious, but not fatal or life-threatening.

7.4.4 Notifying Participating Investigators

It is the responsibility of the 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 Medical Monitoring

It is the responsibility of the Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of AEs as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 9). Medical monitoring will include a regular assessment of the number and type of SAEs.

7.5.1 Independent Safety Committee

Additional oversight of subject safety will be provided by an independent Safety Committee (SC) comprised of individuals with pertinent medical expertise who will serve in advisory capacity to the Sponsor to ensure that clinical trial participants are not exposed to unreasonable or unnecessary risks.

Collectively, the SC members will have methodological and clinical expertise relevant to the study design and population. SC membership will begin before the start of the clinical trial and is expected to last for its duration. Core members of the SC 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 SC. Neither members of the SC nor their immediate families will have a direct financial interest in the Sponsor or an interest that is dependent on the outcome of the trial. To be considered for SC membership, all candidates must disclose all actual or potential conflicts of interest, including any financial interests in, or research activity on a competing product. SC members will be compensated at an appropriate market rate for time spent reviewing, discussing, and attending the meetings. The Sponsor will also reimburse SC members for any out-of-pocket travel expenses required for attendance at the meetings. Aside from the above, SC members will receive no additional compensation for their membership on the committee.

The SC will perform periodic reviews of aggregate safety data from study LAL-CL04 on at least a biannual basis (i.e., every 6 months) from the date of enrollment of the first subject until completion of dosing for all subjects in the study. Ad-hoc reviews of safety data will also be performed by the SC on an as needed basis in the event of emerging safety signals of clinical concern in one or more subjects, including potential safety risks that meet the pre-defined stopping rules for study treatment (see Section 7.6). Following each periodic and ad-hoc review of safety data, the SC will indicate whether dosing of sebelipase alfa may continue (or be resumed) for all subjects or a subset of subjects in the study.

The composition and activities of the SC will be outlined in the SC Charter, which will be ratified during the initial meeting of the SC and prior to commencement of dosing in the extension study.

7.6 Dose Modification and Stopping Rules

The Sponsor or independent SC (see Section 7.5.1) may suspend dosing at any time for an individual subject, a cohort of subjects receiving a given dose, or all subjects enrolled in the study due to poor tolerance or potential safety risks.

Possible reasons for suspending dosing in an individual subject include SAE(s), Grade 3 (severe) or higher IAR(s). Specific dose modification and stopping rules for study LAL-CL04 are provided in Appendix E.

8 Statistical Plan

The Sponsor 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 report.

Prior to locking the database, all data editing will be complete and decisions regarding the evaluability of all subject data for inclusion in the statistical analysis will be made. The rationale for excluding any data from the statistical analyses will be prospectively defined, and classification of all or part of a subject's data as non-evaluable will be completed and documented before the entire database is locked.

A separate Statistical Analysis Plan (SAP) will be finalized prior to locking the database. The SAP will document any changes from the analyses as specified in the protocol and its amendments. The final clinical study report will document any changes from the SAP. The analysis will be performed using the SAS® statistical software system. If appropriate, other commercially available software may be utilized for graphical presentations.

8.1 General Considerations

All data collected in this study will be provided in subject data listings sorted by subject number. Data collected in this study will be reported using summary tables and graphs as appropriate to the data. Descriptive summary statistics (n, mean, median, standard deviation, minimum and maximum) will be calculated for the continuous variables and shift tables and/or frequencies and percentages will be produced for the categorical variables. As noted, 95% two-sided confidence interval (CI) will be calculated around the estimates based on the exact binomial distribution for categorical endpoints and the t-distribution for continuous endpoints. Effect of anti-drug antibodies will be examined for efficacy, safety, and PK endpoints. Numbers permitting, analyses may be conducted in other subgroups of interest.

Baseline will be defined as the last measurement prior to the first infusion of sebelipase alfa in study LAL-CL04. As appropriate, a CL01 Study Baseline defined as the last measurement prior to the first infusion in study LAL-CL01, may also be used for selected study endpoints. For endpoints that are computed as changes from baseline, a comparison between change from Baseline and change from the CL01 Study Baseline will be performed, as appropriate.

Unless otherwise noted, all tabulations will present data overall and by dose and dosing frequency (qw, qow) – i.e., dosing regimen.

8.2 Determination of Sample Size

Sample size is based on the estimated total enrollment in study LAL-CL01, and assumes that all subjects treated in that study will be eligible and willing to participate in this extension study.

8.3 Analysis Sets

Full Analysis Set (FAS): This analysis set consists of all subjects who received at least one complete infusion of IMP in the extension study, and have at least one post-treatment measurement in the extension study. This analysis set will be used for analysis of efficacy, pharmacodynamic, and patient health outcomes data.

Safety Analysis Set: This analysis set consists of all subjects who received any amount of IMP in the extension study, and will be used for all safety analyses.

Per-Protocol Analysis Set: This analysis set will consist of all subjects in the FAS who have no protocol violations that could potentially confound the interpretation of serum transaminase or lipid results. The list of subjects to be included in the per-protocol analysis set will be determined before database lock. If all patients in the FAS are also in the per-protocol analysis set, then separate analyses for the per-protocol analysis set will not be performed.

PK Analysis Set: This analysis set will include all available sebelipase alfa serum concentration data for subjects who receive at least one complete infusion of IMP in the extension study, and will be used for all PK analyses.

8.4 Demographics and Baseline Characteristics

Demographic and baseline data (e.g., medical history, disease history) collected during study LAL-CL01 will be listed and tabulated overall for those subjects who enroll in the extension study. Dose of sebelipase alfa administered at the start of LAL-CL04 will be listed and summarized.

8.5 Subject Accountability

A subject data listing, sorted by subject number, will be prepared and will include dose of sebelipase alfa first administered on the LAL-CL04 study, age, gender, date of consent, date of first dose of sebelipase alfa under LAL-CL01, date of first dose of study drug under LAL-CL04, date of completion or premature discontinuation from the study and reason for discontinuation if the subject discontinues prematurely. Data from all subjects who are enrolled in the study will be included in the summary of subject accountability. The frequency and percentage of subjects who are enrolled in the study, discontinued from the study, and completed 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 overall, by dosing regimen, by dose across all frequencies and by frequency (qw or qow). Descriptive summaries of rate of infusion, volume, and number (percent) of subjects who receive all study infusions 'per protocol' (i.e., subjects without missed infusions or infusion interruptions or rate changes) will also be provided.

8.7 Safety Analysis

Safety will be analyzed in Safety Analysis Set. As appropriate, the effect of dosing regimen and/or treatment duration on safety endpoints will also be explored.

8.7.1 Adverse Events

All AEs, SAEs, and IARs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented in by-subject listings that will include dosing regimen prior to the event, time of onset, severity, causality, actions taken regarding treatment, and outcome. The number and percent of subjects experiencing any AE, any SAE, any IAR, any related AE, any related SAE, and discontinuations due to an AE will be tabulated.

Treatment-emergent AEs, SAEs, and IARs will be tabulated (frequencies and percentages) by Preferred Term (PT) within System Organ Class (SOC), for all events and for events by severity and causality. If a subject experiences more than one occurrence of the same AE, and these differ in severity and/or causality, the AE will be tabulated according to the greatest severity and nearest relationship to IMP. As appropriate, additional listings and summary statistics 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.

8.7.2 Clinical Laboratory Tests

Observed measurements and changes from baseline to study timepoints in clinical chemistry, hematology, and urinalysis will be summarized. All laboratory values will be classified as normal, above normal, or below normal based on normal ranges provided by the laboratory. All laboratory values, and all clinical significant abnormal laboratory values, will be presented in by-subject listings. Frequencies of abnormal values relative to the laboratory normal range and clinically significant abnormal values will also be summarized.

Percentage of subjects who become ADA positive, time to ADA positivity and time to peak titer, and median and peak immunoglobulin G (IgG) antibody titer will be summarized. IgG antibody titer values will be tabulated using summary statistics at each study visit. All data will be presented in by-subject listings. Descriptive summaries may also be provided as appropriate.

8.7.3 Other Safety Data

Observed measurements and changes from baseline to study timepoints in vital signs (blood pressure, heart rate, respiratory rate, and temperature), and 12-lead ECG parameters will be summarized. Listings of abnormal findings/values for physical examinations, vital signs, and ECGs will be presented, as appropriate.

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

8.8 Efficacy, Pharmacodynamic, and Patient Health-Related Quality of Life (HRQOL) Outcomes Analyses

Data will be presented for subjects in the Full Analysis Set. All data will be presented by study visit in subject data listings. Observed measurements and changes or percent changes from baseline to study timepoints in liver and spleen volumes and liver and spleen fat content, liver cholesteryl ester signature, serum transaminases, plasma lipids, and acute phase reactants (e.g., serum ferritin) will be summarized overall and by dosing regimen. The percentage of subjects with abnormal transaminases at each timepoint will also be summarized overall and by dosing regimen. Scores and changes from baseline to study timepoints for the SF-36®, FACIT-Fatigue, and CLDQ will be summarized.

8.9 Pharmacokinetics

C_{max} and C_{min} will be recorded from direct observation, and other PK parameters will be derived by non-compartmental analysis. Pharmacokinetics will be characterized using the PK Analysis Set. All PK parameters will be summarized by dosing by dosing regimen.

8.10 Other Statistical Issues

8.10.1 Significance Levels

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

8.11 Missing or Invalid Data

All data will be analyzed as they were collected in the database. Missing data will not be imputed using statistical methods.

8.12 Interim Analysis

Summaries of interim data will be created to support a regulatory filing(s). Safety, efficacy, PK, and/or PD data available by a designated cutoff date prior to the regulatory filing(s) will be presented in subject data listings and reported using summary tables and graphs, as appropriate to the data. No inferential statistical analyses are planned.

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 study necessary for the reconstruction and evaluation of the study. 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 indicate 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 IMP. 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 bodies, 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.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their 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 or legally acceptable surrogate, 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

An interim clinical study report (CSR) will be produced to support regulatory filings. A final CSR to summarize the long-term efficacy, safety, and PK parameters will be produced after study completion.

A coordinating Investigator will be designated to review and sign the completed clinical study reports. The process for identifying the coordinating Investigator will include evaluation of relevant criteria such as:

1. Member of the external Scientific Advisory Board
2. Contribution to study development and/or implementation
3. Demonstrated understanding of, and adherence to, this protocol

All information concerning study medication and the Sponsor operations, such as patent applications, formula, manufacturing processes, basic scientific data, or formulation information, supplied by the Sponsor and not previously published, is considered confidential. The Investigator agrees to use this information only in accomplishing this study and will not use it for their purposes without the prior written consent of the Sponsor.

All information developed in this clinical study is the sole and exclusive property of the Sponsor. This information will be used by the Sponsor and its affiliates in connection with the development of the study medication and, therefore, may be disclosed by the Sponsor, as required, to other clinical Investigators, other pharmaceutical companies, and other regulatory authorities, and to other governmental agencies. In order to allow for the use of the information derived from clinical studies, the Investigator agrees to provide the Sponsor with complete test results and all data developed in this study. All test results, data, and information provided to the Sponsor must be complete and accurate.

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: Schedules of Assessments

Schedule of Assessments: Screening through Week 24*

Assessments	Screening	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24
	Day -14 to Day -1	±2 days	±2 days	±2 days	±2 days	±4 days	±4 days	±4 days	±4 days	±4 days	±4 days	±4 days	±4 days	±4 days	±4 days
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Medical History	X														
Health-Related Quality of Life[1]	X								X						X
12-lead ECG	X								X[P]						
Physical Examination[2]	X				X[P]				X[P]						
Pregnancy Test[3]	X[8]				X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
Clinical Laboratory Tests[4]	X[8]				X[P]				X[P]						X[P]
Liver and Lipid Panels	X[8]	X[P]			X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
Coagulation Tests[4]	X[8]	X[P]			X[P]				X[P]						X[P]
Anti sebelipase alfa Antibody	X				X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
Serum and Urine Exploratory Biomarker Collection	X				X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
PK Profile[5]															X
Abdominal MRI/MRS[6]	X							X							X
Vital Signs[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sebelipase alfa Infusion		X	X	X	X	X	X	X	X	X[9]	X	X	X	X	X
Adverse Events	Continuous														
Concomitant Meds/Therapies	Continuous														

* All visits will be calculated from Week 1; consecutive infusions must be administered at least 7 days apart.

[P] Pre-dose

[1] Includes SF-36, FACIT-Fatigue, and CLDQ.

[2] Physical examination will include measurement of weight (height only at screening), assessment of liver and spleen size, lymphadenopathy and arterial disease.

[3] Serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed at all visits thereafter.

[4] Clinical laboratory tests include CBC/hematology, serum chemistry, acute phase reactants and urinalysis. Coagulation tests will be performed at screening and, if results are abnormal, tests will be repeated until normal.

[5] Pre-dose, 10, 15, 20, 40, 60, and 90 minutes during the infusion, at the end of the infusion, and at 5, 10, 20, 30, 40, 60 and 120 minutes after the end of infusion.

[6] An MRI and ^{1}H-MRS (if available) will be performed for all subjects. ^{13}C-MRS will also be performed for subjects enrolled at sites with access to this imaging modality.

[7] Vital signs will be measured pre-dose, every 30 (±10) minutes during the infusion, and from 0 to 4 hours post-infusion.

[8] Results must be reviewed prior to the start of dosing in the extension study.

[9] After Week 12, a dose adjustment from 1 mg kg^{-1} qow to 3 mg kg^{-1} qow, or from 3 mg kg^{-1} qow to 3 mg kg^{-1} qw, may be considered based on safety and tolerability and/or clinical response to treatment. All such decisions will be made jointly by the Investigator and Sponsor.

Schedule of Assessments: Week 25 through Week 52*

Assessments	Week 25[8] ±1 days	Week 26[8] ±7 days	Week 28[8] ±7 days	Week 30 ±7 days	Week 32 ±7 days	Week 34 ±7 days	Week 36 ±7 days	Week 38 ±7 days	Week 40 ±7 days	Week 42 ±7 days	Week 44 ±7 days	Week 46 ±7 days	Week 48 ±7 days	Week 50 ±7 days	Week 52 ±7 days
Health-Related Quality of Life [1]								X							X
12-lead ECG								X^P							X^P
Physical Examination[2]								X^P							X^P
Urine Pregnancy Test			X^P		X^P		X^P		X^P		X^P		X^P		X^P
Clinical Laboratory Tests[3]								X^P							X^P
Liver and Lipid Panels[4]	X				X^P			X^P							X^P
Coagulation Tests[3]								X^P							X^P
Anti sebelipase alfa Antibody					X^P			X^P							X^P
Serum and Urine Exploratory Biomarker Collection								X^P							X^P
PK Profile[5]															X
Abdominal MRI/MRS[6]															X
Vital Signs[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sebelipase Dosing		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	Continuous														
Concomitant Meds/Therapies	Continuous														

* All visits will be calculated from Week 1; consecutive infusions must be administered at least 7 days apart.

P Pre-dose

1 Includes SF-36, FACIT-Fatigue and CLDQ

2 Physical examination will include measurement of weight, assessment of liver and spleen size, lymphadenopathy and arterial disease.

3 Clinical laboratory tests include CBC/hematology, serum chemistry, acute phase reactants and urinalysis. Coagulation tests will be performed, only if abnormal at previous visit.

4 In subjects with prior abnormal lipid results, more frequent monitoring of lipid levels may be performed; the need for such monitoring will be jointly assessed by the Investigator and Sponsor

5 Pre-dose, 10, 15, 20, 40, 60, and 90 minutes during the infusion, at the end of the infusion, and at 5, 10, 20, 30, 40, 60 and 120 minutes after the end of infusion.

6 An MRI and ^{1}H-MRS (if available) will be performed for all subjects. ^{13}C-MRS will also be performed for subjects enrolled at sites with access to this imaging modality.

7 Vital signs will be measured pre-dose, every 30 (±10) minutes during the infusion, and from 0 to 4 hours post-infusion. Post-infusion observation period may be shortened to 2 hours after 6 months of treatment with no occurrence of IARs, and to 1 hour after 12 months of treatment with no occurrence of IARs, contingent upon approval by the Sponsor.

8 This visit should occur 7 days after the Week 24 infusion. If scheduling does not permit, the visit may instead be scheduled 7 days after either the Week 26 or Week 28 infusion.

Repeating 52-Week Schedule of Assessments: Week 54 through Study Completion*¥

Year 2 Year 3 Year 4 Year 5	Wk 54 106 158 210	Wk 56 108 160 212	Wk 58 110 162 214	Wk 60 112 164 216	Wk 62 114 166 218	Wk 64 116 168 220	Wk 66 118 170 222	Wk 68 120 172 224	Wk 70 122 174 226	Wk 72 124 176 228	Wk 74 126 178 230	Wk 76 128 180 232	Wk 78 130 182 234	Wk 80 132 184 236	Wk 82 134 186 238	Wk 84 136 188 240	Wk 86 138 190 242	Wk 88 140 192 244	Wk 90 142 194 246	Wk 92 144 196 248	Wk 94 146 198 250	Wk 96 148 200 252	Wk 98 150 202 254	Wk 100 152 204 256	Wk 102 154 206 258	Wk 104 156 208/ 260 End of Study[8,9]
Assessments	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
Health-Related Quality of Life[1]													X														X
12-lead ECG													X^P														X^P
Physical Examination[2]							X^P						X^P						X^P								X^P
Urine Pregnancy Test		X^P		X^P		X^P		X^P		X^P		X^P		X^P		X^P		X^P		X^P		X^P		X^P		X^P	X^P
Clinical Laboratory Tests[3]							X^P						X^P						X^P								X^P
Liver and Lipid Panels							X^P						X^P						X^P								X^P
Coagulation Tests[3]							X^P						X^P						X^P								X^P
Anti sebelipase alfa Antibody							X^P						X^P						X^P								X^P
Serum and Urine Exploratory Biomarker Collection							X^P						X^P						X^P								X^P
PK Profile[4]																											X^7
Abdominal MRI/MRS[5]																											X
Liver Biopsy[6]	X^6																										
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X^8
Sebelipase alfa Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X^8
Adverse Events	Continuous																										
Concomitant Meds/Therapies	Continuous																										

* All visits will be calculated from Week 1; consecutive infusions must be administered at least 7 days apart
P Pre-dose
¥ Weeks will be numbered chronologically in the repeating 52-week modules (i.e., beginning in year 3, Week 106, 108, 110, etc).
1 Includes SF-36, FACIT-Fatigue, and CLDQ.
2 Physical examination will include measurement of weight, assessment of liver and spleen size, lymphadenopathy, and arterial disease.

[3] Clinical laboratory tests include CBC/hematology, serum chemistry, acute phase reactants and urinalysis. Coagulation tests will be performed, only if abnormal at previous visit.

[4] Performed only at Week 104 of the first 52-week period (i.e., non-repeating). Pre-dose, 10, 15, 20, 40, 60, and 90 minutes during the infusion, at the end of the infusion and at 5, 10, 20, 30, 40, 60 and 120 minutes after the end of infusion.

[5] An MRI and ^{1}H-MRS (if available) will be performed for all subjects. ^{13}C-MRS will also be performed for subjects enrolled at sites with access to this imaging modality.

[6] Liver biopsy can be scheduled at any time between Week 52 and 104.

[7] Vital signs will be measured pre-dose, every 30 (±10) minutes during the infusion, and from 0 to 4 hours post-infusion. Post-infusion observation period may be shortened to 2 hours after 6 months of treatment with no occurrence of IARs, and to 1 hour after 12 months of treatment with no occurrence of IARs, contingent upon approval by the Sponsor.

[8] All subjects will have an End of Study visit 30 (+7) days after last dose of IMP. All Week 104 procedures, excepting dosing, serial vital signs and PK assessments, will be performed.

[9] Subjects prematurely discontinuing treatment in the study will have an End of Study visit.

Appendix B: SF-36® v2 Health Survey

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
i Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

THANK YOU FOR COMPLETING THESE QUESTIONS!

Appendix C: FACIT Fatigue Scale

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix D: The Chronic Liver Disease Questionnaire (CLDQ)

The Chronic Liver Disease Questionnaire (CLDQ)

This questionnaire is designed to find out how you have been feeling during the last two weeks. You will be asked about your symptoms related to your liver disease, how you have been affected in doing activities, and how your mood has been. Please complete all of the questions and select only **one** response for each question.

1. How much of the time during the last two weeks have you been troubled by a feeling of abdominal bloating?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

2. How much of the time have you been tired or fatigued during the last two weeks?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

3. How much of the time during the last 2 weeks have you experienced bodily pain?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

4. How often during the last two weeks have you felt sleepy during the day?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

Revised December 28, 1998

5. How much of the time during the last two weeks have you experienced abdominal pain?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

6. How much of the time during the last two weeks has shortness of breath been a problem for you in your daily activities?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

7. How much of the time during the last two weeks have you not been able to eat as much as you would like?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

8. How much of the time in the last two weeks have you been bothered by having decreased strength?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

9. How often during last 2 weeks have you had trouble lifting or carrying heavy objects?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

Revised December 28, 1998

10. How often during the last two weeks have you felt anxious?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

11. How often during the last 2 weeks have you felt a decreased level of energy?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

12. How much of the time during the last two weeks have you felt unhappy?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

13. How often during the last two weeks have you felt drowsy?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

14. How much of the time during the last two weeks have you been bothered by a limitation of your diet?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

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15. How often during the last two weeks have you been irritable?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

16. How much of the time during the last two weeks have you had difficulty sleeping at night?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

17. How much of the time during the last two weeks have you been troubled by a feeling of abdominal discomfort?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

18. How much of the time during the last two weeks have you been worried about the impact your liver disease has on your family?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

19. How much of the time during the last two weeks have you had mood swings?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

Revised December 28, 1998

20. How much of the time during the last two weeks have you been unable to fall asleep at night?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

21. How often during the last two weeks have you had muscle cramps?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

22. How much of the time during the last two weeks have you been worried that your symptoms will develop into major problems?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

23. How much of the time during the last two weeks have you had a dry mouth?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

24. How much of the time during the last two weeks have you felt depressed?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

Revised December 28, 1998

25. How much of the time during the last two weeks have you been worried about your condition getting worse?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

26. How much of the time during the last two weeks have you had problems concentrating?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

27. How much of the time have you been troubled by itching during the last two weeks?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

28. How much of the time during the last two weeks have you been worried about never feeling any better?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

29. How much of the time during the last two weeks have you been concerned about the availability of a liver if you need a liver transplant?

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

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Appendix E: Dose Modification and Stopping Rules for Study LAL-CL04

In the absence of an approved grading scale that can be applied to specific patient populations, this protocol will apply the National Cancer Institute Common Toxicity Classification of Adverse Events (NCI CTCAE), version 4.0 or higher. (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

The following dose modification and stopping rules apply to the decision to pause dosing in individual subjects:

For IARs (refer to the definition in Section 7.1.3), the following stopping rules will apply:

- Subjects who develop a Grade 3 (severe) or higher IAR, defined as significant hypo/hypertension, increased temperature and rigors, significant tachypnea with wheezing and/or stridor, **OR** are IgE or skin test positive must stop treatment until their information is reviewed by the SC. Dosing with alterations to the dose or infusion regimen (e.g., pretreatment and/or slowing the rate of infusion) may resume once the SC and the Sponsor approve. Confirmation may also be sought from regulatory authorities prior to resuming dosing. Subjects with Grade 1 (mild) and/or Grade 2 (moderate) IARs can continue in the study. The SC and/or Sponsor may recommend alterations to the infusion regimen (e.g., pretreatment and/or slowing the rate of infusion).

Appendix F: Diagnosis and Management of Infusion Associated Reactions

General guidelines for the diagnosis and management of 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	Management	Post-IAR Activities
Mild IAR (Grade 1)		
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 antihistamine • Decrease infusion rate by a further 25% if symptoms persist • If symptoms continue despite rate reduction stop infusion	• Pre-treat with oral antihistamine and antipyretic prior to (approximately 1.5 hrs) the next infusion
Moderate IAR (Grade 2)*		
• Hyperemia (flushing) • Chest discomfort • Itching and/or raised urticarial rash • Severe headache • Gastro intestinal symptoms, vomiting, diarrhea, abdominal cramping.	• Stop infusion • Give antihistamine IV and consider PO or IV corticosteroids • Consider giving a beta-adrenergic inhaler treatment, if appropriate	• *Collect sample for serum tryptase within 1-2 hours of event • *Obtain serum sample for determination of IgE status at least 3 days after last dose, unless a pre-infusion ADA serum sample was collected • Pre-treat with oral antihistamine and antipyretic prior to (approximately 1.5 hrs) the next infusion • Slowly up-titrate the infusion rate during the subsequent infusion o 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 15 min, then increase to full rate (50 ml/hr) for the remainder of the infusion ***If suspected to be immune mediated IAR**

Symptoms	Management	Post-IAR Activities
Severe, Life-threatening, or Anaphylactic IAR (Grade 3 or higher)		
• Hypo/hypertension (> 40 mmHg SBP) • Respiratory symptoms. Shortness of breath, wheezing, laryngeal edema. • Cardiac arrhythmias • Anaphylactic/Anaphylactoid shock with hypotension and circulatory collapse.	• Stop Infusion • Give oxygen, if available Give epinephrine IM • Give antihistamine IV and consider PO or IV corticosteroids • Consider giving a beta-adrenergic inhaler treatment, if appropriate	• Collect sample for serum tryptase within 1-2 hours of event • Obtain serum sample for determination of IgE status at least 3 days after last dose, unless a pre-infusion ADA serum sample was collected • Pre-treat with oral antihistamine, antipyretic and corticosteroids prior to (approximately 1.5 hrs) the next infusion • Slowly up-titrate the infusion rate during the subsequent infusion o 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

If a subject's serum is IgE+ (positive), the subject may continue in the study after the review of his/her data by the Safety Committee and agreement with the Investigator. If a subject's serum is IgE- (negative) and the event was suspected to be immune mediated and was moderate to severe in nature, the subject will be skin tested (according to the Skin Testing guidelines provided in the Study Operations Manual) prior to receiving the next infusion. If results of skin test are negative, the subject may continue in the study. If results of skin test are positive, the subject may only continue in the study after the review of his/her data by the Safety Committee and agreement with the Investigator.