

**A MULTICENTER, OPEN-LABEL STUDY OF
SEBELIPASE ALFA IN PATIENTS WITH LYSOSOMAL
ACID LIPASE DEFICIENCY**

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Protocol Number: LAL-CL06

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Amendment: 2.0

Product: Sebelipase alfa

IND No.: 108460

EudraCT No.: 2011-004287-30

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

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PROTOCOL SIGNATURE PAGE

Protocol Title: A MULTICENTER, OPEN-LABEL STUDY OF SEBELIPASE ALFA IN PATIENTS WITH LYSOSOMAL ACID LIPASE DEFICIENCY

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PPD



Alexion Pharmaceuticals, Inc.

7 DEC 2015

Date

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 enrollment 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 (IRBs/IECs) review and approval are met. I will provide the Sponsor with any material that 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 subjects.

Print Name

Institution

Signature

Date

Protocol Synopsis

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| Title | A MULTICENTER, OPEN-LABEL STUDY OF SEBELIPASE ALFA IN PATIENTS WITH LYSOSOMAL ACID LIPASE DEFICIENCY |
| Protocol Number | LAL-CL06 |
| Methodology | <p>This is an open-label, multicenter study to evaluate the safety and efficacy of SBC-102 (United States adopted name: sebelipase alfa) in a broad population of subjects with Lysosomal Acid Lipase Deficiency (LAL Deficiency). Such subjects may have been excluded from enrollment in other studies of LAL Deficiency because of age, disease progression, previous treatment by hematopoietic stem cell or liver transplantation, less common disease manifestations, or disease characteristics that would preclude participation in a placebo-controlled study.</p> <p>The study will consist of a screening period of up to 45 days, a treatment period of up to 96 weeks, an expanded treatment period of a maximum of up to 48 weeks, and a follow-up phone call at least 4 weeks after the last dose of sebelipase alfa. All subjects will initiate treatment with sebelipase alfa at a dose of 1 mg·kg⁻¹ through intravenous administration every other week (qow). Dose escalations up to 3 mg·kg⁻¹ once weekly (qw) will be allowed if the subject meets dose escalation criteria (e.g., significant clinical progression) after a minimum time on the previous dose.</p> <p>All infusions will initially be administered at a study center. After Week 48 of the treatment period, home infusions may be permitted for subjects who have had no moderate-to-severe hypersensitivity reactions requiring medical intervention/management and no serious adverse events (SAEs) related to study drug within the prior 24 weeks, contingent on Sponsor approval, local regulations, and the availability of established regional infrastructure and resources for home infusions.</p> <p>Safety and efficacy assessments will be performed at regular intervals throughout the study. Exploratory safety and efficacy assessments may be performed for subjects who exhibit specific atypical manifestations of LAL Deficiency at the discretion of the Investigator in consultation with the Sponsor (e.g., pulmonary function tests for an individual presenting with significant pulmonary involvement, etc). In addition, the PK of sebelipase alfa will be assessed for the pediatric population (where local regulations permit), those with severe hepatic dysfunction, and those who have had a previous liver or hematopoietic stem cell transplant.</p> <p>Effects on health-related quality of life (HRQOL) will be characterized for all subjects at selected time points. Blood samples will also be collected for an additional analysis of potential disease-related biomarkers in this population.</p> <p>An independent program-level safety committee appointed by the Sponsor will provide additional oversight of subject safety in this study through periodic and ad hoc reviews of safety data.</p> |
| Study Duration | <p>Screening will occur within 45 days. Each subject will receive sebelipase alfa for at least 52 weeks and up to 96 weeks in the treatment period. Subjects who complete the 96-week treatment period may continue to receive sebelipase alfa in the expanded treatment period for an additional duration of up to 48 weeks, unless discontinued sooner after sebelipase alfa is registered and available as a long-term enzyme replacement therapy for the treatment of patients with LAL Deficiency in the region where the subject resides and/or is receiving treatment (in accordance with country-specific requirements).</p> |

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| | The follow-up period will be at least 4 weeks from the last infusion of sebelipase alfa. |
| Study Center(s) | Approximately 20 study centers will participate in this study. |
| Study Objectives | <p>The primary objective of this study is to evaluate the safety of sebelipase alfa in a more broad population of subjects with LAL Deficiency than have been previously studied.</p> <p>The secondary objectives of this study are (1) to evaluate effects of sebelipase alfa relative to Baseline assessment of lipid metabolism and liver function (including histopathology); (2) to evaluate the effects of sebelipase alfa on additional clinical parameters of LAL Deficiency including those not previously well characterized in the literature, and (3) to evaluate the effects of sebelipase alfa on growth parameters in pediatric subjects presenting with evidence of growth delay, (4) to evaluate the immunogenicity of sebelipase alfa.</p> <p>The exploratory objectives of this study are (1) to further characterize the PK of sebelipase alfa in pediatric subjects, subjects with severe hepatic dysfunction, and those who have had a previous liver or hematopoietic stem cell transplants; and (2) to evaluate the effect of sebelipase alfa on HRQOL assessments.</p> |
| Number of Subjects | Approximately 30 subjects; including at least 4 children from 2-4 years of age at study initiation. |
| Main Inclusion and Exclusion Criteria | <p>A subject must meet all of the following inclusion criteria to be eligible for this study:</p> <ol style="list-style-type: none"> 1. Subject will be > 8 months of age at the time of dosing. 2. Subject or subject's parent or legal guardian (if applicable) consents to participation in the study. If the subject is of minor age, he/she is willing to provide assent where required per local regulations, and if deemed able to do so. 3. Confirmation of LAL Deficiency diagnosis as determined by the central lab; a subject who received a liver or hematopoietic stem cell transplant who does not show evidence of LAL enzyme deficiency by DBS due to the effects of transplantation must have either: <ol style="list-style-type: none"> a. Molecular genetic testing which confirms mutations in both alleles of the <i>LIPA</i> gene (<i>Note: in a highly suggestive case of LAL Deficiency where only 1 mutation is identified, subjects may be included based on a fibroblast enzyme activity assay</i>); OR b. Appropriately documented (based on consultation with the Sponsor) historical result of an enzyme test prior to hematopoietic or liver transplantation (performed in dry blood spots, leukocytes or fibroblasts). 4. Subjects > 8 months but < 4 years of age at Screening will have at least 1 of the following documented clinical manifestations of LAL Deficiency: <ol style="list-style-type: none"> a. Dyslipidemia (defined as Screening low-density lipoprotein cholesterol (LDL-C) > 130 mg/dL; triglycerides (TG) > 200 mg/dL); b. Elevated transaminases (ALT \geq1.5x ULN (based on the age- and gender-specific normal ranges of the central laboratory performing the assay); c. Impaired growth as defined as: |

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| | <ul style="list-style-type: none"> i. Weight-for-age (WFA) or stature-for-age (SFA) less than the age- and gender- appropriate 5th percentile on a standard World Health Organization (WHO) (subjects ≤ 24 months of age) or Centers for Disease Control and Prevention (CDC) (subjects > 24 months and < 4 years of age) WFA or SFA chart for at least 3 months prior to study entry; OR ii. Poor weight gain as evidenced by calculated weight percentile decreasing across 2 major percentile (99th, 97th, 95th, 90th, 75th, 50th, 25th, 10th, 5th, 3rd, and 1st) lines on a standard WHO (subjects ≤24 months of age) or CDC (subjects > 24 months and <4 years of age) WFA chart over a period of 6 months prior to study entry; d. Suspected malabsorption with: <ul style="list-style-type: none"> i. Persistent unexplained gastrointestinal symptoms such as nausea, diarrhea, abdominal pain, and bloating; OR ii. Unexplained anemia, or other abnormalities suggestive of malabsorption (e.g., osteomalacia, hypoalbuminaemia, prolonged bleeding time due to vitamin K deficiency); AND iii. Documented small intestinal disease involvement on a small bowel biopsy performed within 1 year of Screening e. Other clinical manifestation of LAL Deficiency in the opinion of the investigator and in consultation with the Sponsor (e.g., abnormal cardiac or pulmonary functions, or presence of lymphadenopathy by imaging or palpation). <p>5. Subjects ≥ 4 years of age at Screening will have at least 1 of the following documented clinical manifestations of LAL Deficiency:</p> <ul style="list-style-type: none"> a. Evidence of advanced liver disease (e.g., cirrhosis confirmed by imaging or biopsy) at Screening accompanied by: <ul style="list-style-type: none"> i. Clinically significant portal hypertension as defined by a hepatic venous pressure gradient (HVPG) greater than or equal to 10 mmHg; OR ii. Documented esophageal varices (historical or by esophagogastroduodenoscopy (EGD) at Screening (unless medically contraindicated due to high risk of endoscopy-related bleeding based on presence of esophageal varices on endoscopy carried out within 3 months of assessment). b. Disease recurrence in subjects with past liver or hematopoietic transplants (e.g., re-accumulation of lipid containing Kupffer cells, recurrence of fibrosis); c. Persistent dyslipidemia (defined as LDL-C > 130mg/dL, TG > 200mg/dL, or high-density lipoprotein cholesterol (HDL-C) <40mg/dL in males, and < 50mg/dL in females) that has persisted despite 3 or more months of treatment with one or more lipid-lowering therapies such as statins, cholesterol absorption inhibitors (ezetimibe), combination therapies (single-pill; ezetimibe/simvastatin, niacin/simvastatin), fibrates (fenofibrate, gemfibrozil, fenofibric acid), niacin or bile acid |

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| | <p>sequestrants (cholestyramine, colestipol, colesevelam);</p> <p>d. Suspected malabsorption based on the following manifestations:</p> <ul style="list-style-type: none"> i. Documented small intestinal involvement by small bowel biopsy performed within 1 year of Screening; AND ii. Unexplained iron deficiency, osteopenia, weight loss or chronic diarrhea; OR iii. Impaired growth in pediatric subjects defined as: <ul style="list-style-type: none"> 1. WFA or SFA less than the age- and gender-appropriate 5th percentile on a standard CDC WFA chart for at least 6 months prior to study entry; OR 2. Poor weight gain as evidenced by calculated weight percentile decreasing across 2 major percentile (99th, 97th, 95th, 90th, 75th, 50th, 25th, 10th, 5th, 3rd, and 1st) lines on a standard CDC WFA chart over a period of 6 months prior to study entry; e. Other clinical manifestation of LAL Deficiency in the opinion of the investigator and in consultation with the Sponsor (e.g., abnormal cardiac or pulmonary functions, or presence of lymphadenopathy by imaging or palpation). <p>6. Male and female subjects of childbearing potential must agree to use a highly reliable method of birth control (expected failure rate less than 5% per year) from the screening visit through 4 weeks after the last dose of study drug.</p> <p>7. Women of childbearing potential must have a negative serum pregnancy test prior to entering the study.</p> <p>8. Subjects receiving lipid-lowering therapies must be on a stable dose of the medication or stable apheresis regimen for at least 4 weeks prior to treatment and be willing to remain on a stable dose for at least the first 12 weeks of treatment in the study.</p> <p>9. Subjects receiving medications for the treatment of nonalcoholic fatty liver disease (e.g., glitazones, high-dose vitamin E, metformin, ursodeoxycholic acid [UDCA]) must be on a stable dose for at least 4 weeks prior to treatment and be willing to remain on a stable dose for at least the first 12 weeks of treatment in the study.</p> <p>A subject who meets any of the following exclusion criteria will be ineligible for this study:</p> <ul style="list-style-type: none"> 1. Subject meets eligibility criteria for another interventional study of sebelipase alfa in LAL Deficiency that is open for enrollment in the region where the subject will receive treatment. 2. Subject has known causes of active liver disease other than LAL Deficiency which have not been adequately treated (e.g., chronic viral hepatitis, autoimmune hepatitis, alcoholic liver disease). 3. Subject is unable or unwilling to comply with study procedures. 4. Subject received a hematopoietic stem cell or liver transplant < 2 years from the time of dosing. 5. Females who are nursing or pregnant. 6. Subject with co-morbidities other than complications due to |

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| | <p>LAL Deficiency which, in the opinion of the Investigator and in consultation with the Sponsor, are irreversible or associated with a high mortality risk within 6 months, or would interfere with study compliance or data interpretation (e.g. excessive alcohol consumption).</p> <p>7. Exposure to any investigational product within 30 days of Screening for a small molecule and 60 days of Screening for a biologic.</p> <p>8. Known hypersensitivity to eggs.</p> |
| Investigational Medicinal Product, Dose, Route, Regimen | <p>Sebelipase alfa is a highly purified recombinant human lysosomal acid lipase (rhLAL) manufactured using transgenic hens, which produce rhLAL in egg white.</p> <p>Eligible subjects will receive intravenous infusions of sebelipase alfa for up to 144 weeks. All subjects will receive a starting dose of 1 mg·kg⁻¹ qow in the treatment period. Subjects who complete the 96-week treatment period may enter the expanded treatment period at the same dose of sebelipase alfa that they were receiving at the end of the treatment period. In both study periods, dose increases (up to 3 mg·kg⁻¹ qw) will be permitted during the treatment period and will be at the discretion of the Investigator and with approval of the Sponsor, based on protocol-defined criteria of significant clinical progression. At any time during the study, subjects who cannot tolerate the dose may receive a dose reduction. Subjects who are unable to tolerate the lowest dose (0.35 mg·kg⁻¹ qow) will be discontinued from the study.</p> |
| Reference therapy | There is no placebo or comparator in this study. |
| Criteria for Evaluation | <p><u>Safety</u></p> <p>Safety endpoints will include the incidence of adverse events (AEs), SAEs, and infusion-associated reactions (IARs); changes from Baseline in 12-lead electrocardiograms (ECGs) and clinical laboratory tests (hematology, serum chemistry [including lipid panel], and urinalysis); changes in vital signs during and after infusion, relative to pre-infusion values; physical examination findings; use of concomitant medications/therapies; characterization of anti-drug antibodies (ADAs) including ADA titer by time point, peak ADA titer, and time to peak ADA titer. The effect of ADAs on the safety of sebelipase alfa will also be explored, in particular, the relationship between ADA-positive subjects and the incidence of IARs. Functional and overall development in subjects ≤ 6 years of age will be assessed, as determined by Denver II scores.</p> <p><u>Efficacy</u></p> <p>Secondary outcome measures include the following changes or percent change from Baseline to the end of the treatment period: (1) decrease in Alanine Aminotransferase (ALT); (2) decrease in Aspartate Aminotransferase (AST); (3) decrease in LDL-C; (4) decrease in non-HDL-C; (5) increase in HDL-C; (6) decrease in TG, (7) decrease in Child-Pugh status, (8) decrease in United Kingdom Model for End-Stage Liver Disease (UK-ELD) score. In the subset of subjects for whom these assessments are performed: (9) improvement in hepatic histology; (10) decrease in liver and spleen volume by magnetic resonance imaging (MRI); and (11) decrease in liver fat fraction by MRI. The effect of sebelipase alfa on growth parameters in pediatric subjects with manifestations of impaired growth will be measured.</p> |

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| | <p>Additional clinical, biochemical and hematological abnormalities will also be evaluated, including (1) total and conjugated bilirubin, (2) gamma glutamyltransferase (GGT), (3) markers of macrophage activation, (4) high-sensitivity C-reactive protein, (4) hemoglobin level, and (5) platelet count.</p> <p>Exploratory measures of additional clinical manifestations of LAL Deficiency not previously well characterized in the literature will include changes in functional assessments outcomes.</p> <p><u>Pharmacokinetics</u></p> <p>PK parameters (in subjects for whom these assessments are performed) will be reported, as the data permit, and may include serum clearance and apparent volume of distribution estimates along with secondary parameters of area under the concentration-time curve, maximum observed concentration, time to maximum observed concentration, and terminal elimination half-life ($t_{1/2}$). The effect of ADAs on sebelipase alfa PK will also be explored. PK analysis will be discussed in the statistical analysis plan (SAP).</p> <p><u>Health-Related Quality of Life</u></p> <p>Exploratory HRQOL measures will include changes from Baseline in scores for the Functional Assessment of Chronic Illness Therapy-Fatigue scale, Chronic Liver Disease Questionnaire, or Pediatric Quality of Life Inventory (PedsQL™) Generic Core Scales, as appropriate to the age of the subject.</p> <p><u>Pharmacodynamics</u></p> <p>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 over time.</p> |
| Statistical Methodology | <p><u>Sample Size</u></p> <p>No formal sample size calculations were performed for this study; projected enrollment is based on feasibility. It is expected that approximately 30 subjects will be treated.</p> <p><u>Analysis Sets</u></p> <p>Full Analysis Set: The Full Analysis Set will include all subjects who received at least 1 infusion of sebelipase alfa. Other analysis sets may be defined in the SAP.</p> <p><u>General Analysis Conventions</u></p> <p>The following standard conventions will be used for creating descriptive summaries.</p> <ul style="list-style-type: none"> • Continuous numeric endpoints will be summarized by providing the number of subjects with non-missing data, the mean and standard deviation of the data, and the minimum, first quartile, median, third quartile, and maximum value; • For categorical endpoints, the number and percentage of subjects with each possible outcome will be displayed. The denominator for percentages will include subjects with missing data. |

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| | <p>Changes and percentage changes from baseline, if applicable, will be summarized at each planned assessment time point using these general techniques.</p> <p><u>The general techniques will be used to describe:</u></p> <ul style="list-style-type: none"> • Demographics and baseline characteristics; • Subject accountability • Clinical laboratory tests (shift tables indicating changes relative to reference ranges may be constructed for some parameters; spaghetti plots of values over time may also be constructed) • Results of MRI assessments (spaghetti plots of values over time may also be constructed) • Physical exam and ECG data • Denver-II Assessment • Concomitant medication use • HRQOL <p><u>Safety Analyses</u></p> <p>Safety will be examined for the Full Analysis Set overall and, as subject numbers permit, stratified by dose, by ADA status, and for other subgroups of interest.</p> <p><u>Adverse Events</u></p> <p>AEs will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities. All AEs, SAEs, and IARs will be listed; separate listings will also be provided for subjects who die while on study and who discontinue sebelipase alfa due to an AE. The number and percentage of subjects experiencing any AE, any related AE, any SAE, any related SAE, and any IAR and deaths and any other discontinuations due to an AE will be tabulated.</p> <p>Frequency of treatment-emergent AEs, SAEs, and IARs will be tabulated by preferred term within the system organ class. Frequencies will also be presented by the classifications of severity and causality within dose. In addition, frequency of AEs, SAEs, and IARs will be presented for time periods spanning the entire course of sebelipase alfa treatment: up to 24 weeks after the first dose, > 24 to 48 weeks, > 48 to 72 weeks, and > 72 to 96 weeks. As appropriate, additional listings, summary tables, and graphics will be generated to evaluate IAR frequency and severity over time. The incidence of AEs leading to study discontinuation will be summarized.</p> <p><u>Anthropometric Parameters</u></p> <p>Anthropometric indicators of growth status (WFA, plus additional parameters if sufficient data are available) will be evaluated for subjects < 18 years of age. Weight-for-length/weight-for-stature and body mass index, if computed, will be derived from data on weight and length/stature. Anthropometric parameters will be plotted on standard growth curves. Z-scores and percentiles based on the age-gender standardized norms will be calculated in accordance with the methodology described by the WHO (subjects ≤ 24 months) or CDC (subjects > 24 months to 18 years) and using the growth charts relevant to the respective methodology. The primary means for describing the impact of sebelipase alfa</p> |

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| | <p>on anthropometric parameters will be graphical displays; tabular summaries may be created to support the graphs. In addition, the percentages of subjects who meet criteria for under nutrition (underweight, stunting, and wasting) will be tabulated at each time point.</p> <p><u>Exploratory Efficacy Analyses</u></p> <p>Evaluation of the relationship between non-invasive measurements of liver fat content and liver histopathology may also be conducted. Exploratory analyses of the effect of ADAs on the efficacy of sebelipase alfa may be performed as suggested by the type and amount of data available.</p> <p><u>Pharmacokinetic Analyses</u></p> <p>The Pharmacokinetic Set (PK Set) will be comprised of subjects who received at least 1 dose of sebelipase alfa, and have sufficient data for analyses of the PK profile following at least 1 infusion. Pharmacokinetic Analyses will be performed for the PK Set. Sebelipase alfa serum concentration data will be incorporated into a population PK model, which is to be reported separately, and will not part of the reporting of this study.</p> <p><u>Subgroup Analyses</u></p> <p>Effect of ADAs will be examined for efficacy and safety endpoints. As subject numbers permit, analyses may be conducted in other subgroups of interest (e.g., subjects who undergo major changes in diet and/or use of lipid-lowering medications).</p> <p><u>Missing or Invalid Data</u></p> <p>All data will be analyzed as they were collected in the database. Missing data in general will not be imputed; any imputation techniques if deemed necessary will be discussed in the clinical study report.</p> <p><u>Extension Analyses</u></p> <p>At the completion of the study, analyses will also be performed on cumulative data from the treatment period and expanded treatment period. Efficacy endpoints will be analyzed using techniques similar to those described for the analyses of data in the treatment period. Safety endpoints, as well as PK and HRQOL endpoints, will also continue to be analyzed in the extension analyses.</p> |

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List of Abbreviations

| | |
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| ADA | Anti-drug Antibody |
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| aPTT | Activated Partial Thromboplastin Time |
| AST | Aspartate Aminotransferase |
| AUC | Area Under the Serum Concentration Time Curve |
| AUDIT | Alcohol Use Disorder Identification Test |
| BMI | Body Mass Index |
| CDC | Centers for Disease Control and Prevention |
| CDT | Carbohydrate-Deficient Transferrin |
| CLDQ | Chronic Liver Disease Questionnaire |
| C _{max} | Maximum Observed Concentration |
| CS | Clinically Significant |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DBS | Dried Blood Spot |
| DNA | Deoxyribonucleic acid |
| EGD | Esophagogastroduodenoscopy |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ERT | Enzyme Replacement Therapy |
| FACIT-Fatigue | Functional Assessment of Chronic Illness Therapy-Fatigue |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GGT | Gamma-Glutamyl Transferase |
| GlcNAc | N-acetylglucosamine |
| HbA1c | Glycosylated Hemoglobin |
| hCG | Human Chorionic Gonadotropin |
| HDL-C | High-Density Lipoprotein Cholesterol |
| HRQOL | Health-Related Quality of Life |
| hs-CRP | High-Sensitivity C-Reactive Protein |
| HVPG | Hepatic Venous Pressure Gradient |
| IAR | Infusion-Associate Reaction |
| IB | Investigator Brochure |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IMP | Investigational Medicinal Product |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IV | Intravenous |
| LAL | Lysosomal Acid Lipase |
| LAL Deficiency | Lysosomal Acid Lipase Deficiency |
| LDL-C | Low-Density Lipoprotein Cholesterol |
| LLOQ | Lower Limit of Quantification |
| LSD | Lysosomal Storage Disorder |
| M6P | Mannose-6-phosphate |
| MCV | Mean Corpuscular Volume |

| | |
|-----------|---|
| MCH(C) | Mean Corpuscular Hemoglobin (Concentration) |
| MMR | Macrophage Mannose Receptor |
| MRI | Magnetic Resonance Imaging |
| NCS | Not Clinically Significant |
| PD | Pharmacodynamics |
| PedsQL | Pediatric Quality of Life Inventory |
| PK | Pharmacokinetic(s) |
| PT (INR) | Prothrombin Time (International Normalized Ratio) |
| 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 |
| SOM | Study Operations Manual |
| $t_{1/2}$ | Terminal Elimination Half-Life |
| TG | Triglyceride(s) |
| TEAE | Treatment-Emergent Adverse Event |
| T_{max} | Time to Maximum Observed Concentration |
| UDCA | Ursodeoxycholic Acid |
| UK-ELD | United Kingdom Model for End-Stage Liver Disease |
| US | United States |
| WFA | Weight-for-Age |
| WHO | World Health Organization |

1. Introduction

This document is a protocol for a human research study. This study is to be conducted according to United States (US) and international standards of Good Clinical Practice (GCP) 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 (LAL Deficiency) (Online Mendelian Inheritance in Man database number 278000) is a serious and life-threatening multisystem storage disorder caused by a marked decrease in LAL enzyme activity. LAL plays a key role in the metabolism and degradation of lipids, predominantly cholesteryl esters, and triglycerides, and its marked reduction or absence in patients with LAL Deficiency leads to accumulation of these lipids in various tissues and cell types throughout the body. There are no safe or effective therapies for LAL Deficiency.

LAL Deficiency is caused by mutations affecting the *LIPA* gene located on chromosome 10q23.2-q23.3. The most rapidly progressive form of LAL Deficiency presents in infants and is associated with a variety of private mutations that likely result in a complete loss of enzyme function ([Grabowski et al., 2012](#)); LAL Deficiency presenting in children and adults is frequently associated with a common exon-8 splice-junction mutation that may result in some residual enzyme activity.

1.1.2. Clinical Presentation of LAL Deficiency

LAL Deficiency is associated with significant ill health and a shortened life expectancy. As is the case for many other lysosomal storage disorders, subjects with LAL Deficiency present and progress as a continuum, with prominent liver pathology, and dyslipidemia.

LAL Deficiency presenting in children and adults, sometimes called cholesteryl ester storage disease, is the most common presentation, and is an underappreciated cause of cirrhosis, dyslipidemia and accelerated atherosclerosis. In the majority of reported cases, subjects are diagnosed before the age of 20. Although disease presentation can be variable, hepatic manifestations typically dominate the clinical picture ([Bernstein et al., 2013](#)). Diagnosis of LAL Deficiency requires a high index of clinical suspicion, since elevated transaminases, fatty liver, and hyperlipidemia (either alone or in combination) are also seen in subjects with other liver and metabolic diseases.

In LAL Deficiency, the presence of increased lysosomal cholesteryl esters and triglycerides in the liver is associated with liver fibrosis and progression to cirrhosis. Published cases clearly demonstrate that progression of fibrosis to cirrhosis or clinical complications of chronic liver disease, including bleeding ascites and esophageal varices, occur across the age spectrum (Bernstein, et al., 2013).

Dyslipidemia with elevated total cholesterol, triglycerides, and low-density lipoprotein-cholesterol (LDL-C) and decreased high-density lipoprotein-cholesterol (HDL-C) levels is common and has been shown to be associated with accelerated atherosclerosis (Beaudet et al., 1977; Anderson et al., 1999; Elleder et al., 2000). Although textbook descriptions describe elevated LDL and triglycerides (TG) in affected cases (Type II hyperlipidemia), recent insights suggest that isolated elevation of LDL may be present in a number of cases (Tripuraneni et al, 2013).

In addition to the more common manifestations of LAL Deficiency, other clinical presentations and complications have been described, including pulmonary hypertension (Cagle et al., 1986), severe hypersplenism and splenic infarcts (Guzzetta et al., 1990), and mesenteric lipodystrophy (vom Dahl et al., 1999). Growth failure, defined as > 2 standard deviations below normal weight and height measurements for age, has been noted in some children and adults with LAL Deficiency. Gastrointestinal involvement occurs in most LAL Deficiency subjects. However, infants with LAL Deficiency typically present with chronic diarrhea, emesis, malabsorption and failure to thrive.

LAL Deficiency presenting in infants, historically called Wolman disease, is a more rare presentation of the disease and is usually fatal within the first 6 months of life. Named after the physician who first described it (Abramov et al., 1956), this is the most aggressive presentation of LAL Deficiency, with growth failure as the predominant clinical feature and a key contributor to the early mortality. Rapidly progressive hepatic disease, as evidenced by liver enlargement, elevation of transaminases, hyperbilirubinemia, coagulopathy, and hypoalbuminemia, also occurs in these infants and contributes to mortality (Anderson et al., 1999; Mayatepek et al., 1999).

At present, there are no therapies approved by regulatory authorities for the treatment of LAL Deficiency. In infants, a variety of supportive therapies are used in an attempt to mitigate some of the effects of this rapidly fatal disease. Although some temporary stabilization of the clinical condition has been described, these interventions are not believed to substantially modify the outcome in affected subjects (Hoeg et al., 1984; Meyers et al., 1985). With few exceptions, success has not been achieved using bone marrow/hematopoietic stem cell transplantation. These methods are frequently limited in use and/or associated with high mortality due to the condition of the subjects at the time of diagnosis. Additionally, bone marrow/hematopoietic stem cell transplantation carries the inherent risks associated with these procedures, including graft-versus-host disease (Krivit et al., 2000; Stein et al., 2007; Tolar et al., 2009; Yanir et al., 2013).

Treatment for children or adults presenting with LAL Deficiency is limited to management of dyslipidemia through diet and the use of lipid-lowering therapies. The impact of lipid-lowering agents such as hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) is limited, since they do not address the root cause of LAL Deficiency, and disease progression to end stage liver failure still occurs (Ginsberg et al., 1987; Di Bisceglie et al., 1990; Tarantino et al., 1991; Yokoyama & McCoy, 1992; Glueck et al., 1992; Gasche et al., 1997; Assmann & Seedorf, 2001; Tadiboyina et al., 2005). As liver function deteriorates, liver transplantation may be required. At present, there is limited information on the long-term outcomes of liver transplantation in subjects with LAL Deficiency (Ferry et al., 1991; Hansen & Horslen, 2008).

1.1.3. Medical Plausibility of Enzyme Replacement Therapy for LAL Deficiency

LAL Deficiency resembles other lysosomal storage disorders (LSDs) with the accumulation of substrate in a number of tissues. Enzyme replacement therapy (ERT) in subjects with LAL Deficiency is a rational approach given the demonstrated medical value and long-term safety of ERTs for other LSDs, including Gaucher disease, Pompe disease, Fabry disease, and mucopolysaccharidosis I and II (Barton et al., 1990; Barton et al., 1991; Kishnani et al., 2007; van der Ploeg et al., 2010; Wilcox et al., 2004; Wraith et al., 2004; Muenzer et al., 2007).

In LAL Deficiency, substrate accumulation is most marked in hepatocytes and cells of the reticuloendothelial system, including Kupffer cells in the liver, histiocytes in the spleen and macrophages in the lamina propria of the small intestine. Reticuloendothelial cells express the macrophage mannose/N-acetylglucosamine receptor (also known as macrophage mannose receptor or CD206), which mediates binding, cell uptake and lysosomal internalization of proteins with N-acetylglucosamine or mannose terminated N-glycans, and provides a pathway for the potential correction of the enzyme deficiency in these key cell types (Stahl et al., 1978). This knowledge and the precedent established for other LSDs provides plausibility that ERT with sebelipase alfa, a recombinant human lysosomal acid lipase (rhLAL) with the appropriate glycan characteristics for targeting macrophages and other key cells will benefit subjects with LAL Deficiency.

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

1.2. *Investigational Agent*

Sebelipase alfa (SBC-102) is a recombinant human lysosomal acid lipase (rhLAL) with the same amino acid sequence as the native enzyme. Sebelipase alfa is a highly purified recombinant form of the naturally occurring human lysosomal acid lipase enzyme responsible for the metabolism and degradation of cholesteryl esters and triglycerides that are delivered to lysosomes by a variety of routes including LDL receptor-mediated endocytosis. Sebelipase alfa is a glycoprotein with a molecular weight of approximately 55-kD with 6 N-linked glycosylation sites.

Sebelipase alfa is produced by recombinant deoxyribonucleic acid (DNA) technology in egg white using a transgenic *Gallus* expression system and contains predominantly N-acetylglucosamine (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 macrophage mannose receptor (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 with Sebelipase Alfa*

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

Homozygous LAL-deficient rats demonstrate liver and spleen abnormalities, which resemble the abnormalities seen in patients with LAL Deficiency including accumulation of cholesteryl esters and triglycerides, hepatosplenomegaly, transaminase elevation, Kupffer cell expansion with disruption of normal liver architecture and liver fibrosis (Leavitt, et al., 2011). In addition, the LAL-deficient rats show other abnormalities that are prominent in infants with LAL Deficiency, including gastrointestinal involvement with abnormal lipid accumulation in macrophages in the lamina propria of the small intestine, markedly impaired weight gain, and early mortality (Leavitt, et al., 2011). In homozygous LAL-deficient rats, intravenous (IV) administration of sebelipase alfa restored LAL enzymatic activity, as evidenced by reduction in abnormal lysosomal lipid content in the liver and other key target tissues. LAL substrate reduction in affected tissues was accompanied by a dose-dependent reversal of the pathology with restoration of more normal body weight gain, reduction in organ size, improvements in histopathological abnormalities, decreases in serum transaminases and markedly improved survival.

Refer to the Investigator Brochure (IB) for further information on nonclinical studies with sebelipase alfa.

1.4. Clinical Data with Sebelipase Alfa

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

1.4.1. Completed Study LAL-CL01

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

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

All 3 doses of sebelipase alfa were biologically active, as evidenced by decreases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and increases in serum lipids (total cholesterol, triglycerides, and LDL-C), which were observed within 2 and 4 weeks, respectively, and were reversible following discontinuation of sebelipase alfa therapy. Effects on serum lipids appeared more pronounced in the $3 \text{ mg}\cdot\text{kg}^{-1}$ dose cohort, whereas effects on ALT and AST appeared to be independent of dose.

PK data in adult subjects with LAL Deficiency indicate that sebelipase alfa has a short plasma half-life, ranging from 0.07 to 2.04 hours at the lowest dose of $0.35 \text{ mg}\cdot\text{kg}^{-1}$ and from 0.09 to 0.21 hours at higher doses of 1 or $3 \text{ mg}\cdot\text{kg}^{-1}$. Sebelipase alfa area under the concentration-time curve (AUC) and maximum observed concentration (C_{max}) increased proportional to dose from 0.35 to $1 \text{ mg}\cdot\text{kg}^{-1}$ and more than proportional to dose from 1 to $3 \text{ mg}\cdot\text{kg}^{-1}$.

1.4.2. Ongoing Study LAL-CL04

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

1.4.3. Ongoing Study LAL-CL02

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

1.4.4. Ongoing Study LAL-CL03

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

1.5. Dose Rationale and Risk/Benefits

1.5.1. Dose Rationale

An initial dose of $1 \text{ mg}\cdot\text{kg}^{-1}$ qow will be administered to all subjects. Dose increases to $3 \text{ mg}\cdot\text{kg}^{-1}$ qow and then to $3 \text{ mg}\cdot\text{kg}^{-1}$ qw will be allowed based on disease progression, after a minimum time on the previous dose, and with approval from the Sponsor (see [Section 6.1](#)). Doses were selected based on the following information:

- Results from the first clinical study in adult subjects with LAL Deficiency (LAL-CL01) as well as ongoing study LAL-CL04 support selection of a $1 \text{ mg}\cdot\text{kg}^{-1}$ qow dose based on the following:
 - All 3 doses of sebelipase alfa (0.35 , 1 , and $3 \text{ mg}\cdot\text{kg}^{-1}$ qw) were well tolerated in adult subjects with LAL Deficiency treated in study LAL-CL01.
 - Sebelipase alfa AUC and C_{max} increased proportionally to dose from 0.35 to $1 \text{ mg}\cdot\text{kg}^{-1}$ and more than proportionally to dose from 1 to $3 \text{ mg}\cdot\text{kg}^{-1}$.
 - All 3 doses of sebelipase alfa were biologically active, as evidenced by decreases in ALT and AST and increases in serum lipids (total cholesterol, triglycerides, and LDL-C), which were observed within 2 and 4 weeks, respectively, and were reversible following discontinuation of sebelipase alfa therapy.
- Given the requirement for chronic administration in subjects with LAL Deficiency, a qow dosing regimen is preferable to a qw dosing regimen. In a nonclinical model of LAL Deficiency, the PD effects of $0.35 \text{ mg}\cdot\text{kg}^{-1}$ qw and $1 \text{ mg}\cdot\text{kg}^{-1}$ qw were comparable to those of $1 \text{ mg}\cdot\text{kg}^{-1}$ qow and $3 \text{ mg}\cdot\text{kg}^{-1}$ qow, respectively, based on a number of parameters. A dose of $0.2 \text{ mg}\cdot\text{kg}^{-1}$ qow was only marginally active in this nonclinical model.
- Long-term dosing of $1 \text{ mg}\cdot\text{kg}^{-1}$ qow in adult subjects treated in LAL-CL04 study demonstrated sustained reduction in ALT and AST and, following an initial increase in serum lipids, sustained reduction in serum lipid.
- Infants treated in study LAL-CL03 initially received $0.35 \text{ mg}\cdot\text{kg}^{-1}$ qw for 2 infusions and then $1 \text{ mg}\cdot\text{kg}^{-1}$ qw. Dose escalation to $3 \text{ mg}\cdot\text{kg}^{-1}$ qw was allowed. All subjects treated for > 3 months are currently receiving $\geq 3 \text{ mg}\cdot\text{kg}^{-1}$ qw and have demonstrated improved growth. Dosing has been generally well tolerated.
- There is an adequate safety margin for sebelipase alfa based on nonclinical toxicology studies. Refer to the IB for further discussion.

1.5.2. Risk/Benefit Assessment

LAL Deficiency is a rare disease, with no approved therapies, that leads to significant morbidity and mortality. Nonclinical studies conducted in a relevant 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 (see [Section 1.3](#) and IB).

Clinical investigations with sebelipase alfa in subjects with LAL Deficiency, including 1 completed, and 3 ongoing clinical studies, support that sebelipase alfa is well tolerated at doses ranging from 0.35 mg·kg⁻¹ to 3 mg·kg⁻¹ qow and qw, with rapid improvements in serum transaminases, LDL, triglycerides, and/or HDL-C dyslipidemia and evidence of other biological effects including improved weight gain in infants (see [Section 1.4](#) and IB). Thus, there is a reasonable basis to conclude that sebelipase alfa therapy in this study may be well tolerated and associated with beneficial effects on disease activity.

In a completed study and ongoing clinical study in adult subjects with LAL Deficiency (LAL-CL01 and LAL-CL04 respectively), sebelipase alfa therapy was associated with initial increases in serum total cholesterol, triglycerides, and LDL-C, likely as a result of lipid mobilization from intracellular lysosomal storage, followed by sustained reduction, including > 60% reduction in LDL-C at Week 52.

In LAL-CL06, initial serum lipid levels will continue to be closely monitored by the Investigator, Medical Monitor, and through periodic reviews of all subject data by an independent Safety Committee (SC) (see [Section 7.5](#)). A subject with treatment-emergent persistent elevations in serum lipid levels of clinical concern may remain on treatment at the Investigator's discretion and, as medically necessary, may be managed by temporarily interrupting the infusions of study drug and/or initiating or adjusting lipid-lowering therapy.

In addition to clinical experience with sebelipase alfa, extensive human experience exists for ERTs in the treatment of other LSDs 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, data from these studies can inform the use of investigational products of this class, and is also relevant to the risk evaluation of sebelipase alfa.

The most common adverse events (AEs) associated with administration of approved ERTs, including but not restricted to imiglucerase ([Cerezyme](#)[®]), velaglucerase alfa ([VPRIV](#)[®]), alglucosidase alfa ([Myozyme](#)[®]/[Lumizyme](#)[®]) and agalsidase beta ([Fabrazyme](#)[®]) are IARs, which typically occur during or within several hours following completion of the infusion and are usually mild and manageable by changes in infusion rate and/or administration of antipyretics and antihistamines. While severe infusion reactions (including anaphylaxis) and SAEs related to ERT administration rarely occur, these can require intensive medical intervention. Given the propensity for infusion reactions with ERT administration, measures have been incorporated in this protocol to minimize risk and monitor subject safety.

Anti-drug antibodies (ADA) have also been reported with approved ERTs and may be associated with altered response to treatment and/or increased risk of IARs. Subjects will be monitored throughout the study to evaluate the development of ADAs (see [Section 5.9](#)).

Overall, the risk-benefit assessment for sebelipase alfa is considered favorable, given the relatively low risk of adverse reactions with sebelipase alfa relative to the progressive and potentially life-threatening nature of untreated LAL Deficiency.

2. Study Objectives

2.1. Primary Objective

The primary objective of this study is to evaluate the safety of sebelipase alfa in a more broad population of subjects with LAL Deficiency than have been previously studied.

2.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate effects of sebelipase alfa relative to Baseline assessment of lipid metabolism and liver abnormalities (including histopathology);
- To evaluate the effects of sebelipase alfa on additional clinical parameters of LAL Deficiency including those not previously well characterized in the literature;
- To evaluate the effects of sebelipase alfa on growth parameters in pediatric subjects presenting with evidence of growth delay;
- To evaluate the immunogenicity of sebelipase alfa.

2.3. Exploratory Objectives

The exploratory objectives of this study are:

- To further characterize the pharmacokinetics of sebelipase alfa in pediatric subjects, subjects with severe hepatic dysfunction, and those who have had a previous liver or hematopoietic stem cell transplant;
- To evaluate the effect of sebelipase alfa on health-related quality of life (HRQOL) assessments.

3. Study Design

3.1. Overview of Study Design

This open-label, multicenter study will evaluate the safety and efficacy of sebelipase alfa in a broad population of subjects with LAL Deficiency. Such subjects may have been excluded from enrollment in other studies of LAL Deficiency because of age, disease progression, previous treatment by hematopoietic stem cell or liver transplantation, less common disease manifestations, or disease characteristics that would preclude participation in a placebo-controlled study. Factors which may have rendered a subject ineligible include but are not limited to the following:

- Age at symptom onset,
- Severity of symptoms due to disease progression,
- Previous hematopoietic or liver transplantation,
- Atypical or underappreciated clinical manifestation of LAL Deficiency in the absence of elevated ALT or early onset growth failure, including, for example, mesenteric lymphadenopathy, pulmonary hypertension, or impaired growth.

The study will consist of a screening period of up to 45 days, a treatment period of up to 96 weeks, an expanded treatment period of a maximum of up to 48 weeks, and a follow-up phone call at least 4 weeks after the last dose of sebelipase alfa.

All subjects will initiate treatment with sebelipase alfa at a dose of $1 \text{ mg}\cdot\text{kg}^{-1}$ qow. A dose escalation to $3 \text{ mg}\cdot\text{kg}^{-1}$ qow may be considered for a subject who exhibits significant clinical progression and meets protocol-defined criteria for dose-escalation. A further dose increase to $3 \text{ mg}\cdot\text{kg}^{-1}$ qw may be considered for subjects exhibiting significant clinical progression. All dose escalations are contingent upon acceptable safety and tolerability of preceding infusions (see [Section 6.1](#)) and Sponsor approval.

At any time during the study, subjects who are receiving a dose of sebelipase alfa that is not well tolerated may receive a dose reduction at the Investigator's discretion. If a subject cannot tolerate the lowest possible dose of $0.35 \text{ mg}\cdot\text{kg}^{-1}$ qow, despite measures taken to manage any IARs, he/she will be discontinued from the study. The per-protocol schedule of assessments will be modified for subjects who have a dose change to allow for closer monitoring of laboratory values around the period of change.

Sebelipase alfa dosing is thoroughly discussed in [Section 6.1](#).

Each subject will receive treatment with sebelipase alfa for at least 52 weeks and up to 96 weeks in the treatment period. Subjects who complete the 96-week treatment period may continue to receive sebelipase alfa in the expanded treatment period for an additional duration of up to 48 weeks unless discontinued sooner after sebelipase alfa is registered and available as a long-term enzyme replacement therapy for the treatment of patients with LAL Deficiency in the region where the subject resides and/or is receiving treatment (in accordance with

country-specific requirements). The follow-up period will be at least 4 weeks from the last infusion of sebelipase alfa. All infusions will initially be administered at the study center. After Week 48 of the treatment period, home infusions may be permitted for subjects who have met criteria discussed in [Section 6.5.2](#).

Safety and efficacy assessments will be performed at regular intervals throughout the study, as defined in the Schedule of Assessments. Exploratory safety and efficacy assessments will be considered for subjects who exhibit specific atypical manifestations of LAL Deficiency (e.g., pulmonary function test for an individual presenting with significant pulmonary involvement, etc.) and will be at the discretion of the Investigator in consultation with the Sponsor.

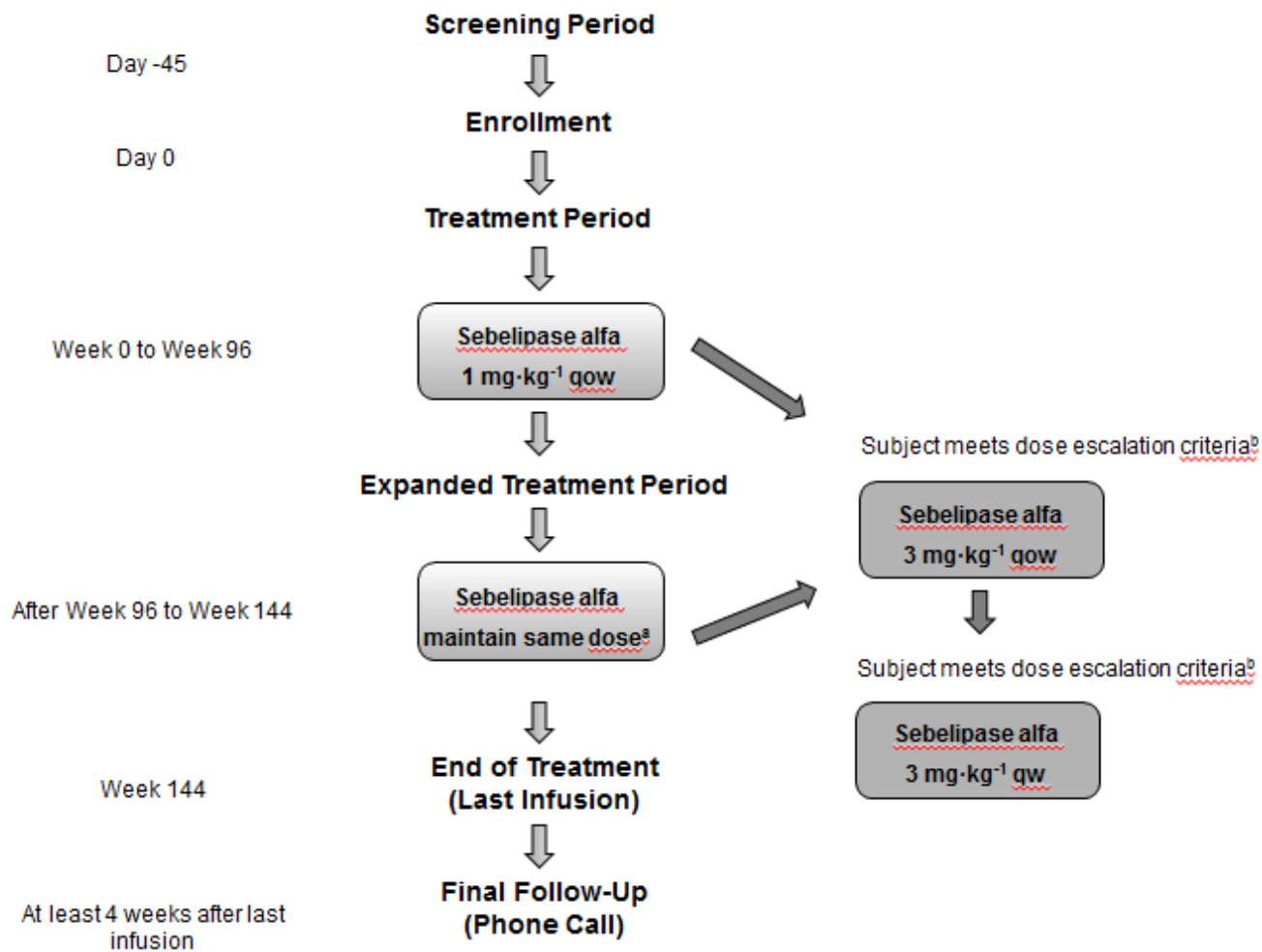
In addition, the pharmacokinetics of sebelipase alfa will be assessed for the pediatric population, for those with severe hepatic dysfunction (e.g., Child-Pugh Class C, see [Appendix A](#)), and those who have had a previous liver or hematopoietic stem cell transplant.

Effects on HRQOL will be characterized for all subjects at selected time points. Blood samples will also be collected for an additional analysis of potential disease-related biomarkers in this population.

The established independent program-level safety committee appointed by the Sponsor will provide additional oversight of subject safety in this study through periodic and ad-hoc reviews of safety data.

A follow-up phone call to assess AEs and concomitant medications will be conducted for all subjects at least 4 weeks after the last dose of study drug administered under this protocol.

Figure 1 Study Flow Diagram



a – Each subject will initiate treatment in the open-label extension period (Week 100) at the same dose of sebelipase alfa that they received during the last infusion of the treatment period (Week 96), unless criteria for dose modification are met (see Section 6.1)
 b – Refer to Section 6.1 for dose escalation criteria

3.2. Rationale for Study Design

Clinical studies are ongoing to evaluate the safety and efficacy of sebelipase alfa in subjects with LAL Deficiency. As noted in [Section 1.1.2](#), LAL Deficiency presents as a clinical continuum and the current clinical studies are designed to accommodate differences in the presentation and rapidity of progression.

Given the potential for variable presentation and progression of LAL Deficiency, it is important to expand the clinical experience by evaluating additional subjects not previously studied who are not eligible for ongoing clinical studies, such as subjects between 8 months and 4 years of age, subjects presenting with growth failure or other evidence of rapidly progressive disease that develops later than 6 months of age, previously transplanted subjects, subjects presenting with complications other than hepatic dysfunction, subjects with advanced liver disease or other complications that may put them at undue risk during the placebo controlled phase of a trial. The data from this study may provide supportive information on the activity of sebelipase alfa on additional less common clinical manifestations of LAL Deficiency.

Studies in a highly relevant animal disease model of LAL Deficiency have demonstrated favorable effects on growth and survival. A strong concordance was demonstrated between liver fat content (cholesterol esters and triglyceride), liver weight, and serum transaminases during both disease progression and in response to different doses of sebelipase alfa. In this model, treatment with sebelipase alfa was associated with substantial improvements in liver pathology, with complete resolution of abnormalities and restoration of normal liver architecture at maximally effective doses ([Leavitt et al., 2011](#)). To provide supportive data of this concordance in humans, the current study will evaluate liver histopathology at Baseline and at Week 48 (or at the end of treatment, if earlier than Week 48) in all adult subjects, and in pediatric subjects where local regulations allow. In order to minimize the need for this invasive procedure, a baseline biopsy will be performed only if acceptable historical liver histopathology data are not available (see [Section 5.12](#)).

An expanded treatment period was included in this study to ensure continued access to treatment for each subject until sebelipase alfa is registered and available in the region where the subject resides or is receiving treatment.

3.2.1. Outcome Variable Selection

3.2.1.1. Safety

The study is designed to primarily evaluate the safety of intravenous (IV) infusions of sebelipase alfa. Outcome variables selected to characterize the safety profile of sebelipase alfa in subjects with LAL Deficiency include:

- The incidence of AEs, SAEs, and IARs;
- Changes from Baseline in 12-lead electrocardiograms (ECGs), and clinical laboratory tests (hematology, serum chemistry [including lipid panel], urinalysis);
- Changes in vital signs during and after infusion, relative to pre-infusion values;

- Physical examination findings;
- Use of concomitant medications/therapies;
- Characterization of ADAs, including ADA titer by time point, peak ADA titer, and time to peak ADA titer;
- Functional and overall development in subjects ≤ 6 years of age, as determined by Denver-II scores.
- Given the potential for ADAs to impact the safety profile of a biological product, the effect of ADAs on the safety of sebelipase alfa will also be explored, in particular, the relationship between ADA-positive subjects and the incidence of IARs.

3.2.1.2. Efficacy

Literature review and insights from completed and ongoing clinical studies and the nonclinical disease model (see [Section 1.3](#)) suggest that a successful therapy for LAL Deficiency should mitigate the liver abnormalities and correct the dyslipidemia associated with the disease. Therefore, the study will investigate changes or percent changes over time from Baseline including the following:

- Decrease in ALT;
- Decrease in AST;
- Decrease in LDL-C;
- Decrease in non-HDL-C;
- Decrease in TG;
- Increase in HDL-C;
- Decrease in Child-Pugh status for subjects with Child-Pugh class C or B at Baseline;
- Decreased United Kingdom Model for End-Stage Liver Disease (UK-ELD) score;
- Improvement in liver histopathology;
- Decrease in liver and spleen volume by magnetic resonance imaging (MRI);
- Decrease in liver fat fraction by MRI.

Growth failure and other manifestations of impaired growth occur in subjects with LAL Deficiency. Early growth failure is the predominant clinical feature of LAL Deficiency in infants, and a key contributor to the early mortality. Positive effects on growth in subjects with LAL Deficiency would be supportive of a favorable effect of sebelipase alfa. Therefore, for pediatric subjects with evidence of impaired growth at Baseline, efficacy endpoints will also include changes over time in the following growth parameters:

- For subjects ≤ 24 months of age, z-scores and percentile scores based on World Health Organization (WHO) growth charts ([WHO Multicentre Growth Reference Study Group, 2006](#) and [2007](#)) will be determined for the following parameters:
 - Weight-for-age (WFA);
 - Weight-for-length;
 - Length-for-age;
 - Body-mass-index (BMI)-for-age;
 - Head circumference-for-age.

- For subjects > 24 months of age to 18 years, z-scores and percentile scores based on Centers for Disease Control and Prevention (CDC) growth charts ([Kuczmarski et al., 2002](#)) will be determined for the following parameters:
 - WFA;
 - Weight-for-stature (weight-for-height);
 - Stature-for-age (SFA);
 - BMI-for-age.
- For all subjects < 18 years, the proportion of subjects who meet criteria for under nutrition (underweight, wasting, and stunting) based on WFA, weight-for-length/weight-for-stature, and length-for-age/SFA, respectively ([UNICEF, 2009](#)), and combinations of these indicators, will be determined.

Additional clinical, biochemical and hematological abnormalities will also be evaluated. These will include the following:

- Total and conjugated bilirubin;
- Gamma glutamyltransferase (GGT);
- Markers of macrophage activation, including absolute reductions in serum ferritin, serum chitotriosidase and high-sensitivity C-reactive protein (hs-CRP);
- Hemoglobin level;
- Platelet count.

Changes over time in additional clinically significant manifestations of LAL Deficiency in subjects with complications and/or an atypical clinical presentation affecting other organs, will also be evaluated to better understand disease progression and the potential therapeutic benefit of sebelipase alfa. As described in [Section 5.16](#), additional assessments will be performed at the discretion of the Investigator in consultation with the Sponsor to support these analyses.

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

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, and a very limited LAL Deficiency subject population to perform typical scientific validation per FDA guidance, HRQOL will be assessed using tools developed for other diseases. Changes from Baseline in scores for the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale, Chronic Liver Disease Questionnaire (CLDQ), and Pediatric Quality of Life Inventory (PedsQL™) Generic Core Scales will be determined, as appropriate to the age of the subject. Assessment of HRQOL will be restricted to subjects ≥ 5 years of age, where validated self-reporting tools are available.

See [Section 5.18](#) and the Study Operation Manual (SOM) for further discussion of the HRQOL Assessments.

3.2.1.3. *Pharmacokinetics*

Descriptive PK parameters will be reported for subjects < 18 years of age, for those defined as having severe hepatic impairment, and in subjects with historical liver or bone marrow transplantation, as the data permit. PK parameters include clearance and volume estimates along with secondary parameters of AUC, C_{max} , time to maximum observed concentration (T_{max}), and terminal elimination half-life ($t_{1/2}$). The effect of ADAs on sebelipase alfa PK will also be explored.

4. Study Population

4.1. Target Population

The target population for this study is male and female subjects with LAL Deficiency with clinical presentations of the disease that have not been previously studied, including subjects < 4 years of age who were not eligible for study LAL-CL03, those with severe liver disease, or a previous liver or hematopoietic stem cell transplant and those with an atypical or underappreciated presentation of LAL Deficiency.

4.2. Number of Subjects

Approximately 30 subjects will be treated. At least 4 subjects between the ages of 2-4 years will be treated.

4.3. Inclusion Criteria

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

1. Subject will be > 8 months of age at the time of dosing.
2. Subject or subject's parent or legal guardian (if applicable) consents to participation in the study. If the subject is of minor age, he/she is willing to provide assent where required per local regulations, and if deemed able to do so.
3. Confirmation of LAL Deficiency diagnosis as determined by the central lab; a subject who received a liver or hematopoietic stem cell transplant who does not show evidence of LAL enzyme deficiency by dried blood spot (DBS) due to the effects of transplantation must have either:
 - a. Molecular genetic testing which confirms mutations in both alleles of the *LIPA* gene (*Note: in a highly suggestive case of LAL Deficiency where only 1 mutation is identified, subjects may be included based on a fibroblast enzyme activity assay*); **OR**
 - b. Appropriately documented (based on consultation with the Sponsor) historical result of an enzyme test prior to hematopoietic or liver transplantation (performed in DBS, leukocytes or fibroblasts).
4. Subjects > 8 months but < 4 years of age at Screening will have at least 1 of the following documented clinical manifestations of LAL Deficiency:
 - a. Dyslipidemia (defined as Screening LDL-C > 130 mg/dL; TG > 200 mg/dL);
 - b. Elevated transaminases (ALT ≥ 1.5 x ULN (based on the age- and gender-specific normal ranges of the central laboratory performing the assay);

- c. Impaired growth as defined as:
 - i. WFA or SFA less than the age- and gender- appropriate 5th percentile on a standard WHO (subjects \leq 24 months of age) or CDC (subjects $>$ 24 months and $<$ 4 years of age) WFA or SFA chart for at least 3 months prior to study entry; **OR**
 - ii. Poor weight gain as evidenced by calculated weight percentile decreasing across 2 major percentile (99th, 97th, 95th, 90th, 75th, 50th, 25th, 10th, 5th, 3rd, and 1st) lines on a standard WHO (subjects \leq 24 months of age) or CDC (subjects $>$ 24 months and $<$ 4 years of age) WFA chart over a period of 6 months prior to study entry;
 - d. Suspected malabsorption with:
 - i. Persistent unexplained gastrointestinal symptoms such as nausea, diarrhea, abdominal pain, and bloating; **OR**
 - ii. Unexplained anemia, or other abnormalities suggestive of malabsorption (e.g., osteomalacia, hypoalbuminaemia, prolonged bleeding time due to vitamin K deficiency); **AND**
 - iii. Documented small intestinal disease involvement on a small bowel biopsy performed within 1 year of Screening
 - e. Other clinical manifestation of LAL Deficiency in the opinion of the investigator and in consultation with the Sponsor (e.g., abnormal cardiac or pulmonary functions, or presence of lymphadenopathy by imaging or palpation).
5. Subjects \geq 4 years of age at Screening will have at least 1 of the following documented clinical manifestations of LAL Deficiency:
- a. Evidence of advanced liver disease (e.g., cirrhosis confirmed by imaging or biopsy) at Screening accompanied by:
 - i. Clinically significant portal hypertension as defined by a hepatic venous pressure gradient (HVPG) greater than or equal to 10 mmHg; **OR**
 - ii. Documented esophageal varices (historical or by esophagogastroduodenoscopy (EGD) at Screening (unless medically contraindicated due to high risk of endoscopy-related bleeding based on presence of esophageal varices on endoscopy carried out within 3 months of assessment)).
 - b. Disease recurrence in subjects with past liver or hematopoietic transplants (e.g., re-accumulation of lipid containing Kupffer cells, recurrence of fibrosis);
 - c. Persistent dyslipidemia (defined as LDL-C $>$ 130mg/dL, triglycerides $>$ 200mg/dL, or HDL-C $<$ 40mg/dL in males, and $<$ 50mg/dL in females) that has persisted despite 3 or more months of treatment with one or more lipid-lowering therapies such as statins, cholesterol absorption inhibitors (ezetimibe), combination therapies (single-pill; ezetimibe/simvastatin, niacin/simvastatin), fibrates

(fenofibrate, gemfibrozil, fenofibric acid), niacin or bile acid sequestrants (cholestyramine, colestipol, colesevelam);

- d. Suspected malabsorption based on the following manifestations:
 - i. Documented small intestinal involvement by small bowel biopsy performed within 1 year of Screening; **AND**
 - ii. Unexplained iron deficiency, osteopenia, weight loss or chronic diarrhea; **OR**
 - iii. Impaired growth in pediatric subjects defined as:
 1. WFA or SFA less than the age- and gender- appropriate 5th percentile on a standard CDC WFA chart for at least 6 months prior to study entry; **OR**
 2. Poor weight gain as evidenced by calculated weight percentile decreasing across 2 major percentile (99th, 97th, 95th, 90th, 75th, 50th, 25th, 10th, 5th, 3rd, and 1st) lines on a standard CDC WFA chart over a period of 6 months prior to study entry;
 - e. Other clinical manifestation of LAL Deficiency in the opinion of the investigator and in consultation with the Sponsor (e.g., abnormal cardiac or pulmonary functions, or presence of lymphadenopathy by imaging or palpation).
6. Male and female subjects of childbearing potential must agree to use a highly reliable method of birth control (expected failure rate less than 5% per year) from the screening visit through 4 weeks after the last dose of study drug.
 7. Women of childbearing potential must have a negative serum pregnancy test prior to entering the study.
 8. Subjects receiving lipid-lowering therapies must be on a stable dose of the medication or stable apheresis regimen for at least 4 weeks prior to treatment and be willing to remain on a stable dose for at least the first 12 weeks of treatment in the study.
 9. Subjects receiving medications for the treatment of nonalcoholic fatty liver disease (e.g., glitazones, high-dose vitamin E, metformin, ursodeoxycholic acid [UDCA]) must be on a stable dose for at least 4 weeks prior to treatment and be willing to remain on a stable dose for at least the first 12 weeks of treatment in the study.

4.4. Exclusion Criteria

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

1. Subject meets eligibility criteria for another interventional study of sebelipase alfa in LAL Deficiency that is open for enrollment in the region where the subject will receive treatment.

2. Subject has known causes of active liver disease other than LAL Deficiency which have not been adequately treated (e.g., chronic viral hepatitis, autoimmune hepatitis, alcoholic liver disease).
3. Subject is unable or unwilling to comply with study procedures.
4. Subject received a hematopoietic stem cell or liver transplant < 2 years from the time of dosing.
5. Females who are nursing or pregnant.
6. Subject with co-morbidities other than complications due to LAL Deficiency which, in the opinion of the Investigator and in consultation with the Sponsor, are irreversible or associated with a high mortality risk within 6 months, or would interfere with study compliance or data interpretation (e.g. excessive alcohol consumption).
7. Exposure to any investigational product within 30 days of Screening for a small molecule and 60 days of Screening for a biologic.
8. Known hypersensitivity to eggs.

4.5. Concomitant Medications and Treatments

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., lipid-lowering diet, surgery, physical therapy). Information on all concomitant medications and treatments will be recorded in the electronic case report form (eCRF) and will include the name of the medication (brand or generic) or therapy, reason for use, start date, stop date, dose, route of administration (if applicable), and frequency of administration.

Reasonable efforts will be made to ascertain all concomitant medications and treatments received by the subject from 4 weeks prior to Screening until the subject completes the follow-up phone call at a minimum of 4 weeks after the last dose of study drug administered under this protocol. As applicable, information about a subject's dose and dosing regimen of lipid-lowering medications will be collected for at least 4 weeks prior to Screening and information about a subject's dose and dosing regimen of medications prescribed for the treatment of nonalcoholic fatty liver disease (e.g., glitazones, high-dose vitamin E, metformin, and UDCA) and corticosteroids will be collected for at least 16 weeks prior to Screening.

Any changes in medications or treatments during the study will be captured in the eCRF. Subjects treated with lipid-lowering medication, UDCA, metformin, glitazones, or vitamin E at the time of Screening, must remain on the same dosing regimen for at least 12 weeks of treatment in the study. If a subject's dose of sebelipase alfa is increased during the first 12 weeks of treatment, the subject should continue to remain on the same lipid-lowering medication for an additional 12 weeks. Dose adjustments or discontinuation of these medications should occur only when there is a clear medical reason and must be pre-approved by the Sponsor. For example, adjustment of a subject's lipid-lowering medication will be permitted if deemed medically necessary to manage high serum lipid levels or in instances

where lipids are being adequately controlled with sebelipase alfa. The reason for all such dose adjustments will be collected.

For female subjects of childbearing potential, as defined in [Section 4.3](#), the use of a highly reliable method of birth control will be confirmed at Screening.

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;
- Medically significant AEs;
- Pregnancy;
- Protocol deviation or noncompliance;
- Termination of the study by the Sponsor.

A 48-week expanded treatment period has been included in the LAL-CL06 protocol (Amendment 2.0) to ensure that each subject has continued access to treatment until sebelipase alfa is registered and available in the region where the subject resides and/or is receiving treatment. Subjects receiving treatment in this expanded treatment period will be discontinued from study treatment once sebelipase alfa is registered and available in their region.

4.6.2. Procedures for Discontinuation

If a subject is discontinued from the study, the subject or their parent or legal guardian will be asked about the presence of AEs. The date and reason(s) for discontinuation will be recorded in the eCRF. The date of discontinuation will be the date that the Investigator discontinues the subject from the study or that the subject notifies the Investigator of the decision to discontinue. The reason for discontinuation will be that identified by the Investigator or voluntarily reported by the subject. If a subject withdraws consent and does not voluntarily provide a reason for discontinuation, "withdrawal of consent" will be recorded in the eCRF.

A subject will be considered discontinued due to an AE if the subject received any infusion or partial infusion of study drug, but did not complete the study because of an AE, whether or not the AE is considered drug related.

Subjects who prematurely discontinue treatment in the study will have an end-of-study visit prior to withdrawal, and a follow-up call at least 4 weeks after the last infusion, whenever feasible (see [Appendix B](#) for a list of the assessments to be performed at this visit). Post-study SAEs

and IARs 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, efforts must be made to contact the subject (or the subject's parent or legal guardian) to determine a reason for the failure to return. If 2 or more consecutive visits are missed, the Investigator should contact the Sponsor to determine whether the subject will be allowed to continue on study. After all reasonable efforts to reach a subject (or the subject's parent or legal guardian) have been exhausted, the subject will be identified as lost to follow up in the eCRF.

4.7. Subject Replacement Policy

Subjects who discontinue prior to completing the treatment period of the study (Day 0 to Week 96) may be replaced. Data from the discontinued subject will be included in analysis; however, additional subjects may be added.

4.8. Subject Re-Screening

Subjects will be allowed to return for re-screening.

A subject will be re-consented if re-screening occurs outside of the 45-day screening window. In this case, all screening procedures must be repeated with the exception of LAL enzyme activity and DNA blood sampling, MRIs, biopsies, hepatic venous pressure gradient, transient elastography, and esophagogastroduodenoscopy (EGD). MRIs and biopsies must only be repeated if the previously obtained MRI or biopsy (either from an earlier screening visit or an acceptable historical biopsy procedure as per [Section 5.12](#)) was obtained more than 26 weeks prior to Screening.

5. Schedule of Assessments and Study Procedures

The type and frequency of study assessments is outlined in the schedule of assessments in [Appendix B](#). All study visits will be scheduled relative to Week 0. The Investigator may also conduct an unscheduled visit at any time during the study at his/her discretion. Assessments performed at an unscheduled visit will be symptom directed and will be recorded in the eCRF. Assessments performed only for subjects of a certain age are based on the subject's age on the date that informed consent is obtained, unless otherwise indicated below.

5.1. *Informed Consent/Assent*

The subject (or the subject's parent or legal guardian, if applicable) will be given a verbal explanation of the study, including information about the study drug and the study procedures, and will have all questions adequately addressed. The subject (or the subject's parent or legal guardian, if applicable) 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 (or their parents or legal guardians) will be given a copy of the signed and dated informed consent form. In addition, age-appropriate assent will be obtained as required from subjects who are of minor age according to local regulations.

5.2. *Subject Eligibility*

All subjects will be assessed for eligibility against the inclusion and exclusion criteria described in [Section 4.3](#) and [Section 4.4](#), and supportive clinical information collected.

5.3. *Medical History*

5.3.1. *Subject Medical History*

A complete medical history will be obtained for each subject at Screening, including the following:

- Complications of liver disease (e.g., jaundice, cirrhosis, portal hypertension, esophageal varices including history of prior variceal bleeding, ascites, encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome) or gallstones.
- Any prior major cardiovascular events such as myocardial infarction, stroke, or requirement for arterial revascularization (e.g., coronary angioplasty, stent insertion, bypass surgery or other vascular procedure);
- History of allergies (e.g., food allergies, atopic dermatitis)
- History of angina, transient ischemic episodes, intermittent claudication;
- Other significant health complications that may represent an atypical, or underappreciated manifestation of LAL Deficiency, including, but not limited to significant history of pulmonary complications or lymphadenopathy.

5.3.2. Family Medical History

In addition, a family medical history will be obtained, documenting the number of siblings and the medical status of each sibling, including the presence of abnormalities suggestive of LAL Deficiency (e.g., liver disease, liver cancer, cardiovascular disease, dyslipidemia, or cerebrovascular accidents). Where LAL enzyme activity or genetic testing has confirmed the presence of LAL Deficiency in additional family members, information will be collected on relationship, age of diagnosis, medical complications, age, and, if applicable, cause of death.

For subjects who are ≥ 18 years of age, a history of alcohol use will also be obtained at Screening via the subject's completion of the Alcohol Use Disorder Identification Test (AUDIT).

5.4. Demographic Information

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

5.5. Physical Examination

A complete, age-appropriate physical examination will be performed by the Investigator or qualified designee, at the time points specified in [Appendix B](#). The examination will include an assessment of the subject's general appearance, skin, head (including head circumference for children up to 3 years of age), eyes, ears, nose, throat, heart, lungs, abdomen, extremities/joints, and neurological status. Whenever possible, the same person should perform the physical examination at each study visit. Abnormal findings will be recorded in the eCRF.

Every physical examination will also include the following:

- Child-Pugh Score (see [Appendix A](#));
- Abdominal photograph for subjects < 4 years of age at Screening;
- Liver size: A clinical assessment of liver size (palpable/non palpable and centimeters below costal margin), regularity (smooth/nodular), and sensitivity (tender/nontender);
- Spleen size: A clinical assessment of spleen size (palpable/nonpalpable and centimeters below costal margin), regularity (smooth/nodular), and sensitivity (tender/nontender);
- Lymphadenopathy: An assessment of the size, location, and character of any palpable lymph nodes. 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 nontender;
- Arterial disease: A clinical assessment of the right and left posterior tibialis and dorsalis pedis pulses and carotid bruits;
- Skin manifestations: A clinical assessment of signs of liver disease and portosystemic anastomoses such as periumbilical venous engorgement (caput medusae), spider nevia, or gynecomastia, dylipidemia such as xanthomas (tendinous, tuberos) and xanthelasma, and allergies including assessment of allergic skin rashes.

5.6. Height and Weight

Height and weight will be measured at the time points specified in [Appendix B](#). For subjects who are ≤ 18 years of age, height and weight data will be used to derive WFA and SFA. Z-scores and percentiles for WFA and SFA will be determined based on CDC growth charts ([Kuczmarski et al., 2002](#)). For subjects who are > 18 years of age, age-normalized percentiles for height will be derived at Baseline, to provide insights into the potential impact of LAL Deficiency on growth.

Refer to the SOM for further detail on the measurement of height and weight.

5.7. Vital Signs

Vital signs, including pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature (obtained by a consistent method for all measurements at a given infusion visit) will be obtained at the time points specified in [Appendix B](#). On dosing days, vital signs will be recorded pre-infusion, every 30 minutes (± 10 min) during the infusion and every 30 minutes (± 10 min) from 0 to 2 hours after the end of the infusion. Note: The end of the infusion occurs before administration of the sodium chloride flush.

Beginning at Week 24, the post-infusion period for vital sign monitoring may be shortened to 1 hour for subjects who have completed at least 22 weeks of treatment with no occurrence of moderate or severe IARs and with approval from the Sponsor. In such cases, the post-infusion monitoring period may need to be extended back to 2 hours if subjects begin experiencing moderate or severe IARs during or shortly after the infusions.

Throughout the study, additional readings may be taken at the discretion of the Investigator.

5.8. Electrocardiogram

Age-appropriate 12-lead ECGs will be obtained at the time points specified in [Appendix B](#). ECGs will be reviewed by a qualified clinician, and any abnormalities will be specified as clinically significant (CS) or not clinically significant (NCS).

5.9. Clinical Laboratory Assessments

Blood and urine samples for clinical laboratory tests will be collected at the time points indicated in [Appendix B](#). [Table 1](#) lists the clinical laboratory tests to be performed in this study.

Note that not all tests are performed at the same time points. Due to the limitations on the volume of blood collection that is considered to be acceptable in young children with very small total circulating blood volumes, the laboratory tests will be ranked in the order corresponding to the study objectives, as follows:

5.9.1. Tier 1 Laboratory Assessments

Tier 1 assessments include safety laboratory tests, including serum chemistry (including glycosylated hemoglobin [HbA1c]), liver function tests, serum lipids, hematology, coagulation panel (local), serum human chorionic gonadotropin (hCG), ADA, DBS LAL enzyme activity, viral hepatitis screen, carbohydrate-deficient transferrin (CDT), and PK. These tests include all efficacy laboratory tests. If a subject's blood volume threshold for weight or clinical status limit collection of any Tier 1 laboratory assessments, the medical monitor should be consulted for guidance with regard to a modified schedule for that visit.

5.9.2. Tier 2 Laboratory Assessments

Tier 2 assessments include all other laboratory tests, including exploratory biomarkers, macrophage activation markers, and hsCRP. Tier 2 assessments are considered mandatory and all efforts will be made to collect these samples in all subjects as indicated in [Appendix B](#).

If a subject's blood volume threshold for weight or clinical status limit collection of samples on the scheduled visit date, the Tier 2 laboratory assessments may be collected at the next scheduled visit, or when clinical status permits.

Blood volume threshold based on subject weight is discussed further in the SOM.

The blood sample for deoxyribonucleic acid (DNA) extraction is not included in either tier of laboratory assessments, unless it is necessary to establish subject eligibility (e.g., for subjects with previous hematopoietic stem cell or liver transplant without evidence of LAL enzyme deficiency by DBS). For all other subjects, this sample may be collected whenever blood volume permits, preferably at Screening, or as soon as practically possible thereafter (see [Section 5.9.7](#)).

5.9.3. Clinical Laboratory Collection and Analysis

Laboratory samples will be collected under the following conditions:

- Blood samples will be drawn prior to the study drug infusion on infusion visits, and in the morning (whenever feasible) on noninfusion visits;
- Subjects ≥ 18 will fast for at least 9 hours prior to collection of blood samples;
- Subjects will refrain from ingestion of alcohol for 24 hours prior to collection of blood samples for lipid and liver panels.

Refer to the SOM and Laboratory Manual for further details regarding the collection, processing, and storage of clinical laboratory samples.

A central laboratory will be responsible for analysis of all laboratory tests, with the exception of prothrombin time (international normalized ratio), activated partial thromboplastin time, urinalysis, and urine pregnancy.

Any identified laboratory abnormalities will be specified as CS or NCS by the Investigator or designee. In the event of unexplained clinically significant abnormal laboratory test results, the tests will be repeated as soon as possible (preferably within 24 hours of receiving the result) and followed up until they have returned to within the normal range and/or an adequate explanation has been identified. Clinically significant changes from a subject's baseline value or previous values will be recorded as AEs.

5.9.4. Clinical Laboratory Collection for Dose Changes

Subjects who undergo 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:

- Prior to the first infusion of new dose/schedule or change in lipid-lowering medication: serum lipid panel, liver panel, hematology, serum chemistry, ferritin, hs-CRP;
 - For dose modifications only: at the first infusion of new dose/schedule, a predose blood sample will be collected for ADA and serial blood samples will be collected for a determination of sebelipase alfa serum concentrations according to the sampling schedule shown in [Table 2](#) (pediatric subjects) or [Table 3](#) (adult subjects).
- 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 (see [Appendix B](#)).

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

Table 1 Clinical Laboratory Tests

| Laboratory Panel | Tests |
|---|---|
| Hematology | White blood cell count; red blood cell count; hemoglobin; hematocrit; mean corpuscular volume, hemoglobin, and hemoglobin concentration (MCV, MCH, MCHC); platelet count; neutrophil; lymphocytes; monocytes; eosinophils; basophils; peripheral smear for examination of cell morphology |
| Liver Function Tests | ALT, AST, alkaline phosphatase, GGT, albumin, bilirubin (direct, indirect, total) |
| Serum Lipids | LDL-C, total cholesterol non-HDL-C, triglyceride, HDL-C |
| Other Chemistries | Serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus), glucose, creatinine, bicarbonate, total protein, blood urea nitrogen, hs-CRP |
| | HbA1c |
| Macrophage Activation Markers | serum chitotriosidase, serum ferritin, hs-CRP, CK-18 |
| Urinalysis ¹ | pH, clarity, color, specific gravity, glucose, ketones, blood, protein, nitrite, and leukocytes (microscopic examination will only be done if urinalysis is positive for blood, nitrite, or leukocytes, or if protein is >1+) |
| Viral Hepatitis Screen | HBsAg and HCV serology |
| Alcohol Use | CDT |
| Coagulation Parameters ¹ | PT (INR), aPTT |
| Pregnancy ² | Serum hCG at Screening and urine hCG ¹ at all other visits |
| Anti-drug Antibody | Anti-sebelipase alfa antibody |
| Exploratory Biomarkers | See Section 5.9.5 . |
| LAL Enzyme Activity | Dried blood spot. See Section 5.9.6 . |
| DNA Sample | See Section 5.9.7 |
| PK Samples | See Section 5.9.4 |
| Malnutrition Markers and Fat Soluble Vitamins | See Laboratory Manual for details |

¹ Test performed by a local laboratory.

² Performed for female subjects of childbearing potential only. In the event of a positive pregnancy test result, refer to [Section 7.2.3](#) for information on pregnancy reporting and follow-up.

5.9.5. Exploratory Biomarkers

Blood samples (for serum isolation) will be obtained at the time points specified in [Appendix B](#), where local regulations and blood volume limitations permit, for exploratory analyses to identify and evaluate disease-related biomarkers.

Biomarker assays will be performed by a central laboratory or, as appropriate, by academic research laboratories with expertise in the analysis of specific biomarkers. The intent is to investigate baseline disease and dynamic markers that will enable the Sponsor to better understand the pathogenesis of LAL Deficiency and related comorbidities and response to sebelipase alfa therapy. Given the rarity of LAL Deficiency and the paucity of information on disease characteristics, the definitive list of analytes remains to be determined.

Collection of samples for exploratory biomarker analysis will be subject to discretionary approval from each center's IRB/IEC and the specific written consent of the subject and/or the subject's parent or legal guardian. This section of the protocol only applies if approval for collection of these additional samples has been granted by the IRB/IEC and consent is provided by the subject (or the subject's parent or legal guardian).

Samples will be stored by the Sponsor or designee in a secure and controlled environment until analysis, and will be destroyed by the Sponsor or designee after all worldwide obligations have been met, or sooner if required by local regulations.

Refer to the SOM or Laboratory Manual for further details regarding the collection, processing, and storage of these samples.

5.9.6. LAL Enzyme Activity in Dried Blood Spots

A blood sample will be spotted on filter paper at the site for each subject and then shipped to the central laboratory for measurement of DBS LAL enzyme activity. A sample will be collected from all subjects, irrespective of whether historical LAL activity data are available. For subjects who have undergone liver transplantation the DBS will be performed, but it will not be used to determine study eligibility. Samples will be collected at the time points specified in [Appendix B](#).

All samples will be assayed by a central laboratory to ensure consistency of LAL activity measurements across all subjects in the study. Refer to the SOM and Laboratory Manual for further details regarding the collection, processing, and storage of this sample.

5.9.7. DNA Sample

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

1. LAL (LIPA);

Genes coding for other proteins involved in lipid biology that may contribute to and/or modify the disease phenotype of LAL Deficiency (e.g. ABCA1);

2. Genes that may modify susceptibility to AEs related to sebelipase alfa.

Where local regulations permit and subject to discretionary approval from each center's IRB/IEC, a blood sample for DNA extraction will be collected from each subject at Screening, or as soon as practically possible thereafter, for subjects who do not require sample collection to establish study eligibility. The DNA will be used as part of a later pooled analysis, which will include a determination of the spectrum of LAL mutations in subjects with LAL Deficiency and the relationship between gene mutation, safety, efficacy, and susceptibility to development of ADAs. The Sponsor will only analyze DNA sequences within genes relevant to the mode of action and response to sebelipase alfa, including variants important in understanding AEs, and candidate genes with a potential role in the etiology, pathogenesis, and progression of LAL Deficiency. No additional testing will be performed on the samples collected in the study.

DNA samples will be stored by the Sponsor, or designee, in a secure, monitored, and controlled environment until analysis, and will be destroyed by the Sponsor after all worldwide obligations have been met, or sooner if required by local regulations.

Refer to the SOM and Laboratory Manual for further details regarding the collection, processing, and storage of these samples.

5.9.8. Pharmacokinetic Assessments

Blood samples for determination of sebelipase alfa serum concentrations will be collected from subjects < 18 years of age, from subjects with severely impaired liver functioning (e.g. based on imaging, biopsy or Child-Pugh Class C status at Screening), and for subjects who have previously undergone liver or hematopoietic stem-cell transplantation. Sampling will be completed as blood volume permits (see [Section 5.9](#)) at Baseline, Week 24 and Week 48, and on the day of a dose modification, as applicable. If a subject's blood volume threshold for weight or clinical status limit collection of samples on the scheduled visit date, the Sponsor or medical monitor should be consulted for guidance with regard to a modified schedule.

A sparse sampling scheme will be employed for pediatric subjects (< 18 years of age at informed consent) to reduce the risk of iatrogenic anemia. As shown in [Table 2](#), up to 4 blood samples will be collected at each study visit requiring a PK assessment. These samples will be collected within broad time windows, rather than at discrete time points, to allow more flexibility in the management of PK sampling for these subjects and to provide opportunities for measurement of drug concentrations across a broader time period with limited sampling.

A more extensive sampling scheme will be employed for adult subjects (≥ 18 years of age at informed consent) with severe liver disease, and those who have received a hematopoietic stem cell or liver transplant, in order to assess the PK profile in this population of adult subjects previously not evaluated in other clinical studies of sebelipase alfa. As shown in [Table 3](#), up to 12 blood samples will be collected from these adult subjects at each study visit requiring a PK assessment. A majority of these samples will be collected at discrete time points.

PK samples will not be taken from the extremity used for the study drug infusion. PK sampling at time points that coincide with a vital sign measurement will be obtained before cuff inflation for the blood pressure measurement, and PK samples at other time points will be obtained at least 5 minutes after cuff deflation. The exact start time and stop time of each infusion and the exact time of collection of each sample will be recorded in the eCRF.

Refer to the SOM and Laboratory Manual for further details regarding the collection, processing, and storage of these samples.

Table 2 PK Sampling in Pediatric Subjects (Age < 18 Years at Informed Consent)

| | Week 0 | Week 24 | Week 48 | Dose Modification |
|--|--------|---------|---------|-------------------|
| During Infusion | | | | |
| 0 hour to end of infusion ¹ | X | X | X | X |
| After Completion of Infusion | | | | |
| 0 to 30 minutes | X | X | X | X |
| 30 minutes to 1 hour | X | X | X | X |
| 1 to 2 hours | X | X | X | X |

¹ A sample will be obtained any time after the start of the infusion up until the end of the infusion (i.e., after the infusion bag has been emptied, but prior to the sodium chloride flush).

Table 3 PK Sampling in Select Adult Subjects (Age ≥ 18 Years at Informed Consent)

| | Week 0 | Week 24 | Week 48 | Dose Modification |
|--|--------|---------|---------|-------------------|
| Pre-infusion | | | | |
| Within 30 minutes before start of infusion | X | X | | X |
| During Infusion¹ | | | | |
| 15 minutes (±5 minutes) | X | | | X |
| 30 minutes (±5 minutes) | X | X | | X |
| 1 hour (±5 minutes) | X | | | X |
| End of infusion ² (±5 minutes) | X | X | X | X |
| After Completion of Infusion | | | | |
| 5 minutes (±2 minutes) | X | X | | X |
| 10 minutes (±2 minutes) | X | X | | X |
| 15 minutes (±2 minutes) | X | X | | X |
| 30 minutes (±5 minutes) | X | X | | X |
| 45 minutes (±5 minutes) | X | X | | X |
| 1 hour (±5 minutes) | X | X | | X |
| 2 hours (±5 minutes) | X | X | | X |
| 0 to 1 hour | | | X | |
| 1 to 2 hours | | | X | |

¹ Sampling times are relative to the start of the infusion.

² After the infusion bag has been emptied, but prior to the sodium chloride flush.

5.10. Abdominal Magnetic Resonance Imaging

Abdominal MRI will be performed at the time points specified in [Appendix B](#) to quantify organ volume, and to evaluate the aorta and other intra-abdominal vessels for atherosclerosis. All imaging scans will be acquired by an MRI technician or other qualified individual using standardized imaging protocols and will be read by a central reader, who will be blinded to time point of image acquisition.

Imaging scans are required for all subjects, except those who have internal metal medical devices or other non-removable metal items that may pose a risk to subject safety (e.g., cardiac pacemakers, aortic or cerebral aneurysm clips, artificial heart valves, ferromagnetic implants, shrapnel, wire sutures, joint replacements, bone or joint pins/rods/screws/clips), and children in whom sedation would be required but is medically contraindicated. In such populations, abdominal ultrasound will be substituted for an MRI.

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

5.11. Carotid MRI

Carotid MRI will be performed at the time points specified in [Appendix B](#) to quantify degree of stenosis in the carotid arteries. All imaging scans will be acquired by an MRI technician or other qualified individual using standardized imaging protocols and will be read by a central reader, who will be blinded to time point of image acquisition.

Imaging scans are required for all subjects, except those who have internal metal medical devices or other non-removable metal items that may pose a risk to subject safety (e.g., cardiac pacemakers, aortic or cerebral aneurysm clips, artificial heart valves, ferromagnetic implants, shrapnel, wire sutures, joint replacements, bone or joint pins/rods/screws/clips), and children in whom sedation would be required but is medically contraindicated.

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

5.12. Liver Biopsy

Liver biopsies will be obtained for subjects who are ≥ 18 years of age at Screening and at Week 48, or at the end of study treatment in the case of early withdrawal after at least 20 weeks of treatment. A liver biopsy will also be obtained on an optional basis at Week 96 after subject and/or legal guardian consent (as appropriate).

Biopsies for subjects < 18 years of age will be performed where local regulations permit. Liver biopsies will be obtained at Screening and at Week 48, or at the end of study treatment in the case of early withdrawal after at least 20 weeks of treatment. A liver biopsy will also be obtained on an optional basis at Week 96 after subject assent (as appropriate) and legal guardian consent.

If a subject had a liver biopsy within 26 weeks prior to Screening as part of clinical standard of care, and this historical biopsy is deemed adequate for histological assessment of liver pathology in this study (see SOM for minimum criteria), then a biopsy procedure will not be required at Screening.

Liver biopsy procedures will be performed according to the local institutional practices by a qualified professional. In those subjects with advanced liver disease, the biopsy must be obtained using the transjugular method, where local regulations and facilities permit, so the hepatic venous pressure gradient (HVPG) can be measured and collected during the procedure.

All biopsies collected during this study will be evaluated centrally by pathologists who will be blinded to assessment time point. Any biopsy done for other medical reasons during the course of the study will also be evaluated by central pathologists (stained and unstained samples). Blinded histological evaluation will include a comparison of overall disease activity at Baseline and Week 48. If applicable, comparisons will also be made with biopsies obtained at additional time points. Additional histological analysis of exploratory measures of disease activity may be performed, if tissue volume permits.

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

5.13. Endoscopic Biopsy of Small Bowel

For subjects with evidence of growth abnormalities or malabsorption, an endoscopic biopsy will be performed, unless medically contraindicated, at the time points noted in [Appendix B](#). Historical biopsy results will be accepted in lieu of a Screening assessment, if the biopsy was performed within 1 year of Screening.

If no evidence of lipid substrate accumulation confirmatory of malabsorption is present at Screening, a follow-up biopsy will not be required. However, results of any additional biopsies conducted during the study period should be recorded in the CRF.

Biopsy procedures will be performed according to the local institutional practices by a qualified professional. Biopsies for subjects < 18 years of age will be performed with consent from a parent or legal guardian (and assent from the subject, if applicable), and where local regulations allow.

5.14. Esophagogastroduodenoscopy

Subjects with evidence of advanced liver disease (e.g., cirrhosis on imaging or biopsy) will undergo an esophagogastroduodenoscopy (EGD) at the time points noted in [Appendix B](#), to document the presence, size and quality of esophageal varices. Exception to requirement is made for subjects for whom the procedure is medically contraindicated due to high risk of endoscopy-related bleeding based on presence of esophageal varices on endoscopy carried out within 3 months of assessment.

EGD will be performed according to the local institutional practices by a qualified professional. EGD for subjects < 18 years of age will be performed with consent from a parent or legal guardian (and assent from the subject, if applicable), and where local regulations allow.

5.15. Transient Elastography

Transient elastography will be performed for all subjects at the time points noted in [Appendix B](#), to assess liver stiffness (measured in kPa), unless medically contraindicated. The assessment will be performed according to the local institutional practices by a qualified professional, in locations where the technology is available.

5.16. Additional Imaging and Functional Assessments

In the event of clinically significant manifestations due to disease complications or an atypical clinical presentation of LAL Deficiency affecting other organs, additional imaging and functional assessments may be performed based on standard of care, and at the discretion of the Investigator and with Sponsor approval. All additional imaging and functional assessments will be recorded in the CRF.

5.17. Denver II Developmental Screening Test

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

The Denver II must be administered by a trained clinician and takes an average of 10 to 20 minutes to complete, and up to an hour depending on the age of the child and number of assessments completed. Administration and scoring of the Denver II is based upon the child's age. Refer to the SOM for further information on administration and scoring of the Denver II.

5.18. Health-Related Quality of Life

HRQOL questionnaires will be completed at the time points specified in [Appendix B](#) for subjects who are ≥ 5 years of age. The specific HRQOL questionnaires completed by each subject will be based on the subject's age on the date that informed consent is obtained as indicated in [Table 4](#). Questionnaires will be administered prior to any other study procedures being conducted at that visit.

The 13-item Functional Assessment of Chronic Illness Therapy (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 by all subjects who are ≥ 17 years of age at informed consent.

The Chronic Liver Disease Questionnaire (CLDQ) is a disease-specific instrument designed to assess health-related quality of life in subjects with chronic liver disease ([Younossi et al., 1999](#)). The CLDQ will be self-administered by all subjects who are ≥ 17 years of age at informed consent.

The PedsQL™ is composed of generic core scales and disease-specific modules. The 23-item PedsQL™ 4.0 Generic Core Scales was designed to measure the core dimensions of health, as delineated by the World Health Organization, as well as role (school) functioning in healthy children and those with acute or chronic health conditions. The PedsQL™ Generic Core Scales includes 4 multidimensional scales of physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items). In addition to the total scale score (all 23 items), two summary scores, the Physical Health Summary (8 items) and Psychosocial Health Summary (15 items), are also reported. In this study, the PedsQL™ 4.0 Generic Core Scales will be self-administered by subjects who are 5 to < 18 years of age on the date of informed consent, using one of the three self-report forms (ages 5-7, 8-12, or 13-18), as appropriate to the subject's age ([Varni et al., 2009](#)). Parent proxy reports will not be used in this study.

Table 4 Health-Related Quality of Life Assessments

| Subject Age | FACIT-Fatigue | CLDQ | PedsQL™ Generic Core Scales |
|--------------------------------------|----------------------|-------------|--|
| 5 to <17 years¹ | | | X |
| 17 to 18 years¹ | X | X | X |
| >18 years¹ | X | X | |

¹ Based on the subject's age on the date that informed consent is obtained.

Sample questionnaires and detailed instructions on administration of HRQOL questionnaires are provided in the SOM.

6. Treatments

6.1. Treatment Administered

All eligible subjects will receive repeat IV infusions of sebelipase alfa at an initial dose of $1 \text{ mg}\cdot\text{kg}^{-1}$ qow. Consecutive infusions must be at least 7 days apart. All study infusions will be administered by qualified medical personnel. Up to and including Week 24, study infusions are recommended to be administered over approximately 2 hours. After Week 24, infusions may be administered over approximately 1 hour, as tolerated by the subject (see [Section 6.5.2](#)). Prior to any infusion of sebelipase alfa, the subject will be assessed for signs and symptoms of an acute illness, including but not limited to: vomiting, fever, upper respiratory or gastrointestinal infection. If an acute illness is suspected, it is recommended that the Investigator determine whether to hold the study drug dose for that visit. In case of any questions, the Medical Monitor must be consulted.

6.1.1. Dose Escalation Criteria

Dose escalation up to $3 \text{ mg}\cdot\text{kg}^{-1}$ qw will be considered for each individual subject based on observed safety and tolerability and disease progression. Dose escalation will occur at the discretion of the Investigator and with approval of the Sponsor. An initial dose increase to $3 \text{ mg}\cdot\text{kg}^{-1}$ qow may be considered if the subject meets dose escalation criteria (as defined below), after receiving at least 8 consecutive infusions at the initial dose. A further increase in dose to $3 \text{ mg}\cdot\text{kg}^{-1}$ qw may be considered if a subject continues to demonstrate persistence of disease manifestations after receiving at least 8 consecutive infusions at a dose of $3 \text{ mg}\cdot\text{kg}^{-1}$ qow.

Prior to considering a dose increase, the subject will be evaluated for other potential causes of any observed clinical manifestations (e.g., initiation of a potentially hepatotoxic concomitant medication in a subject with abnormal ALT or AST, missed study infusions, or development of viral or autoimmune hepatitis or other alternative etiology of liver disease or inadequate weight gain). Protocol defined clinical laboratory assessments will be modified around any dose modification, as described in [Section 5.9](#).

A subject **meets dose escalation criteria** when any of the following are present:

- ALT or AST remaining abnormal, and either not improved or worsened from Baseline after 8 consecutive infusions from Baseline or worsened from the previously achieved lowest value over the preceding 8 consecutive qow infusions;
- LDL-C or triglyceride remaining abnormal, and either not improved or worsened over the preceding 8 consecutive qow infusions;
- The subject is < 18 years of age at the time of assessment for dose escalation, has a WFA z-score that is 2 standard deviations below the mean that either did not improve or worsened during the preceding 6 months, and the subject did not miss more than 20% of study infusions during the preceding 6 months. All possible etiologies for inadequate weight gain, not related to LAL Deficiency, will be ruled out by the Investigator before considering a dose increase.

6.1.2. Accelerated Dose Escalation Criteria

Dose escalation may be accelerated in exceptional cases with a particularly severe clinical presentation or evidence of rapid or substantial clinical deterioration, including but not limited to inadequate weight gain, ongoing weight loss deemed to be related to LAL Deficiency or a symptomatic progression of liver disease. Dose escalation will occur at the discretion of the Investigator and with approval of the Sponsor. A $3 \text{ mg}\cdot\text{kg}^{-1}$ qow dose may be considered after at least 4 consecutive infusions at the initial $1 \text{ mg}\cdot\text{kg}^{-1}$ qow dose. A further increase in dose to $3 \text{ mg}\cdot\text{kg}^{-1}$ qw may be considered if a subject continues to demonstrate significant clinical progression after receiving at least 4 consecutive infusions at the $3 \text{ mg}\cdot\text{kg}^{-1}$ qow dose.

In special cases, and only with approval from the Sponsor, it may be allowable to increase the dose to $3 \text{ mg}\cdot\text{kg}^{-1}$ qw, without mandating 4 infusions of qow dosing.

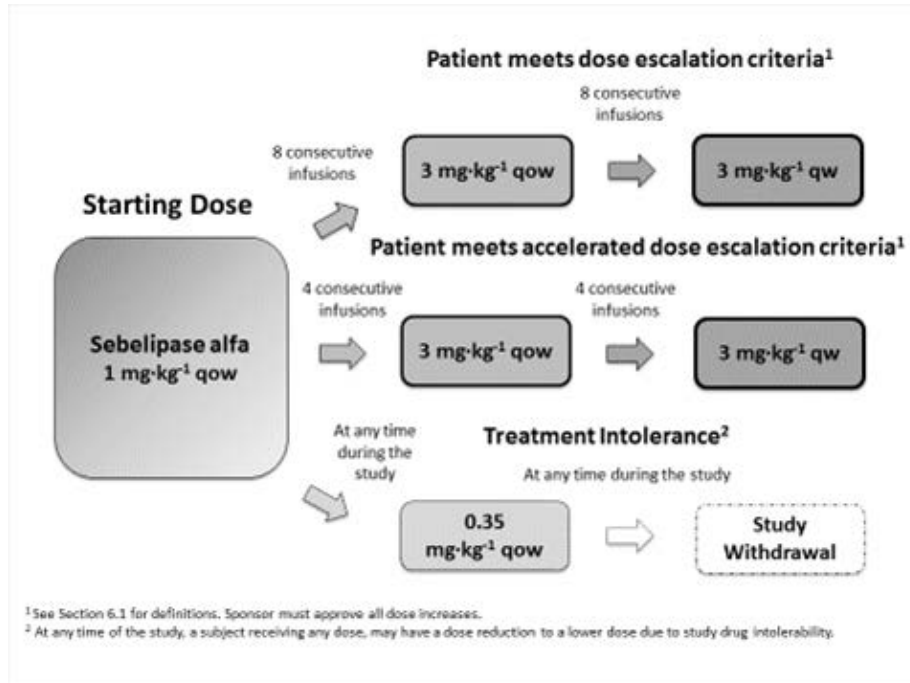
Significant clinical progression of liver disease is met if the subject presents with the following criteria:

- Confirmed elevation of ALT or AST to $> 5 \times$ upper limit of normal and at least twice the highest pre-treatment value and presence of one of the following:
 - Increase of total bilirubin to $> 3 \times$ upper limit of normal and at least twice the highest pre-treatment value;
 - Prolongation of prothrombin time (international normalized ratio) ≥ 4 seconds above Baseline;
 - Development or worsening of ascites;
 - Development of encephalopathy.

6.1.3. Dose Decreases

Decreases in dose will be permitted and will be at the discretion of the Investigator and in consultation with the Sponsor, based upon evidence of intolerance to sebelipase alfa treatment. Subjects who are receiving a dose of $3 \text{ mg}\cdot\text{kg}^{-1}$ qw, $3 \text{ mg}\cdot\text{kg}^{-1}$ qow or $1 \text{ mg}\cdot\text{kg}^{-1}$ qow but cannot tolerate this dose may receive a dose reduction to $1 \text{ mg}\cdot\text{kg}^{-1}$ qw, $1 \text{ mg}\cdot\text{kg}^{-1}$ qow, or $0.35 \text{ mg}\cdot\text{kg}^{-1}$ qow, respectively. If a subject cannot tolerate a dose of $0.35 \text{ mg}\cdot\text{kg}^{-1}$ qow despite measures taken to manage any IARs, the subject will be discontinued from the study after completion of early discontinuation procedures (see [Section 4.6.2](#)). Dose decreases may also be considered by the Investigator for subjects who are exhibiting evidence of clinical improvement and stability (ALT, AST and LDL), based on clinical judgment on the $3 \text{ mg}\cdot\text{kg}^{-1}$ qw dose, for a period of at least 24 weeks. In such an instance, a qow dosing schedule can be considered and must be discussed with the Sponsor.

Protocol defined clinical laboratory assessments will be modified around any decrease in dose, as described in [Section 5.9](#).

Figure 2 Dosing Flow Diagram

6.2. Description of Investigational Medicinal Product

Sebelipase alfa is an rhLAL produced by recombinant DNA technology in egg white using a transgenic *Gallus* expression system. Study kits containing study drug will be supplied by the Sponsor or designee. The study drug will be delivered in a 10-mL glass vial containing approximately 10.5 mL (including 5% overfill) of a buffered solution of sebelipase alfa at an approximate concentration of 2 mg·mL⁻¹. The study drug contains no preservatives and is designed for single use only. Details of the nonclinical and clinical experience to date with sebelipase alfa, as well as stability information, can be found in the current version of the IB.

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

6.3. Method for Assigning Subjects to Treatment

Each subject will be assigned a subject number at Screening upon providing informed consent. The subject will maintain the same screening number throughout the study.

6.4. Receipt, Storage, and Disposition of Study Drug

6.4.1. Receipt of Study Drug

Upon receipt of study kits, a drug inventory will be performed and verified by the person accepting the shipment. Designated study staff will verify and document that each shipment contains all items noted in the shipment inventory, and that no temperature excursions occurred

during study drug transport. Confirmatory documentation of shipment contents will be provided to the Sponsor or designee. Any damaged or unusable vials in a shipment will also be documented. The Sponsor or designee must be notified of any damaged or unusable study treatments that were supplied to the Investigational site.

6.4.2. Storage of Study Drug

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

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

6.4.3. Disposition of Study Drug

The Investigator, designee (e.g., licensed pharmacist), or other appropriate person according to local regulations, will be responsible for maintaining accurate records for all supplies used. Opened vials containing any residual volume may be stored at room temperature for study drug accountability. Following study drug accountability, the Sponsor or designee will give written authorization to return or destroy the study drug as instructed.

6.4.4. Return or Destruction of Study Drug

If any unused study drug material is remaining upon completion of the study, the material will be returned to the Sponsor or destroyed only after the Sponsor or designee has performed final drug accountability and provided written authorization for the return or destruction of study drug. Refer to the IMP Manual for further instructions.

6.5. Preparation and Administration of Study Drug

Dose preparation and administration will be performed using sterile, nonpyrogenic disposable materials including, but not restricted to syringes, needles, transfer tubing, and stopcocks. Under no circumstances will the study drug be used other than as directed in the protocol.

6.5.1. Preparation of Study Drug

The infusion bag (or syringe) containing sebelipase alfa will be prepared just prior to the start of infusion administration. Prior to preparation of the infusion, the vials of study drug will be visually inspected. The solution should not be used if it contains foreign particulate matter or is discolored. The solution may be used if a small number of visible translucent to opalescent or

white amorphous or threadlike particles are present in the vial. The contents should NOT be warmed using a microwave or other heat source. Sebelipase alfa is a protein and will be handled and mixed gently to prevent foaming.

The subject's most recent protocol-scheduled weight measurement, rounded to the nearest 0.1 kg, will be used for calculating the volume of study drug to be withdrawn from the vial(s) to prepare the infusion. If subject weight cannot reliably be obtained on the morning of the infusion because of the subject's condition, then the last available accurate weight will be used.

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 Study Drug

All infusions must be administered under close supervision of the Investigator or designee. Study drug should not be infused with other products in the same infusion tubing, as the compatibility of sebelipase alfa in solution with other products has not been evaluated.

It is required that all infusions of study drug be administered using in-line filtration with a low-protein binding 0.2- or 0.22- μ filter. Occlusion of the in-line filter may occur, which is not uncommon with IV infused proteins. Studies of sebelipase alfa with several commercially available 0.2- or 0.2- μ filters have shown that the IV line occlusion is primarily attributed to the surface area of the filter. Since several 0.2- or 0.22- μ filters are available at both 4.5 cm² and 10 cm², it is recommended to contact the filter manufacturer to determine the surface area of the 0.2- or 0.22- μ filter that is being used if occlusion of the in-line filter occurs. In this situation, a larger surface area 0.2- or 0.22- μ filter may be used.

The sebelipase alfa dose and infusion rate will be as directed in the investigational protocol and IMP Manual.

The IMP infusion will be administered at an infusion rate depending on the subject's weight. Sebelipase alfa should not be administered at an infusion rate exceeding 4 mL·kg⁻¹·hr⁻¹. Refer to the IMP manual for detailed instructions pertaining to duration and rate of infusion.

From Week 0 to Week 48, all infusions will be administered at the study center. After Week 48, home infusions may be permitted for subjects who have received the same dose and regimen for the prior 24 weeks and had no moderate-to-severe hypersensitivity reactions requiring medical intervention/management and no SAEs related to study drug within the prior 24 weeks, contingent upon Sponsor approval, local regulations, and the availability of established regional infrastructure and resources for home infusions.

6.6. Blinding of Study Drug

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

7. Assessment of Safety

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

7.1. Adverse Events and Laboratory Abnormalities

7.1.1. Clinical Adverse Events

An **Adverse Event** is any untoward medical occurrence in a subject, which does not necessarily have to have a causal relationship with the administration of a study drug. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the medicinal product. Pre-existing conditions that worsen in severity during the course of the study are to be reported as AEs. All AEs occurring during the clinical study and related to study conduct, will be reported on the AE page of the eCRF, as described in [Section 7.3](#). The Investigator will assess the severity, causality (relationship to study drug), and seriousness of each AE.

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

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

Causality: AEs will be assessed as not related, unlikely related, possibly related, or related to study drug. [Table 5](#) 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 study drug, and AEs assessed as possibly related or related will be reported as related to study drug. Assessment of causality will be based on the Investigator's medical judgment and the observed symptoms associated with the event.

Table 5 Assessment of Causality

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

Seriousness: AEs will be classified as serious or nonserious 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;
- 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.

All AEs that do not meet any of the criteria for an SAE will be regarded as nonserious AEs. Given the severity and life threatening nature of LAL Deficiency in infants, it is plausible that some pediatric subjects will be hospitalized during the first several weeks on study. Continuation of this initial hospitalization for participation in the trial is not considered an SAE. Also, a hospitalization to accommodate a study procedure is not considered an SAE. However, during the hospitalization, AEs will be collected and assessed for seriousness and reported appropriately. 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 in the eCRF, or electronically produced laboratory reports will be submitted directly from the central laboratory. Out-of-range laboratory test values should not be reported on the AE page of the eCRF unless the Investigator considers the test result to be a clinically significant change from the subject's baseline value or previous values.

7.1.3. Medical Events of Interest: 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 is completed and is assessed by the Investigator as at least possibly related to study drug will be designated as an IAR. In addition, if at any time during the study, the Investigator observes symptoms that he/she considers to be consistent with an IAR or hypersensitivity reaction related to the administration of study drug, the symptoms should be recorded as an AE(s) and designated as an IAR(s). Individual AE terms should be recorded rather than 'IAR' or 'infusion-associated reaction'.

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

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.

[Table 6](#) includes dose modifications required for all IARs and general guidance for the diagnosis and management of IARs in accordance with the institution's standard of care. The Investigator should use clinical judgement 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.

Table 6 Management of Infusion-Associated Reactions

| Mild Reaction | |
|--|--|
| <p><i>Common</i></p> <ul style="list-style-type: none"> • Hyperemia • Flushing • Lightheadedness • Nausea • Mild chest discomfort (tightness) <p><i>Less Common</i></p> <ul style="list-style-type: none"> • Fever and/or shivering • Palpitations • Headache • Irritability (especially in young children) | <ul style="list-style-type: none"> • Slow infusion rate by 50% • Give anti-pyretic and/or anti-histamine • Decrease infusion rate by a further 25% if symptoms persist • If the event resolves, the infusion should continue at a reduced rate for a minimum of 30 minutes before the infusion is increased to 75% of original rate. If the subject tolerates the infusion at 75% of the original rate for at least 30 minutes the original rate may be restored for the remainder of the infusion. • If reaction persists despite rate reduction stop infusion • Pre-treat with antihistamine and antipyretic prior (approximately 1.5h) to the next infusion <ul style="list-style-type: none"> ◦ e.g., diphenhydramine (1 mg/kg po) and acetaminophen (15 mg/kg po) |
| Moderate Reaction | |
| <ul style="list-style-type: none"> • Hyperemia (flushing) • Chest discomfort • Itching and/or raised urticarial rash • Severe headache • Gastro-intestinal symptoms, vomiting, diarrhoea, abdominal cramping. | <ul style="list-style-type: none"> • Stop infusion • Give antihistamine IV and consider IV or oral steroids • Consider giving a beta-adrenergic inhaler treatment, if appropriate • If the event resolves, the infusion may continue at a reduced rate of 50% of the original for a minimum of 30 minutes before the infusion is increased to 75% of the original rate. If the subject tolerates the infusion at 75% of the original rate for at least 30 minutes the original rate may be restored for the remainder of the infusion. • If reaction persists despite rate reduction stop infusion • Pre-treat with antihistamine and antipyretic prior to next infusion • Collect serum sample for tryptase 1-3 hours after the IAR onset and another serum sample for tryptase and anti-drug antibody (ADA) during the next study visit (> 4 days after the IAR) prior to the infusion. • Consider skin testing |

| Severe Reaction | |
|---|--|
| <ul style="list-style-type: none"> • Clinically significant cardiovascular effects: e.g., hypertension or hypotension defined as a decline approaching 20-30% of their preinfusion value without alternative etiology, agitation, pain, fluid overload, dehydration • Respiratory symptoms: Significant shortness of breath, stridor, wheezing, laryngeal oedema, swelling of tongue. • Cardiac arrhythmias • Anaphylactic/Anaphylactoid shock with hypotension and circulatory collapse. | <ul style="list-style-type: none"> • Stop Infusion • Give oxygen, if available • Give epinephrine (adrenaline) • Give antihistamines IV and steroids IV • Consider giving a beta-adrenergic inhaler treatment, if appropriate • Collect serum sample for tryptase 1-3 hours after the IAR onset and another serum sample for tryptase and ADA during the next study visit (> 4 days after the IAR) prior to the infusion. • Consider skin testing • Dosing of the subject will be suspended until the Safety Committee has completed the review of the IAR and any other relevant safety data (Section 7.5) • In the event subject is approved by Safety Committee for resumption of dosing: <ul style="list-style-type: none"> o Pre-treat with antihistamine and antipyretic prior to next infusion o Slowly up-titrate the infusion rate during the subsequent infusion: e.g. if previous rate was 50 mL/hr, begin at 0.25 x previous rate (12.5 mL/hr) x 15min, then increase to 0.5 x rate (25 mL/hr) x 15 min, 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. |

7.2. Handling of Safety Parameters

7.2.1. Serious Adverse Events and Moderate or Severe Infusion-Associated Reactions (Immediately Reportable to 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.

Adverse Event Reporting Period

The study period during which AEs must be reported is defined as the period from signature of the informed consent to the end of the study treatment follow-up. Adverse events occurring after signing the informed consent but prior to the first dose of study medication will only be recorded if assessed as related to protocol procedures or requirements. For this study, the study treatment follow-up is defined as a minimum of 4 weeks following the last administration of study treatment. If a subject experiences an SAE that is considered to be related to study treatment at any time after the study, it must be reported to the Sponsor.

7.2.2. Treatment and Follow-up of Adverse Events

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

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

Follow-up of Abnormal Laboratory Test Values

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

7.2.3. Pregnancy

Although sebelipase alfa is a recombinant form of a normal human enzyme and may therefore have a lower reproductive risk potential than other medications, formal testing has not been completed. Male and female subjects of childbearing potential must therefore agree to use a highly effective and approved contraceptive method for the duration of the study and until 4 weeks after the last dose of study drug administered under this protocol. Regular pregnancy tests will be performed for female subjects of childbearing potential, as defined in [Section 5.9](#).

The Investigator must immediately be informed if a subject or partner of a male subject becomes pregnant during the study. A subject who has become pregnant during the study must not receive further study drug infusions. Pregnancies occurring up to 4 weeks after the completion of the last infusion must also be reported to the Investigator. The Investigator must report all pregnancies to the Sponsor or designee immediately and no later than 24 hours after the first knowledge of the pregnancy. 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 (or the subject's parent or legal guardian) the Investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs must be recorded in the source document, and in the eCRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded under one diagnosis.

AEs will be recorded from the time of signing of the informed consent until completion of the last scheduled visit, i.e., the follow-up visit. Adverse events occurring after signing the informed consent but prior to the first dose of study medication will only be recorded if assessed as related to protocol procedures or requirements.

Any AEs remaining unresolved after completion of the last scheduled visit should be recorded as ongoing. Ongoing AEs/SAEs should continue to be followed up for the period specified in [Section 7.2.2](#) but without further recording in the eCRF. However, follow-up information on SAEs must be reported to the Sponsor or designee as described in Section 7.4. Any SAE that occurs after the study period and is considered to be related to the study treatment or study participation should be recorded and reported immediately.

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

7.4. Reporting of Serious Adverse Events, 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 (§13 GCP-V; Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ['CT-3']; US Code of Federal Regulations Title 21, §312.32, Investigational New Drug [IND] safety reporting).

The Sponsor or designee will report all reportable events to all regulatory authorities, IECs or IRBs, and Investigators as required by local regulations.

Periodic safety reporting to regulatory authorities will be done by the Sponsor according to national and local regulations.

7.4.1. Investigator Reporting: Notifying the Sponsor

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

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

Report SAEs and IARs by phone, fax or email to:

Europe and Asia Pacific

24-Hour Hotline:

PPD

SAE Fax:

PPD

Email:

PPD

North, Central and South America:

Hotline (Urgent Calls Only)

PPD

24-Hour Hotline:

PPD

Fax:

PPD

7.4.2. Investigator Reporting: Notifying the IRB/IEC

Unanticipated problems posing risks to subjects or others as noted above will be reported to the IRB/IEC per their institutional policy by the Investigator, Sponsor, or designee according to country requirements. 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 or designee is required to report certain study events in an expedited manner to the FDA, the European Medicines Agency's EudraVigilance Clinical Trial Module and to all country Regulatory Authorities where the study is being conducted. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

Immediately and within 7 calendar days

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

Immediately and within 15 calendar days

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

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

7.4.4. Sponsor Reporting: Notifying Participating Investigators

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

7.5. Independent Safety Committee

Primary oversight for subject safety will be the responsibility of the Investigators and Sponsor. Additional oversight of subject safety will be provided by an independent 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 is expected to last for the duration of the study. Core members of the SC will not participate in the trial as Investigators or subinvestigators, 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 aggregated safety data for study LAL-CL06 on an at least biannual basis (i.e., approximately every 6 months) from the date of enrollment of the first subject until completion of dosing for all subjects in the study.

The SC will also perform ad hoc reviews of safety data on an as needed basis in the event of emerging safety signals of clinical concern in 1 or more subjects, including potential safety risks such as a severe IAR with clinically significant cardiovascular, respiratory or other effects.

Following each periodic and ad-hoc review of safety data, the SC will indicate whether dosing of sebelipase alfa may continue 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.

8. Statistical Plan

8.1. General Considerations

No formal inferential statistical testing will be performed. P-values and 95% confidence intervals, where presented, will be considered descriptive and will be provided to facilitate clinical review and interpretation.

All data collected in this study will be provided in subject data listings sorted by subject number; the dose of sebelipase alfa temporally associated with the data will be included on the listing. Summary tables and/or graphs will be presented for each endpoint, as appropriate to the data, by evaluation time point. Unless otherwise noted, the following standard conventions will be used for creating descriptive summaries.

- Continuous numeric endpoints will be summarized by providing the number of subjects with nonmissing data, the mean and standard deviation of the data, and the minimum, first quartile, median, third quartile, and maximum value;
- For categorical endpoints, the number and percentage of subjects with each possible outcome will be displayed. The denominator for percentages will include subjects with missing data.

8.2. Determination of Sample Size

No formal sample size calculations were performed for this study; the projected enrollment is based on feasibility. It is expected that approximately 30 subjects will be treated.

8.3. Analysis Sets

The Full Analysis Set will include all subjects who received at least 1 infusion of sebelipase alfa. Other analysis sets may be defined in the Statistical Analysis Plan (SAP).

8.4. Demographics and Baseline Characteristics

Demographics and baseline characteristics, including results of DNA and LAL enzyme activity testing, will be listed for each subject and tabulated overall, according to the methods in Section 8.1. Chronological age will be reported in years to one decimal (i.e., xx.x years).

8.5. Subject Accountability

Subject accountability will be presented in a listing, and will include age, gender, date of consent, date and dose of first infusion of study drug, date and dose of last infusion of study drug, date of completion or premature discontinuation from the study, and reason for discontinuation if the subject discontinues prematurely. Data from all subjects who are treated in the study will be included in the summary of subject accountability. The frequency and

percentage of subjects who are treated in the study, completed the study, and discontinued from 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 will be summarized overall and; any changes in dose will be described in listings, and may also be provided in tabular summaries. Other data summaries describing sebelipase alfa usage and compliance may be created, as applicable, and will be outlined in the SAP.

8.7. Safety Analyses

Safety will be examined for the Full Analysis Set overall and, as subject numbers permit, stratified by dose, by ADA status, and for other subgroups of interest.

8.7.1. Adverse Events

Adverse events will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities. All AEs, SAEs, and IARs will be listed; separate listings will also be provided for subjects who die while on study and who discontinue the study due to an AE. The number and percentage of subjects experiencing any AE, any related AE, any SAE, any related SAE, and any IAR and, deaths and any other discontinuations due to an AE will be tabulated.

Frequency of treatment-emergent AEs, SAEs, and IARs will be tabulated by preferred term within the system organ class. Frequencies will also be presented by the classifications of severity and causality. In addition, frequency of AEs, SAEs, and IARs will be presented for time periods spanning the entire course of treatment with sebelipase alfa: up to 24 weeks after the first dose, > 24 to 48 weeks, > 48 to 72 weeks, > 72 to 96 weeks. As appropriate, additional listings, summary tables, and graphics will be generated to evaluate IAR frequency and severity over time. The incidence of AEs leading to study discontinuation will be summarized.

8.7.2. Clinical Laboratory Tests

Observed measurements and changes from Baseline to each study time point in clinical laboratory data will be summarized. Clinically significant abnormal values will be indicated in the listings of laboratory data, and frequencies of abnormal values relative to the laboratory normal range and clinically significant abnormal values will be summarized, if sufficient data are available for analysis.

Immunogenicity data will be summarized, including the number and percentage of subjects who become ADA-positive, time to peak titer, ADA titer by time point, and median and peak ADA titer. Other exploratory analyses of the effect of ADAs on the safety of sebelipase alfa may also be performed as suggested by the type and amount of data available.

8.7.3. Other Safety Data

Observed measurements and changes from Baseline to each study time point in vital signs, physical examination findings, ECG parameters, and Denver II assessment will be summarized. Abnormal findings/values will also be listed and summarized.

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 Analyses

Efficacy will be examined for the Full Analysis Set and, as subject numbers permit, stratified by dose, by ADA status, and for other subgroups of interest.

Efficacy of sebelipase alfa is expected to be reflected through changes in liver and spleen fat content and organ volume, clinical laboratory data and, where applicable, growth parameters. Evaluation of change in parameters will be made from key assessment time points to the pre-dosing baseline and, as appropriate, to dose-specific baseline assessments (i.e., the assessments taken just prior to escalation to a higher dose level). Additional comparisons of change between sequential assessment time points may also be made.

8.8.1. Abdominal Magnetic Resonance

Change and percent change in liver and spleen volume and fat content will be calculated from Baseline and tabulated for each evaluation time point by multiples of normal (and including percent change from Baseline). Data will be summarized for the endpoints as continuous variables. Spaghetti plots of change in measurements over time (1 line per subject) may also be created for selected endpoints of interest.

8.8.2. Clinical Laboratory Tests

Change and percent change in serum live biochemical parameters, serum lipids, hemoglobin levels, and platelet count will be calculated from Baseline and tabulated for each evaluation time point. Data will be summarized for the endpoints as continuous variables and, for selected endpoints (e.g., transaminases), relative to the laboratory normal range or recognized clinically significant abnormal values indicative of disease (e.g., presence of hepato- or splenomegaly). Spaghetti plots of change in measurements over time (1 line per subject) may also be created for selected endpoints of interest. The UK-ELD assessment, which is computed from clinical laboratory values, will be summarized similarly to laboratory data, although these scores will not be compared against standard laboratory reference ranges for individual laboratory assessments.

8.8.3. Anthropometric Parameters

Anthropometric indicators of growth status (WFA, plus additional parameters if sufficient data are available) will be evaluated for subjects < 18 years of age. Weight-for-length/weight-for-stature and BMI, if computed, will be derived from data on weight and length/stature. Anthropometric parameters will be plotted on standard growth curves. Z-scores and percentiles based on the age-gender standardized norms will be calculated in accordance with the methodology described by the WHO (subjects \leq 24 months) or CDC (subjects > 24 months to 18 years) and using the growth charts relevant to the respective methodology. When possible, historical data on growth parameters will also be incorporated into the analyses. The primary means for describing effects of sebelipase alfa on anthropometric parameters will be graphical displays; tables may be generated in support of the graphs. In addition, the percentages of subjects who meet criteria for under nutrition (underweight, stunting, and wasting) will be tabulated at each time point.

8.8.4. Exploratory Efficacy Analyses

Evaluation of the relationship between non-invasive measurements of liver fat content and liver histopathology may also be conducted. Exploratory analyses of the effect of ADAs on the efficacy of sebelipase alfa may be performed as suggested by the type and amount of data available. In addition to the pre-specified exploratory summary tabulations, other tabulations demonstrating the effects of sebelipase alfa on clinical manifestations of LAL Deficiency, including those not previously well characterized in the literature, may be prepared as appropriate to the type and amount of data. Details of these data presentations will be described in the SAP.

8.9. Pharmacokinetic Analyses

8.9.1. Pharmacokinetic Set

The Pharmacokinetic Set (PK Set) will be comprised of subjects who received at least 1 dose of sebelipase alfa, and have sufficient data for analyses of the PK profile following at least 1 infusion. Pharmacokinetic Analyses will be performed for the PK Set. Sebelipase alfa serum concentration data will be incorporated into a population PK model, which is to be reported separately, and will not part of the reporting of this study.

8.9.2. PK Analysis in Select Adult Subjects (Age \geq 18 Years at Informed Consent)

PK parameters will be derived using standard noncompartmental methods. The actual sampling times will be used in the calculations. The following PK parameters will be derived where possible:

- C_{max} ;
- T_{max} ;
- Area under the serum concentration vs. time curve from time zero to the last measurable time point;

- Area under the serum concentration vs. time curve from time zero to infinity;
- $t_{1/2}$;
- Serum clearance;
- Apparent volume of distribution.

Pre-dose values falling below the lower limit of quantification (LLOQ) will be set to zero as appropriate. Any value below the LLOQ of the assay before the time to maximum concentration will be assumed to be zero. Serum levels below LLOQ appearing in terminal samples will be omitted from the analysis. PK parameters will be summarized by dose and dosing regimen.

8.9.3. PK Analysis in Pediatric Subjects (Age <18 Years at Informed Consent)

Serum concentrations of sebelipase alfa will be summarized in a descriptive manner. Scatter plots may be used and where appropriate concentrations may be summarised by collection interval, in addition to dose and dosing regimen.

8.10. Health-Related Quality of Life

For the subset of subjects ≥ 5 years of age, change in HRQOL measures will be calculated from Baseline and tabulated for each evaluation time point as an exploratory analysis. In addition to the evaluation of changes in the overall scores for each HRQOL measure, changes in subscales and summary scores, as applicable to the HRQOL instrument, will be summarized. For the PedsQL™, in addition to the Generic Core Scale, the 4 subscales (physical functioning, emotional functioning, social functioning, and school functioning) may also be summarized.

8.11. Subgroup Analyses

Effect of ADAs will be examined for efficacy and safety endpoints. As subject numbers permit, analyses may be conducted in other subgroups of interest (e.g., subjects who undergo major changes in diet and/or use of lipid-lowering medications).

8.12. Missing or Invalid Data

All data will be analyzed as they were collected in the database. Missing data in general will not be imputed; any imputation techniques if deemed necessary will be discussed in the clinical study report.

8.13. Interim Analysis

No formal interim analysis is planned. Analyses are descriptive and no adjustments will be made for multiple comparisons.

8.14. Extension Analyses

At the completion of the study, analyses will also be performed on cumulative data from the treatment period and expanded treatment period. Efficacy endpoints will be analyzed using techniques similar to those described for the analyses of data in the treatment period. Safety endpoints, as well as PK and HRQOL endpoints, will also continue to be analyzed in the extension analyses.

Further details of the extension analyses will be provided in the SAP.

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 are 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 in eCRFs via electronic data capture 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 will be obtained from the subject's source documents and then entered into the eCRF by authorized site personnel. Clinical data that are not recorded in the eCRF will be captured and transferred to the Sponsor or designee.

9.4. Records Retention

It is the responsibility of the Investigator's or other appropriate persons according to local regulations, to retain study essential documents for at least 2 years after the last approval of a marketing application in his/her 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 sebelipase alfa. These documents should be retained for a longer period if required by the local legislation requirements and/or 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) 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). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory).

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 (US Code of Federal Regulations 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 applicant and a copy of this decision will be provided to the Sponsor before commencement of this study. The IRB/IEC will be requested to provide a list of IRB/IEC members. A member who is affiliated with the Sponsor should not participate in voting on the IRB/IEC opinion.

Each subject (or the subject's parent or legal guardian) will be given a consent form describing this study and providing sufficient information for the subject (or the subject's parent or legal guardian) to make an informed decision about the subject's participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB/IEC for the study. The formal consent of a subject (or the subject's parent or legal guardian), 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 (if applicable) 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 Data Disclosure

A clinical study report (CSR) will be produced after all subjects have completed the treatment period, and will include all available subject data for this period. A final CSR will be produced upon completion of the study and will include cumulative data for both the treatment period and the open-label extension period. A coordinating Investigator will be designated to review and sign the completed CSRs. Information about this study will be posted on the <http://clinicaltrials.gov/> and <https://www.clinicaltrialsregister.eu/> websites and, where applicable, on other websites required by the local regulatory authorities of participating countries. 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.

13. References

- Abramov A, Schorr S, Wolman M. Generalized xanthomatosis with calcified adrenals. *AMA J Dis Child*. 1956;91(3):282-286.
- Anderson RA, Bryson GM, Parks JS. Lysosomal acid lipase mutations that determine phenotype in Wolman and cholesterol ester storage disease. *Mol Genet Metab*. 1999;68:333-345.
- Assmann G, Seedorf U. Acid lipase deficiency: Wolman disease and cholesteryl ester storage disease. In: Beaudet A, Vogelstein B, Kinzler K, Antonarakis S, Ballabio A, eds. *The Metabolic and Molecular Basis of Inherited Disease* (online). 8th ed. New York: McGraw Hill Inc.; 2001:1-49.
- Balwani M, Breen C, Enns GM, et al. Clinical effect and safety profile of recombinant human lysosomal acid lipase in patients with cholesteryl ester storage disease. *Hepatology*. 2013;54(3):950-957.
- Barton NW, Furbish FS, Murray GJ, Garfield M, Brady RO. Therapeutic response to intravenous infusions of glucocerebrosidase in a patient with Gaucher disease. *Proc Natl Acad Sci*. 1990;87:1913-1916.
- Barton NW, Brady RO, Dambrosia JM, Di Bisceglie AM, Doppert SH, Hill SC, et al. Replacement therapy for inherited enzyme deficiency-macrophage-targeted glucocerebrosidase for Gaucher's disease. *N Engl J Med*. 1991;324(21):1464-1470.
- Beaudet AL, Ferry GD, Nichols BL, Rosenberg HA. Cholesterol ester storage disease: Clinical, biochemical, and pathological studies. *J Pediatr*. 1977;90:910-914.
- Bernstein DL, Hulkova H, Bialer, MG, Desnick RJ. Cholesteryl ester storage disease: Review of the findings in 135 reported patients with an underdiagnosed disease. *J Hepatol*. 2013;58(6):1230-1243.
- Cagle PT, Ferry GD, Beaudet AL, Hawkins EP, Opitz JM, Reynolds JF. Clinicopathologic conference: Pulmonary hypertension in an 18-year-old girl with cholesteryl ester storage disease (CESD). *Am J Med Genet*. 1986;24:711-722.
- Cerezyme® (imiglucerase for injection) prescribing information. Cambridge, MA: Genzyme Corporation; 2005. Di Bisceglie AM, Ishak KG, Rabin L, Hoeg JM. Cholesteryl ester storage disease: hepatopathology and effects of therapy with lovastatin. *Hepatology*. 1990;11:764-772.
- Di Bisceglie AM, Ishak KG, Rabin L, Hoeg JM. Cholesteryl ester storage disease: hepatopathology and effects of therapy with lovastatin. *Hepatology*. 1990;11:764-772.
- Elleder M, Chlumská A, Hyanek J, Poupětová H, Ledvinová J, Maas S, et al. Subclinical course of cholesteryl ester storage disease in an adult with hypercholesterolemia, accelerated atherosclerosis, and liver cancer. *J Hepatol*. 2000;32:528-534.
- Fabrazyme® (agalsidase beta) prescribing information. Cambridge, MA: Genzyme Corporation; 2003.

Ferry GD, Whisennand HH, Finegold MJ, Alpert E, Glombicki A. Liver transplantation for cholesteryl ester storage disease. *J Pediatr Gastroenterol Nutr.* 1991;12:376-378.

Frankenberg, WK, Dodds, J, Archer P, et al. The Denver II: A major revision and restandardization of the Denver Developmental Screening Test. *Pediatrics.* 1992;89:91-97.

Gasche C, Aslanidis C, Kain R, Exner M, Helbich T, Dejaco C, et al. A novel variant of lysosomal acid lipase in cholesteryl ester storage disease associate with mild phenotype and improvement on lovastatin. *J Hepatol.* 1997;27:744-750.

Ginsberg HN, Le NA, Short MP, Ramakrishnan R, Desnick RJ. Suppression of apolipoprotein B production during treatment of cholesteryl ester storage disease with lovastatin. *J Clin Invest.* 1987;80:1692-1697.

Glueck CJ, Lichtenstein P, Tracy T, Speirs J. Safety and efficacy of treatment of pediatric cholesteryl ester storage disease with lovastatin. *Pediatr Res.* 1992;32:547-552.

Grabowski GA, Chamas L, Du H. Lysosomal acid lipase deficiencies: The Wolman disease/cholesteryl ester storage disease spectrum. IN: Valle D, Beaudet AL, Vogelstein B, Kinzler KW, et al, eds. Scriver's Online Metabolic and Molecular Bases of Inherited Disease. <http://dx.doi.org/10.1036/ommbid.172>. Published 2012.

Guzzetta PC, Ruley EJ, Merrick HRW, Verderese C, Barton N. Elective subtotal splenectomy: Indications and results in 33 patients. *Ann Surg.* 1990;211:34-42.

Hansen K, Horslen S. Metabolic liver disease in children. *Liver Transplant.* 2008;14:713-733.

Hoeg JM, Demosky SJ, Pescovitz OH, Brewer HB Jr. Cholesteryl ester storage disease and Wolman disease: Phenotypic variants of lysosomal acid cholesteryl ester hydrolase deficiency. *Am J Hum Genet.* 1984;36:1190-1203.

Investigator's Brochure: Recombinant Human Lysosomal Acid Lipase, Sebelipase Alfa (SBC-102), Treatment of Lysosomal Acid Lipase Deficiency. Version No. 5.0., Lexington, MA: Synageva BioPharma Corp; 2014.

Kishnani PS, Corzo D, Nicolino M, Byrne B, Mandel H, Hwu WL, et al. Recombinant human acid α -glucosidase: Major clinical benefits in infantile-onset Pompe disease. *Neurology.* 2007;68:99-109.

Krivit W, Peters C, Dusenbery K, Ben-Yoseph Y, Ramsay NKC, Wagner JE, Anderson R. Wolman disease successfully treated by bone marrow transplantation. *Bone Marrow Transplant.* 2000;26:567-570.

Kuczmarski RJ, Ogden CL, Guo SS, et al. *2000 CDC growth charts for the United States: Methods and development.* Centers for Disease Control and Prevention, National Center for Health Statistics, US Dept. of Health and Human Services. *Vital Health Stat.* 2002;(246):1-190.

Leavitt M, Burt AD, Hu W, Canty D, Gray M, Bray A, et al. Recombinant lysosomal acid lipase normalizes liver weight, transaminases and histopathological abnormalities in an *in vivo* model of cholesteryl ester storage disease. Abstract presented at: 46th Annual Meeting of the European Association for the Study of the Liver; March 30 - April 3, 2011; Berlin, Germany.

Lumizyme[®] (alglucosidase alfa) prescribing information. Cambridge, MA: Genzyme Corporation; 2010.

Mayatepek E, Seedorf U, Wiebusch H, Lenhartz H, Assmann G. Fatal genetic defect causing Wolman disease (short report). *J Inherited Metab Dis*. 1999;22:93-94.

Meyers WF, Hoeg JM, Demosky SJ, Herbst JJ, Brewer HB. The use of parenteral hyperalimentation and elemental formula feeding in the treatment of Wolman disease. *Nutr Res*. 1985;5:423-429.

Muenzer J, Guzsavas-Calikoglu M, McCandless SE, Schuetz TJ, Kimura A. A phase I/II clinical trial of enzyme replacement therapy in mucopolysaccharidosis II (Hunter syndrome). *Mol Genet Metab*. 2007;90:329-337.

Myozyme[®] (alglucosidase alfa) prescribing information. Cambridge, MA: Genzyme Corporation; 2010.

Stahl PD, Rodman JS, Miller MJ, Schlesinger PH. Evidence for receptor-mediated binding of glycoproteins, glycoconjugates, and lysosomal glycosides by alveolar macrophages. *Proc Natl Acad Sci*. 1978;75:1399-1403.

Stein J, Zion Garty B, Dror Y, Fenig E, Zeigler M, and Yaniv I. Successful treatment of Wolman disease by unrelated umbilical cord blood transplantation. *Eur J Pediatr*. 2007; PMID 17033804.

Tadiboyina VT, Liu DM, Miskie BA, Wang J, Hegele RA. Treatment of dyslipidemia with lovastatin and ezetimibe in an adolescent with cholesteryl ester storage disease. *Lipids in Health and Disease*. 2005;4:26-31.

Tarantino MD, McNamara DJ, Granstrom P, Ellefson RD, Unger EC, Udall JN. Lovastatin therapy for cholesteryl ester storage disease in two sisters. *J Pediatr*. 1991;118:131-135.

Tolar J, Petryk A, Khan K, Bjoraker KJ, Jessurun J, Dolan M, Kivisto T, Charnas L, Shapiro EG, and Orchard PJ. Long-term metabolic, endocrine, and neuropsychological outcome of hematopoietic cell transplantation for Wolman disease. *Bone Marrow Transplant*. 2009;43:21-27. PMID 18776925.

Tripuraneni et al, Dyslipidemia Profile in Cholesteryl Ester Storage Disorder, NLA Scientific Sessions; 2013 (Poster 182).

UNICEF, Tracking Progress on Child and Maternal Nutrition: A survival and development priority, UNICEF, New York, 2009.

Valayannopoulos V, Malinova V, Honzík T, Balwani M, Breen C, Deegan PB, et al. Sebelipase alfa over 52 weeks reduces serum transaminases, liver volume and improves serum lipids in patients with lysosomal acid lipase deficiency. *J Hepatol*. 2014;61:1135-1142

van der Ploeg AT, Clemens PR, Corzo D. A randomized study of alglucosidase alfa in late onset Pompe's disease. *N Engl J Med*. 2010;362:1396-1406.

Varni JW. The PedsQL[™] 4.0 Generic Core Scales Young Adult Version: Feasibility, reliability, and validity in a university student population. *J Health Psychol*. 2009;14:611-622.

vom Dahl, S, Harzer K, Rolfs A, Albrecht B, Niederau C, Vogt C, et al. Hepatosplenomegalic lipidosis: what unless Gaucher? Adult cholesteryl ester storage disease (CESD) with anemia, mesenteric lipodystrophy, increased plasma chitotriosidase activity and a homozygous lysosomal acid lipase -1 exon 8 splice junction mutation. *J Hepatol.* 1999;31:741-746.

VPRIV® (velaglucerase alfa for injection) prescribing information. Cambridge, MA: Shire Human Genetic Therapies, Inc.; 2010.

WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization, 2006 (312 pages).

WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Head circumference-for-age, arm circumference-for-age, triceps skinfold-for-age and subscapular skinfold-for-age: Methods and development. Geneva: World Health Organization, 2007 (217 pages).

Wilcox, WR, Banikazemi M, Guffon N, Waldek S, Lee P, Linthorst GE, et al. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. *Am J Hum Genet.* 2004;75:65-74.

Wraith JE, Clarke LA, Beck M, Kolodny EH, Pastores GM, Muenzer J, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human α -L-iduronidase (Laronidase). *J Pediatr.* 2004;144:581-588.

Yanir A, Allatif MA, Weintraub M, Stepensky P. Unfavorable outcome of hematopoietic stem cell transplantation in two siblings with Wolman disease due to graft failure and hepatic complications. *Mol Genet Metab.* 2013;109(2):224-6.

Yokoyama S, McCoy E. Long-term treatment of a homozygous cholesteryl ester storage disease with combined cholestyramine and lovastatin. *J Inherit Met Dis.* 1992;15:291-292.

Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut.* 1999;45:295-300.

14. Appendices

Appendix A: Child-Pugh Score and Classification

The Child-Pugh score is calculated as the sum of the individual scores for each of the following 5 factors:

| Parameter | | Score | | |
|---------------------------------------|-------------------|---------|-------------------|-------------------|
| | | 1 Point | 2 Points | 3 Points |
| Total Serum Bilirubin | mg/dL | <2.0 | 2.0 to 3.0 | >3.0 |
| | µmol/L | <34 | 34 to 51 | >51 |
| Serum Albumin | g/dL | >3.5 | 3.0 to 3.5 | <3.0 |
| | g/L | >35 | 30 to 35 | <30 |
| Prothrombin Time | Seconds prolonged | 0 to 4 | 4 to 6 | >6 |
| | INR | <1.7 | 1.7 to 2.3 | >2.3 |
| Ascites | | None | Easily controlled | Poorly controlled |
| Hepatic Encephalopathy | | None | Minimal | Advanced |
| INR = International Normalized Ratio | | | | |
| Source: Harrison's Manual of Medicine | | | | |

The Child-Pugh classification is then determined as follows:

| Child-Pugh Classification | Total Child-Pugh Score |
|---------------------------|------------------------|
| Class A | 5 to 6 |
| Class B | 7 to 9 |
| Class C | 10 to 15 |

Appendix B: Schedules of Assessments**Schedule I - Assessments for Adult Subjects (Subjects ≥18 years) - Screening to Week 48 of Treatment Period**

| Assessments* | Screening | Treatment | | | | | | | | | | | | | |
|---|------------------|----------------|------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | Day -45 to Day 0 | Day 0 | Week 2 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 44 | Week 48 |
| | | | ±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 |
| Informed Consent/Assent | X | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X ^p | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | |
| AUDIT | X | | | | | | | | | | | | | | |
| Historical DNA Results ¹ | X | | | | | | | | | | | | | | |
| 12-lead ECG | X | | | | | | | | | | | | | | X ^p |
| Physical Examination ² | X | X ^p | | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Height | | X ^p | | | | | | | | | | | | | |
| Weight | | X ^p | Every two weeks ^p | | | | | | | | | | | | |
| Abdominal MRI ³ | X | | | | | | | | | | | | | | X ^p |
| Carotid MRI | X | | | | | | | | | | | | | | X ^p |
| Esophagogastroduodenoscopy ⁴ | X | | | | | | | | | | | | | | X ^p |
| Endoscopic biopsy ⁵ | X | | | | | | | | X ^p | | | | | | |
| Liver Biopsy ⁶ | X | | | | | | | | | | | | | | X ^p |
| Hepatic Venous Pressure Gradient | X | | | | | | | | | | | | | | X ^p |
| Transient elastography ⁷ | X | | | | | | | | | | | | | | X ^p |
| HRQOL | X | | | | | | | | X ^p | | | | | | X ^p |
| Clinical Laboratory⁸ | | | | | | | | | | | | | | | |
| DNA Blood Sample ⁹ | X | | | | | | | | | | | | | | |
| LAL Enzyme Activity (DBS) | X | | | X ^p | | X ^p | | | X ^p | | | | | | |
| Liver Panel | X | X ^p | X ^p | X ^p | X ^p | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Lipid Panel | X | X ^p | X ^p | X ^p | X ^p | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Hematology, Electrolytes, Glucose, Creatinine | X | | | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Coagulation Panel | X | | | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Pregnancy Test ¹⁰ | X | 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 |
| Anti-drug Antibody | | X ^p | X ^p | X ^p | X ^p | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Urinalysis | X | | | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Macrophage Activation Markers | X | | | | | X ^p | | | X ^p | | | X ^p | | | X ^p |

| Assessments* | Screening | Treatment | | | | | | | | | | | | | | |
|--|------------------|----------------|------------------------------|---------|---------|----------------|---------|---------|----------------|---------|---------|----------------|---------|---------|----------------|--|
| | Day -45 to Day 0 | Day 0 | Week 2 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 44 | Week 48 | |
| | | | ±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 | |
| HbA1c | X | | | | | X ^P | | | X ^P | | | X ^P | | | X ^P | |
| Viral Hepatitis Screen | X | | | | | | | | | | | | | | | |
| CDT | X | X ^P | | | | | | | X ^P | | | | | | X ^P | |
| Blood Exploratory Biomarkers | X | | | | | X ^P | | | X ^P | | | X ^P | | | X ^P | |
| Pharmacokinetic Profile ¹¹ | | X | | | | | | | X | | | | | | X | |
| Vital Signs ¹² | X | X ^P | Every two weeks ^P | | | | | | | | | | | | | |
| Sebelipase alfa Infusion ¹³ | | X | Every two weeks | | | | | | | | | | | | | |
| Adverse Event Assessment | Continuous | | | | | | | | | | | | | | | |
| Concomitant Meds/Treatment ¹⁴ | Continuous | | | | | | | | | | | | | | | |

* **Note: All study visits will be scheduled relative to Day 0 (Baseline); consecutive infusions must be administered at least 7 days apart.**

^P Pre-infusion

¹ Historical DNA will be assessed only for subjects with previous liver transplant or hematopoietic stem cell transplant, when no enzyme deficiency was documented prior to transplant. In a highly suggestive case of LAL Deficiency, where only 1 mutation is identified, subjects may be included based on a fibroblast enzyme test.

² All physical examinations will include assessment of liver and spleen size, lymphadenopathy, arterial disease, and skin manifestations of liver disease or dyslipidemia. Physical examination findings should drive additional functional assessments.

³ Abdominal ultra-sound can be substituted if an abdominal MRI is medically contraindicated.

⁴ Esophagogastroduodenoscopy will be performed at Screening and Week 48 for subjects with evidence of advanced liver disease, unless medically contraindicated ([Section 5.14](#)).

⁵ A historical endoscopic biopsy result will be accepted in lieu of a Screening biopsy if performed within 1 year of Screening. A follow-up biopsy will be performed only at Week 24, if evidence of substrate accumulation was present at Screening. Repeat biopsy during the study are not required, however any biopsy performed will be recorded in the CRF.

⁶ A historical liver biopsy obtained within 26 weeks prior to Screening and adequate for histological examination may be used in lieu of a Screening biopsy. The liver biopsy should be obtained via the transjugular method in those subjects with advanced liver disease, where local regulations and facilities permit, so the hepatic venous pressure gradient can be measured and collected during the procedure. Any biopsy done for other medical reasons during the course of the study will also be evaluated by central pathologists (stained and unstained samples). Subjects who have any prior liver biopsy unstained sections will be analyzed in the same method, if available. Liver biopsy at Week 48 can be ± 2 weeks, for scheduling considerations.

⁷ Transient elastography will be performed in locales where technology is available.

⁸ Refer to [Section 5.9](#) for a list of analytes in each laboratory panel. Subjects ≥ 18 years of age must fast for at least 9 hours prior to collection of samples for the lipid panel and fasting serum glucose, and must abstain from alcohol for at least 24 hours prior to collection of blood for the liver and lipid panels. *Prior to any dose change, serum lipid, serum liver, hematology, chemistry, ferritin and hs-CRP shall be obtained; ADA and PK assessments will be obtained on the day of any study drug dose change, as described in [Section 5.9.4](#). Serum lipid and serum liver assessments should be taken 4, 8, and 12 weeks following any study drug or lipid drug dose change.*

⁹ A sample will be obtained at Screening, or as soon as practically possible thereafter ([Section 5.9.3](#))

¹⁰ For female subjects of childbearing potential only. Serum pregnancy test is required at screening. Urine pregnancy tests at all designated visits thereafter.

¹¹ PK Samples will be taken at Baseline, Week 24, Week 48, and on the first day of any dose modification as per [Table 2](#) and [Table 3](#).

¹² Vital signs will be measured at one time point during Screening. On the day of study drug dosing, vitals will be collected before dosing, every 30 minutes (±10 min) during the infusion, and every 30 minutes (±10 min) from 0 to 2 hours after infusion. Beginning at Week 24, the post-infusion period for vital sign monitoring may be shortened from

2 hours to 1 hour for subjects who have completed at least 22 weeks of treatment with no occurrence of moderate or severe IARs, contingent upon approval from the Sponsor.

- ¹³ Please refer to [Section 6.1](#) for details on treatment administration. Please refer to the IMP manual for detailed instructions on duration and rate of infusions. After Week 24, infusion time may be decreased to 1 hour. If the infusion is not well tolerated; the infusion rate may be decreased ([Section 6.5.2](#)). If dose is increased to weekly infusion, the allowable window for treatment is ± 2 days, and infusions must be at least 5 days apart.
- ¹⁴ Subjects should also be queried about any changes in lipid-lowering medications or lipid-lowering diets, UDCA, metformin, glitazones, or vitamin E.

Schedule I - Assessments for Adult Subjects (Subjects ≥18 years) - Week 52 to Week 96 of Treatment Period

| Assessments* | Treatment | | | | | | | | | | | |
|---|------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| | Week 52 ±7 days | Week 56 ±7 days | Week 60 ±7 days | Week 64 ±7 days | Week 68 ±7 days | Week 72 ±7 days | Week 76 ±7 days | Week 80 ±7 days | Week 84 ±7 days | Week 88 ±7 days | Week 92 ±7 days | Week 96 ±7 days |
| 12-lead ECG | | | | | | | | | | | | X ^P |
| Physical Examination ¹ | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Weight | Every two weeks ^P | | | | | | | | | | | |
| Abdominal MRI ² | | | | | | | | | | | | X ^P |
| Carotid MRI | | | | | | | | | | | | X ^P |
| Esophagogastroduodenoscopy ³ | | | | | | | | | | | | X ^P |
| Endoscopic biopsy ⁴ | | | | | | | | | | | | X ^P |
| Liver Biopsy ⁵ | | | | | | | | | | | | X ^P |
| Hepatic Venous Pressure Gradient | | | | | | | | | | | | X ^P |
| Transient elastography ⁶ | | | | | | | | | | | | X ^P |
| HRQOL | | | | | | X ^P | | | | | | X ^P |
| Clinical Laboratory⁷ | | | | | | | | | | | | |
| LAL Enzyme Activity (DBS) | | | | | | | | | | | | |
| Liver Panel | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Lipid Panel | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Hematology, Electrolytes, Glucose, Creatinine | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Coagulation Panel | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Pregnancy Test ⁸ | X ^P | X ^P | X ^P | X ^P | X ^P | X ^P | X ^P | X ^P | X ^P | X ^P | X ^P | X ^P |
| Anti-drug Antibody | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Urinalysis | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Macrophage Activation Markers | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| HbA1c | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| CDT | | | | | | X ^P | | | | | | X ^P |
| Blood Exploratory Biomarkers | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Vital Signs ⁹ | Every two weeks ^P | | | | | | | | | | | |
| Sebelipase alfa Infusion ¹⁰ | Every two weeks | | | | | | | | | | | |
| Adverse Event Assessment | Continuous | | | | | | | | | | | |

| Assessments* | Treatment | | | | | | | | | | | |
|--|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| | Week 52 ±7 days | Week 56 ±7 days | Week 60 ±7 days | Week 64 ±7 days | Week 68 ±7 days | Week 72 ±7 days | Week 76 ±7 days | Week 80 ±7 days | Week 84 ±7 days | Week 88 ±7 days | Week 92 ±7 days | Week 96 ±7 days |
| Concomitant Meds/Treatment ¹¹ | Continuous | | | | | | | | | | | |

***Note: All study visits will be scheduled relative to Day 0 (Baseline); consecutive infusions must be administered at least 7 days apart. Assessments performed for subjects of a certain age are based on the subject's age on the date that informed consent is obtained.**

^P Pre-infusion

¹ All physical examinations will include assessment of liver and spleen size, lymphadenopathy, arterial disease, and skin manifestations of liver disease or dyslipidemia. Physical examination findings should drive additional functional assessments.

² Abdominal ultra-sound can be substituted if an abdominal MRI is medically contraindicated.

³ Esophagogastroduodenoscopy at Week 96 is optional.

⁴ Repeat endoscopic biopsy during the study is not required, however any biopsy performed will be recorded in the CRF.

⁵ The liver biopsy should be obtained via the transjugular method in those subjects with advanced liver disease, where local regulations and facilities permit, so the hepatic venous pressure gradient can be measured and collected during the procedure. Any biopsy done for other medical reasons during the course of the study will also be evaluated by central pathologists (stained and unstained samples). Subjects who have any prior liver biopsy unstained sections will be analyzed in the same method, if available.

⁶ Transient elastography will be performed in locales where technology is available.

⁷ Refer to [Table 1](#) for a list of analytes in each laboratory panel. Subjects ≥ 18 years of age must fast for at least 9 hours prior to collection of samples for the lipid panel and fasting serum glucose, and must abstain from alcohol for at least 24 hours prior to collection of blood for the liver and lipid panels. Prior to any dose change, serum lipid, serum liver, hematology, chemistry, ferritin and hs-CRP shall be obtained; ADA and PK assessments will be obtained on the day of any study drug dose change, as described in [Section 5.9.4](#). Serum lipid and serum liver assessments should be taken 4, 8, and 12 weeks following any study drug or lipid drug dose change.

⁸ For female subjects of childbearing potential only. Serum pregnancy test is required at screening. Urine pregnancy tests at all designated visits thereafter.

⁹ On the day of study drug dosing, vitals will be collected before dosing, every 30 minutes (±10 min) during the infusion, and every 30 minutes (±10 min) from 0 to 2 hours after infusion. Beginning at Week 24, the post infusion period for vital sign monitoring may be shortened from 2 hours to 1 hour for subjects who have completed at least 22 weeks of treatment with no occurrence of moderate or severe IARs, contingent upon approval from the Sponsor.

¹⁰ Please refer to IMP manual for detailed instructions on duration and rate of infusions. After Week 24, infusion time may be decreased to 1 hour. If the infusion is not well tolerated; the infusion rate may be decreased ([Section 6.5.2](#)). If dose is increased to weekly infusion, the allowable window for treatment is ±2 days, and infusions must be at least 5 days apart.

¹¹ Subjects should also be queried about any changes in lipid-lowering medications or lipid-lowering diets, UDCA, metformin, glitazones, or vitamin E.

Schedule I - Assessments for Adult Subjects (Subjects ≥18 years) - Expanded Treatment Period through Follow-up

| Assessments* | Expanded Treatment | | | | | | | | | | | | End of Study Visit (Early Withdrawal) | Follow-up Phone Call 4 Weeks (+7) days after last infusion |
|---|------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|---------------------------------------|--|
| | Week 100 ±7 days | Week 104 ±7 days | Week 108 ±7 days | Week 112 ±7 days | Week 116 ±7 days | Week 120 ±7 days | Week 124 ±7 days | Week 128 ±7 days | Week 132 ±7 days | Week 136 ±7 days | Week 140 ±7 days | Week 144 ±7 days | | |
| 12-lead ECG | | | | | | | | | | | | X ^P | X | |
| Physical Examination ¹ | | | X ^P | | | X ^P | | | X ^P | | | X ^P | X | |
| Weight | Every two weeks ^P | | | | | | | | | | | | X | |
| Abdominal MRI ² | | | | | | | | | | | | X ^P | X | |
| Carotid MRI | | | | | | | | | | | | X ^P | X | |
| Esophagogastroduodenoscopy ³ | | | | | | | | | | | | X ^P | | |
| Endoscopic biopsy ⁴ | | | | | | | | | | | | | | |
| Liver Biopsy ⁵ | | | | | | | | | | | | | X | |
| Hepatic Venous Pressure Gradient | | | | | | | | | | | | X ^P | X | |
| Transient elastography ⁶ | | | | | | | | | | | | X ^P | X | |
| HRQOL | | | | | | X ^P | | | | | | X ^P | X | |
| Clinical Laboratory⁷ | | | | | | | | | | | | | | |
| LAL Enzyme Activity (DBS) | | | | | | | | | | | | | X | |
| Liver Panel | | | X ^P | | | X ^P | | | X ^P | | | X ^P | X | |
| Lipid Panel | | | X ^P | | | X ^P | | | X ^P | | | X ^P | X | |
| Hematology, Electrolytes, Glucose, Creatinine | | | X ^P | | | X ^P | | | X ^P | | | X ^P | X | |
| Coagulation Panel | | | X ^P | | | X ^P | | | X ^P | | | X ^P | X | |
| Pregnancy Test ⁸ | 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 | |
| Anti-drug Antibody | | | X ^P | | | X ^P | | | X ^P | | | X ^P | X | |
| Urinalysis | | | X ^P | | | X ^P | | | X ^P | | | X ^P | X | |
| Macrophage Activation Markers | | | X ^P | | | X ^P | | | X ^P | | | X ^P | X | |
| HbA1c | | | X ^P | | | X ^P | | | X ^P | | | X ^P | | |
| CDT | | | | | | X ^P | | | | | | X ^P | | |
| Blood Exploratory Biomarkers | | | X ^P | | | X ^P | | | X ^P | | | X ^P | | |
| Vital Signs ⁹ | Every two weeks ^P | | | | | | | | | | | | X | |
| Sebelipase alfa Infusion ¹⁰ | Every two weeks | | | | | | | | | | | | | |
| Adverse Event Assessment | Continuous | | | | | | | | | | | | | |
| Concomitant | Continuous | | | | | | | | | | | | | |

| Assessments* | Expanded Treatment | | | | | | | | | | | | End of Study Visit (Early Withdrawal) | Follow-up Phone Call 4 Weeks (+7) days after last infusion |
|------------------------------|--------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|---------------------------------------|--|
| | Week 100 ±7 days | Week 104 ±7 days | Week 108 ±7 days | Week 112 ±7 days | Week 116 ±7 days | Week 120 ±7 days | Week 124 ±7 days | Week 128 ±7 days | Week 132 ±7 days | Week 136 ±7 days | Week 140 ±7 days | Week 144 ±7 days | | |
| Meds/Treatment ¹¹ | | | | | | | | | | | | | | |

*Note: All study visits will be scheduled relative to Day 0 (Baseline); consecutive infusions must be administered at least 7 days apart. Assessments performed for subjects of a certain age are based on the subject's age on the date that informed consent is obtained.

^P Pre-infusion

¹ All physical examinations will include assessment of liver and spleen size, lymphadenopathy, arterial disease, and skin manifestations of liver disease or dyslipidemia. Physical examination findings should drive additional functional assessments.

² Abdominal ultra-sound can be substituted if an abdominal MRI is medically contraindicated.

³ Esophagogastroduodenoscopy at Week 144 is optional.

⁴ Repeat endoscopic biopsy during the study is not required, however any biopsy performed will be recorded in the CRF.

⁵ The liver biopsy should be obtained via the transjugular method in those subjects with advanced liver disease, where local regulations and facilities permit, so the hepatic venous pressure gradient can be measured and collected during the procedure. Any biopsy done for other medical reasons during the course of the study will also be evaluated by central pathologists (stained and unstained samples). Subjects who have any prior liver biopsy unstained sections will be analyzed in the same method, if available.

⁶ Transient elastography will be performed in locales where technology is available.

⁷ Refer to [Table 1](#) for a list of analytes in each laboratory panel. Subjects ≥ 18 years of age must fast for at least 9 hours prior to collection of samples for the lipid panel and fasting serum glucose, and must abstain from alcohol for at least 24 hours prior to collection of blood for the liver and lipid panels. Prior to any dose change, serum lipid, serum liver, hematology, chemistry, ferritin and hs-CRP shall be obtained; *ADA and PK assessments will be obtained on the day of any study drug dose change, as described in Section 5.9.4.* Serum lipid and serum liver assessments should be taken 4, 8, and 12 weeks following any study drug or lipid drug dose change.

⁸ For female subjects of childbearing potential only. Serum pregnancy test is required at screening. Urine pregnancy tests at all designated visits thereafter.

⁹ On the day of study drug dosing, vitals will be collected before dosing, every 30 minutes (±10 min) during the infusion, and every 30 minutes (±10 min) from 0 to 2 hours after infusion. Beginning at Week 24, the post infusion period for vital sign monitoring may be shortened from 2 hours to 1 hour for subjects who have completed at least 22 weeks of treatment with no occurrence of moderate or severe IARs, contingent upon approval from the Sponsor.

¹⁰ Please refer to IMP manual for detailed instructions on duration and rate of infusions. After Week 24, infusion time may be decreased to 1 hour. If the infusion is not well tolerated; the infusion rate may be decreased ([Section 6.5.2](#)). If dose is increased to weekly infusion, the allowable window for treatment is ±2 days, and infusions must be at least 5 days apart.

¹¹ Subjects should also be queried about any changes in lipid-lowering medications or lipid-lowering diets, UDCA, metformin, glitazones, or vitamin E.

Schedule II - Assessments for Pediatric Subjects (Subjects <18 years) - Screening to Week 48 of Treatment Period

| Assessments* | Screening | Treatment | | | | | | | | | | | | | |
|---|------------------|----------------|------------------------------|----------------|----------------|----------------|---------|---------|----------------|---------|---------|----------------|---------|---------|----------------|
| | Day -45 to Day 0 | Day 0 | Week 2 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 44 | Week 48 |
| | | | ±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 |
| Informed Consent/Assent | X | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X ^P | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | |
| Historical DNA ¹ | X | | | | | | | | | | | | | | |
| 12-Lead ECG | X | | | | | | | | | | | | | | X ^P |
| Physical Examination ² | X | X ^P | | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Height (<2 years) ³ | X | X ^P | Every two weeks ^P | | | | | | | | | | | | |
| Weight (<2 years) ³ | X | X ^P | Every two weeks ^P | | | | | | | | | | | | |
| Height (2-18 years) | X | | | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Weight (2-18 years) | X | X ^P | Every two weeks | | | | | | | | | | | | |
| Abdominal MRI ⁴ | X | | | | | | | | | | | | | | X ^P |
| Carotid MRI | X | | | | | | | | | | | | | | X ^P |
| Liver Biopsy ⁵ | X | | | | | | | | | | | | | | X ^P |
| Hepatic Venous Pressure Gradient | X | | | | | | | | | | | | | | X ^P |
| Endoscopic Biopsy ⁶ | X | | | | | | | | X ^P | | | | | | |
| Transient elastography ⁷ | X | | | | | | | | | | | | | | X ^P |
| Denver II ⁸ | X | | | | | | | | X ^P | | | | | | X ^P |
| HRQOL (subjects ≥5 years) ⁹ | X | | | | | | | | X ^P | | | | | | X ^P |
| Clinical Laboratory¹⁰ | | | | | | | | | | | | | | | |
| DNA Blood Sample ¹¹ | X | | | | | | | | | | | | | | |
| LAL Enzyme Activity (DBS) | X | | | X ^P | | X ^P | | | X ^P | | | | | | |
| Liver Panel | X | X ^P | X ^P | X ^P | X ^P | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Lipid Panel | X | X ^P | X ^P | X ^P | X ^P | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Hematology, Electrolytes, | X | | | | | X ^P | | | X ^P | | | X ^P | | | X ^P |

| Assessments* | Screening | Treatment | | | | | | | | | | | | | |
|--|------------------|----------------|------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | Day -45 to Day 0 | Day 0 | Week 2 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 44 | Week 48 |
| | | | ±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 |
| Glucose, Creatinine | | | | | | | | | | | | | | | |
| Coagulation Panel | X | | | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Pregnancy Test ¹² | X | 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 |
| Anti-drug Antibody | | X ^P | | X ^P | X ^P | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Urinalysis | X | | | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Macrophage Activation Markers | X | | | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| HbA1c | X | | | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Viral Hepatitis Screen | X | | | | | | | | | | | | | | |
| Blood Exploratory Biomarkers | X | | | | | X ^P | | | X ^P | | | X ^P | | | X ^P |
| Pharmacokinetic Profile ¹³ | | X | | | | | | | X | | | | | | X |
| Vital Signs ¹⁴ | X | X ^P | Every two weeks ^P | | | | | | | | | | | | |
| Sebelipase alfa Infusion ¹⁵ | | X | Every two weeks | | | | | | | | | | | | |
| Adverse Event Assessment | Continuous | | | | | | | | | | | | | | |
| Concomitant Meds/Treatment ¹⁶ | Continuous | | | | | | | | | | | | | | |

* Note: All study visits will be scheduled relative to Day 0 (Baseline); consecutive infusions must be administered at least 7 days apart. Assessments performed for subjects of a certain age are based on the subject's age on the date that informed consent is obtained.

^P Pre-infusion

- ¹ Historical DNA assessed only for subjects with previous liver transplant or bone marrow transplant, when no enzyme deficiency was documented prior to transplant. In a highly suggestive case of LAL Deficiency, where only one mutation is identified, subjects may be included based on a fibroblast enzyme test.
- ² All physical examinations will include assessment of liver and spleen size, lymphadenopathy, arterial disease, and skin manifestations of hepatic disease or dyslipidemia. Physical exam findings should drive any additional functional assessments.
- ³ For subjects <2 years of age, weight, recumbent length or height, and abdominal circumference will be measured at all visits; mid-upper arm circumference will be measured. Head circumference will be measured in children up to 3 years of age.
- ⁴ Abdominal MRI should be considered in subjects receiving general anesthesia and/or sedation for other procedures at the indicated time points. There should be at least 3 months between each MRI. Ultrasound may be substituted at a given time point if an MRI is contraindicated.
- ⁵ Liver biopsies will be obtained in subjects <18 years of age. An historical liver biopsy obtained within 26 weeks prior to Screening and adequate for histological examination may be used in lieu of a Screening biopsy. The liver biopsy should be obtained via the transjugular method in those subjects with advanced liver disease, where local regulations and facilities permit, so the hepatic venous pressure gradient can be measured and collected during this procedure. Any biopsy done for other medical reasons during the course of the study will also be evaluated by central pathologists (stained and unstained samples). Subjects who have any prior liver biopsy unstained sections will be analyzed in the same method, if available. Liver biopsy at Week 48 can be ± 2 weeks, for scheduling considerations.
- ⁶ A historical endoscopic biopsy result will be accepted in lieu of a Screening biopsy if performed within 1 year of Screening. A follow-up biopsy will be performed only at Week 24, if evidence of substrate accumulation was present at Screening. Week 24 biopsy is optional for pediatric subjects. However, any biopsy performed during the study will be recorded in the CRF.

- ⁷ Transient elastography will be performed in locales where technology is available.
- ⁸ Denver II assessments will be completed for subjects who are ≤6 years old during the screening period.
- ⁹ Age-appropriate health-related quality of life questionnaires will be completed prior to any other study procedures.
- ¹⁰ Refer to [Section 5.9](#) for a list of analytes in each laboratory panel. Subjects will refrain from ingestion of alcohol for 24 hours prior to the collection of blood samples for lipid and liver panels. Labs will be drawn as blood volume and clinical status allow. See laboratory manual or SOM for details. Prior to any dose change, serum lipid, serum liver, hematology, chemistry, ferritin and hs-CRP shall be obtained; ADA and PK assessments will be obtained on the day of any study drug dose change, as described in [Section 5.9.4](#). Serum lipid and serum liver assessments should be taken 4, 8, and 12 Weeks following any study-drug or lipid drug dose change.
- ¹¹ A sample will be obtained at Screening, or as soon as practically possible thereafter ([Section 5.9.3](#))
- ¹² For female subjects of childbearing potential only. Serum pregnancy test is required at screening. Urine pregnancy tests at all designated visits thereafter.
- ¹³ PK Samples will be taken at Baseline, Week 24, Week 48, and on the first day of any dose modification as per the table in [Section 5.9.4](#), as blood volume allows.
- ¹⁴ Vital signs will be measured at one time point during Screening. On the day of study drug dosing, vitals will be collected pre-dose, every 30 minutes (±10 min) during the infusion, and every 30 minutes (±10 min) from 0 to 2 hours after infusion. Beginning at Week 24, the post-infusion period for vital sign monitoring may be shortened from 2 hours to 1 hour for subjects who have completed at least 22 weeks of treatment with no occurrence of moderate or severe IARs, contingent upon approval from the Sponsor.
- ¹⁵ Please refer to the IMP manual for detailed instructions on duration and rate of infusions. After Week 24, infusion time may be decreased to 1 hour. If the infusion is not well tolerated; the infusion rate may be decreased ([Section 6.5.2](#)). If dose is increased to weekly infusion, the allowable window for treatment is ±2 days, and infusions must be at least 5 days apart.
- ¹⁶ Subjects/parents should also be queried about any changes in lipid-lowering medications or lipid-lowering diets, UDCA, metformin, glitazones, or vitamin E.

Schedule II - Assessments for Pediatric Subjects (Subjects <18 years) - Week 52 to Week 96 of Treatment Period

| Assessments* | Treatment | | | | | | | | | | | |
|---|------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| | Week 52 | Week 56 | Week 60 | Week 64 | Week 68 | Week 72 | Week 76 | Week 80 | Week 84 | Week 88 | Week 92 | Week 96 |
| | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days |
| 12-lead ECG | | | | | | | | | | | | X ^p |
| Physical Examination ¹ | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Height (<2 years) ² | Every two weeks ^p | | | | | | | | | | | |
| Weight (<2 years) ² | Every two weeks ^p | | | | | | | | | | | |
| Height (2-18 years) | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Weight (2-18 years) | Every two weeks ^p | | | | | | | | | | | |
| Abdominal MRI ³ | | | | | | | | | | | | X ^p |
| Carotid MRI | | | | | | | | | | | | X ^p |
| Liver Biopsy ⁴ | | | | | | | | | | | | X ^p |
| Hepatic Venous Pressure Gradient | | | | | | | | | | | | X ^p |
| Endoscopic Biopsy ⁵ | | | | | | | | | | | | X ^p |
| Transient elastography ⁶ | | | | | | | | | | | | X ^p |
| Denver II ⁷ | | | | | | X ^p | | | | | | X ^p |
| HRQOL (subjects ≥5 years) ⁸ | | | | | | X ^p | | | | | | X ^p |
| Clinical Laboratory Tests⁹ | | | | | | | | | | | | |
| LAL Enzyme Activity (DBS) | | | | | | | | | | | | |
| Liver Panel | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Lipid Panel | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Hematology, Electrolytes, Glucose, Creatinine | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Coagulation Panel | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Pregnancy Test ¹⁰ | X ^p | X ^p | X ^p | X ^p | X ^p | X ^p | X ^p | X ^p | X ^p | X ^p | X ^p | X ^p |
| Anti-drug Antibody | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Urinalysis | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Macrophage Activation Markers | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| HbA1c | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Blood Exploratory Biomarkers | | | X ^p | | | X ^p | | | X ^p | | | X ^p |
| Vital Signs ¹¹ | Every two weeks ^p | | | | | | | | | | | |
| Sebelipase alfa Infusion ¹² | Every two weeks | | | | | | | | | | | |
| Adverse Event Assessment | Continuous | | | | | | | | | | | |
| Concomitant Meds/Treatment ¹³ | Continuous | | | | | | | | | | | |

* Note: All study visits will be scheduled relative to Day 0 (Baseline); consecutive infusions must be administered at least 7 days apart. Assessments performed for subjects of a certain age are based on the subject's age on the date that informed consent is obtained.

^P Pre-infusion

- ¹ All physical examinations will include assessment of liver and spleen size, lymphadenopathy, arterial disease, and skin manifestations of hepatic disease or dyslipidemia. Physical exam findings should drive any additional functional assessments.
- ² For subjects <2 years of age, weight, recumbent length or height, and abdominal circumference will be measured at all visits; mid-upper arm circumference will be measured. Head circumference will be measured in children up to 3 years of age.
- ³ Abdominal MRI should be considered in subjects receiving general anesthesia and/or sedation for other procedures at the indicated time points. There should be at least 3 months between each MRI. Ultrasound may be substituted at a given time point if an MRI is contraindicated.
- ⁴ Liver biopsies will be obtained in subjects <18 years of age. The liver biopsy should be obtained via the transjugular method in those subjects with advanced liver disease, where local regulations and facilities permit, so the hepatic venous pressure gradient can be measured and collected during the procedure. Any biopsy done for other medical reasons during the course of the study will also be evaluated by central pathologists (stained and unstained samples). Subjects who have any prior liver biopsy unstained sections will be analyzed in the same method, if available. A liver biopsy at Week 96 is optional.
- ⁵ Any endoscopic biopsy performed during the study will be recorded in the CRF.
- ⁶ Transient elastography will be performed in locales where technology is available.
- ⁷ Denver II assessments will be completed for subjects who are ≤6 years old during the screening period at the time of Informed Consent.
- ⁸ Age-appropriate health-related quality of life questionnaires will be completed prior to any other study procedures.
- ⁹ Refer to [Table 1](#) for a list of analytes in each laboratory panel. Subjects will refrain from ingestion of alcohol for 24 hours prior to collection of blood samples for lipid and liver panels. Labs will be drawn as blood volume and clinical status allow. See laboratory manual or SOM for details. Prior to any dose change, serum lipid, serum liver, hematology, chemistry, ferritin and hs-CRP shall be obtained; ADA and PK assessments will be obtained on the day of any study drug dose change, as described in [Section 5.9.4](#). Serum lipid and serum liver assessments should be taken 4, 8, and 12 Weeks following any study-drug or lipid drug dose change.
- ¹⁰ For female subjects of childbearing potential only. Serum pregnancy test is required at Screening. Urine pregnancy tests at all designated visits thereafter.
- ¹¹ On the day of study drug dosing, vitals will be collected pre-dose, every 30 minutes (±10 min) during the infusion, and every 30 minutes (±10 min) from 0 to 2 hours after infusion. Beginning at Week 24, the post infusion period for vital sign monitoring may be shortened from 2 hours to 1 hour for subjects who have completed at least 22 weeks of treatment with no occurrence of moderate or severe IARs, contingent upon approval from the Sponsor.
- ¹² Please refer to IMP manual for detailed instructions on duration and rate of infusions. After Week 24, infusion time may be decreased to 1 hour. If the infusion is not well tolerated; the infusion rate may be decreased ([Section 6.5.2](#)). If dose is increased to weekly infusion, the allowable window for treatment is ±2 days, and infusions must be at least 5 days apart.
- ¹³ Subjects/parents should also be queried about any changes in lipid-lowering medications or lipid-lowering diets, UDCA, metformin, glitazones, or vitamin E.

Schedule II - Assessments for Pediatric Subjects (Subjects <18 years) - Expanded Treatment Period through Follow-up

| Assessments* | Expanded Treatment | | | | | | | | | | | | End of Study Visit (Early Withdrawal) | Follow-up Call 4 Weeks (+7) days after last infusion |
|---|------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|---------------------------------------|--|
| | Week 100 | Week 104 | Week 108 | Week 112 | Week 116 | Week 120 | Week 124 | Week 128 | Week 132 | Week 136 | Week 140 | Week 144 | | |
| | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | | |
| 12-lead ECG | | | | | | | | | | | | X ^p | X | |
| Physical Examination ¹ | | | X ^p | | | X ^p | | | X ^p | | | X ^p | X | |
| Height (<2 years) ² | Every two weeks ^p | | | | | | | | | | | | X | |
| Weight (<2 years) ² | Every two weeks ^p | | | | | | | | | | | | X | |
| Height (2-18 years) | | | X ^p | | | X ^p | | | X ^p | | | X ^p | X | |
| Weight (2-18 years) | Every two weeks ^p | | | | | | | | | | | | X | |
| Abdominal MRI ³ | | | | | | | | | | | | X ^p | X | |
| Carotid MRI | | | | | | | | | | | | X ^p | X | |
| Liver Biopsy ⁴ | | | | | | | | | | | | | X | |
| Hepatic Venous Pressure Gradient | | | | | | | | | | | | X ^p | | |
| Endoscopic Biopsy ⁵ | | | | | | | | | | | | | | |
| Transient elastography ⁶ | | | | | | | | | | | | X ^p | X | |
| Denver II ⁷ | | | | | | X ^p | | | | | | X ^p | X | |
| HRQOL (subjects ≥5 years) ⁸ | | | | | | X ^p | | | | | | X ^p | X | |
| Clinical Laboratory Tests⁹ | | | | | | | | | | | | | | |
| LAL Enzyme Activity (DBS) | | | | | | | | | | | | | X | |
| Liver Panel | | | X ^p | | | X ^p | | | X ^p | | | X ^p | X | |
| Lipid Panel | | | X ^p | | | X ^p | | | X ^p | | | X ^p | X | |
| Hematology, Electrolytes, Glucose, Creatinine | | | X ^p | | | X ^p | | | X ^p | | | X ^p | X | |
| Coagulation Panel | | | X ^p | | | X ^p | | | X ^p | | | X ^p | | |
| Pregnancy Test ¹⁰ | 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 | |
| Anti-drug Antibody | | | X ^p | | | X ^p | | | X ^p | | | X ^p | X | |
| Urinalysis | | | X ^p | | | X ^p | | | X ^p | | | X ^p | X | |
| Macrophage Activation Markers | | | X ^p | | | X ^p | | | X ^p | | | X ^p | X | |
| HbA1c | | | X ^p | | | X ^p | | | X ^p | | | X ^p | X | |
| Blood Exploratory Biomarkers | | | X ^p | | | X ^p | | | X ^p | | | X ^p | X | |
| Vital Signs ¹¹ | Every two weeks ^p | | | | | | | | | | | | X | |
| Sebelipase alfa Infusion ¹² | Every two weeks | | | | | | | | | | | | | |
| Adverse Event Assessment | Continuous | | | | | | | | | | | | | |
| Concomitant Meds/Treatment ¹³ | Continuous | | | | | | | | | | | | | |

* Note: All study visits will be scheduled relative to Day 0 (Baseline); consecutive infusions must be administered at least 7 days apart. Assessments performed for subjects of a certain age are based on the subject's age on the date that informed consent is obtained.

^P Pre-infusion

- ¹ All physical examinations will include assessment of liver and spleen size, lymphadenopathy, arterial disease, and skin manifestations of hepatic disease or dyslipidemia. Physical exam findings should drive any additional functional assessments.
- ² For subjects <2 years of age, weight, recumbent length or height, and abdominal circumference will be measured at all visits; mid-upper arm circumference will be measured. Head circumference will be measured in children up to 3 years of age.
- ³ Abdominal MRI should be considered in subjects receiving general anesthesia and/or sedation for other procedures at the indicated time points. There should be at least 3 months between each MRI. Ultrasound may be substituted at a given time point if an MRI is contraindicated.
- ⁴ Liver biopsies will be obtained in subjects <18 years of age. The liver biopsy should be obtained via the transjugular method in those subjects with advanced liver disease, where local regulations and facilities permit, so the hepatic venous pressure gradient can be measured and collected during the procedure. Any biopsy done for other medical reasons during the course of the study will also be evaluated by central pathologists (stained and unstained samples). Subjects who have any prior liver biopsy unstained sections will be analyzed in the same method, if available.
- ⁵ Any endoscopic biopsy performed during the study will be recorded in the CRF.
- ⁶ Transient elastography will be performed in locales where technology is available.
- ⁷ Denver II assessments will be completed for subjects who are ≤6 years old during the screening period at the time of Informed Consent.
- ⁸ Age-appropriate health-related quality of life questionnaires will be completed prior to any other study procedures.
- ⁹ Refer to [Table 1](#) for a list of analytes in each laboratory panel. Subjects will refrain from ingestion of alcohol for 24 hours prior to collection of blood samples for lipid and liver panels. Labs will be drawn as blood volume and clinical status allow. See laboratory manual or SOM for details. Prior to any dose change, serum lipid, serum liver, hematology, chemistry, ferritin and hs-CRP shall be obtained; *ADA and PK assessments will be obtained on the day of any study drug dose change, as described in Section 5.9.4.* Serum lipid and serum liver assessments should be taken 4, 8, and 12 Weeks following any study-drug or lipid drug dose change.
- ¹⁰ For female subjects of childbearing potential only. Serum pregnancy test is required at Screening. Urine pregnancy tests at all designated visits thereafter.
- ¹¹ On the day of study drug dosing, vitals will be collected pre-dose, every 30 minutes (±10 min) during the infusion, and every 30 minutes (±10 min) from 0 to 2 hours after infusion. Beginning at Week 24, the post infusion period for vital sign monitoring may be shortened from 2 hours to 1 hour for subjects who have completed at least 22 weeks of treatment with no occurrence of moderate or severe IARs, contingent upon approval from the Sponsor.
- ¹² Please refer to IMP manual for detailed instructions on duration and rate of infusions. After Week 24, infusion time may be decreased to 1 hour. If the infusion is not well tolerated; the infusion rate may be decreased ([Section 6.5.2](#)). If dose is increased to weekly infusion, the allowable window for treatment is ±2 days, and infusions must be at least 5 days apart.
- ¹³ Subjects/parents should also be queried about any changes in lipid-lowering medications or lipid-lowering diets, UDCA, metformin, glitazones, or vitamin E.