

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

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Alexion Pharmaceuticals, Inc.



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PROTOCOL VERSION: AMENDMENT 3 (08 DEC 2015)

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1. APPROVAL SIGNATURES

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Chiltern International Limited

PPD



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Alexion Pharmaceuticals

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Alexion Pharmaceuticals

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

1.	APPROVAL SIGNATURES	2
2.	TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES	3
3.	LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	7
4.	DESCRIPTION OF THE PROTOCOL	9
4.1.	Changes from Analyses Specified in the Protocol	9
5.	DEFINITIONS	11
5.1.	Safety	11
5.1.1.	Primary Endpoint(s).....	11
5.1.1.1.	Adverse Events (AEs), Serious Adverse Events (SAEs) and Infusion-Associated Reactions (IARs).....	11
5.1.1.2.	Vital Signs, Height and Weight	11
5.1.1.3.	Physical Examination	11
5.1.1.4.	Laboratory Assessments	12
5.1.1.5.	Concomitant Medications and Treatments	13
5.1.1.6.	Electrocardiogram (ECG).....	13
5.1.1.7.	Anti-drug Antibodies (ADAs)	13
5.2.	Efficacy.....	13
5.2.1.	Secondary Endpoint(s).....	13
5.2.2.	Tertiary Endpoint(s).....	14
5.3.	Pharmacokinetic Assessment.....	14
5.4.	Exploratory Biomarker Assessment	14
6.	DATA SETS ANALYZED (STUDY POPULATIONS).....	15
6.1.	Full Analysis Set (FAS).....	15
6.2.	Pharmacokinetic Analysis Set	15
7.	STATISTICAL ANALYSIS	16
7.1.	Study Subjects	16
7.1.1.	Disposition of Subjects	16
7.1.2.	Protocol Deviations	16
7.1.3.	Demographics and Medical History	16

7.1.3.1.	Demographics	16
7.1.3.2.	Disease Characteristics	17
7.1.3.3.	Medical History	17
7.2.	Safety Analyses	17
7.2.1.	SBC-102 Exposure	17
7.2.2.	Adverse Events and Infusion-Related Reactions	18
7.2.2.1.	Overall Summary of Adverse Events	18
7.2.2.2.	AEs, SAEs and IARs by System Organ Class (SOC) and Preferred Term (PT)	18
7.2.2.3.	Deaths	19
7.2.3.	Analyses for Laboratory Tests	19
7.2.4.	Physical Examination	19
7.2.5.	Vital Signs	20
7.2.6.	Electrocardiograms (ECG)	20
7.2.7.	Denver II Developmental Screening Test (DDST)	20
7.2.8.	Antidrug Antibody (ADA) Titer	20
7.3.	Efficacy Analyses	20
7.3.1.	Handling of Dropouts or Missing Data	20
7.3.1.1.	Overall Survival and Survival at 12, 18, 24 and 36 months of age	21
7.3.1.2.	Abdominal Magnetic Resonance or Abdominal Ultrasound	21
7.3.1.3.	Clinical Laboratory Tests	21
7.3.1.4.	Anthropometric Parameters	22
7.3.1.5.	Exploratory Efficacy Analyses	22
7.4.	Pharmacokinetic Analyses	22
7.4.1.	Plasma Concentration Analysis	22
7.4.2.	PK Analysis	22
7.5.	Subgroup Analysis	22
7.6.	Additional Exploratory Analyses	22
7.7.	Interim Analyses	22
7.8.	Data Monitoring Committee	23
8	REFERENCES	24
9	APPENDICES	25
9.1	Protocol Schedule of events	25

9.2	Changes from Analyses Specified in the Previous Version of the SAP	25
9.3	Sample Size, Power, and Randomization	25
9.4	Technical Specifications for Derived Variables	25
9.4.1	Age.....	25
9.4.2	Time to Death (from Birth).....	25
9.4.3	Time to Death (from first Infusion of SBC-102).....	25
9.4.4	Time to Peak ADA Titer.....	25
9.4.5	Time to Transfusion-Free Hemoglobin Normalization	26
9.4.6	Body Mass Index (BMI).....	26
9.4.7	Derivation of Study Day	26
9.4.8	Definition of Baseline Values and Change from Baseline	26
9.4.8.1	Baseline.....	26
9.4.8.2	Change from Baseline.....	26
9.4.8.3	Percent Change from Baseline.....	26
9.4.9	Adverse Events	27
9.4.9.1	Treatment-emergent Adverse Events (TEAEs)	27
9.4.9.2	Missing AE Dates	27
9.4.9.3	AE Duration (Days).....	27
9.4.10	Calculation of Multiples of Normal for Liver and Spleen Volume	28
9.4.11	Geometric Mean of ADA Titer.....	28
9.4.12	The Z-Score (or SD Score) and Percentiles.....	28
9.4.12.1	Z-Score	28
9.4.12.2	Z-Scores in Growth Curves	28
9.4.12.3	Classification of Z-Scores for malnutrition	29
9.4.12.4	Percentiles.....	29
9.4.12.5	Note on Z Scores and Percentiles	29
9.4.12.6	Denver II Developmental Screening Test (DDST)	30

LIST OF TABLES

Table 1:	Abbreviations and acronyms	7
Table 2:	Clinical Laboratory Tests, by Tier.....	12
Table 4:	Age and reference date	25

LIST OF FIGURES

No table of figures entries found.

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and acronyms

Abbreviation or acronym	Explanation
ADA	Antidrug Antibodies
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Class
BMI	Body Mass Index
CDC	Centers for Disease Control
CI	Confidence Interval
C _{max}	The maximum serum level observed over the dose interval
CS	Clinically Significant
DDST	Denver II Developmental Screening Test
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
GGT	Gamma glutamyltransferase
HCFA	Head Circumference-For-Age
HDL-C	High Density Lipoprotein Cholesterol
HFA	Height-For-Age
hs CRP	High-sensitivity C-reactive protein
IAR	Infusion Associated Reaction
INR	International Normalized Ratio
IV	Intravenous
Kg	Kilograms
LAL-D	Lysosomal acid lipase deficiency
LDL-C	Low Density Lipoprotein Cholesterol
LFA	Length-for-Age
LLN	Lower Limit of Normal
M	meters
MedDRA [®]	Medical Dictionary for Regulatory Activities
MUACFA	Mid-Upper Arm Circumference-For-Age
MRI	Magnetic Resonance Imaging
NCS	Not Clinically Significant
pH	Potential of Hydrogen
PK	Pharmacokinetic

Abbreviation or acronym	Explanation
PKS	Pharmacokinetics Analysis Set
PPT (INR)	Partial Thromboplastin Time
PT	Preferred Term
PT (INR)	Prothrombin Time
PTAE	Pre-treatment AE
Q1	1 st Quartile
Q3	3 rd Quartile
QOW	Every Other Week
QW	Weekly dosing
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBC-102	Sebelipase alpha
SD	Standard Deviation
SOC	System Organ Class
SOM	Study Operations Manual
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event
WFA	Weight-For-Age
WFH	Weight-For-Height
WFL	Weight-For-Length
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

4. Description of the Protocol

LAL-CL08 is a phase 2, open-label, multicenter study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of sebelipase alfa (SBC-102) in infants with rapidly progressive Lysosomal Acid Lipase Deficiency (LAL-D).

Following a screening period of up to 3 weeks, each eligible patient will receive an intravenous (IV) infusion of SBC-102 at an initial dose of $1\text{mg}\cdot\text{kg}^{-1}$ every week (qw). During the first 3 months of treatment after at least 4 doses of $1\text{mg}\cdot\text{kg}^{-1}$, a dose escalation to $3\text{mg}\cdot\text{kg}^{-1}$ qw may be considered for a subject who satisfies the criteria outlined in Section 3.1.1 of the study protocol. After 3 months of treatment, subjects who satisfy additional criteria may be escalated to a dose of either $3\text{mg}\cdot\text{kg}^{-1}$ qw or $5\text{mg}\cdot\text{kg}^{-1}$ qw depending on current dose. Subjects who are on treatment for at least 96 weeks and are on a stable dose for at least 24 weeks may be considered to transition to an every other week (qow) dosing schedule. The duration of each subject's treatment in the study is expected to be at least 18 months, and subjects may continue to receive treatment in the study for up to 3 years. The overall duration of a subject's participation in the study, inclusive of a 3-week screening period and a 4-week follow-up period, may be up to 3 years and 7 weeks.

The primary objective of the study is to evaluate the safety and tolerability of SBC-102 in infants with rapidly progressive LAL-D.

The secondary objectives are:

- To evaluate the effect of SBC-102 therapy on:
 - Survival at 12 months of age
 - Survival past 12 months of age
 - Growth parameters
 - Hepatomegaly, splenomegaly, and liver function
 - Hematological parameters
 - Characterize the PK of SBC-102 delivered by IV infusion

The exploratory objectives are:

- To determine the effects of SBC-102 on lipid parameters
- To assess the effects of SBC-102 on achievement of developmental milestones
- To evaluate potential disease-related biomarkers

An independent Safety Review Committee (SRC) will oversee safety in this study. The SRC will review available safety data during at least semiannual periodic meetings and on an ad hoc basis, as needed, in the event of unanticipated safety findings.

Further details on target population, inclusion/exclusion criteria, schedule of assessments and study procedures are available in the study protocol.

4.1. Changes from Analyses Specified in the Protocol

Protocol Section 4.5 defines a concomitant medication as a medication starting or ongoing at the time of the signing of the informed consent. However, concomitant medications will be defined relative to the first dose of sebelipase alpha.

In the protocol, an exploratory objective is to evaluate potential disease-related biomarkers. Biomarker samples are stored for future analysis and will not be analyzed for this analysis plan.

The protocol mentions pharmacokinetic analysis is a secondary objective and will be done by IV infusion. PK analysis will not be analyzed as part of this analysis plan.

No formal inferential statistical testing will be performed.

5. DEFINITIONS

5.1. Safety

5.1.1. Primary Endpoint(s)

This study is designed primarily to evaluate the safety and tolerability of IV infusion of SBC-102. Safety and tolerability will be assessed based on:

- Incidence of treatment-emergent adverse events (TEAEs)
- Serious adverse events (SAEs), and infusion-associated reactions (IARs)
- Changes from baseline through trial completion in clinical laboratory tests
- Changes in vital signs during and post-infusion, relative to pre-infusion values
- Physical examination finding
- Use of concomitant medications/therapies
- Characterization of ADAs, including ADA positivity rate, time to ADA positivity, median and peak ADA titer, and time to peak ADA titer

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

5.1.1.1. Adverse Events (AEs), Serious Adverse Events (SAEs) and Infusion-Associated Reactions (IARs)

See Section 7.1 of study protocol for definitions.

5.1.1.2. Vital Signs, Height and Weight

Vital signs - including pulse rate, respiratory rate, systolic and diastolic blood pressure, and core body temperature (rectal or oral) - will be obtained at the time points specified in the schedule of assessments (Appendix A of study protocol). Assessment of pulse rate and blood pressure will be taken after the subject has been in a supine position. On dosing days, vital signs will initially be recorded pre-infusion, every 15 (± 5) minutes during infusion and every 30 (± 10) minutes from 0 to 4 hours after completion of the infusion. After a subject has successfully completed at least 1 year of treatment with no occurrence of moderate-to-severe IARs, the post-infusion period for vital sign monitoring may be shortened from 4 hours to 2 hours.

Anthropometrics, including weight, recumbent length (subjects ≤ 2 years of age at the time of examination) or height (subjects > 2 years of age at the time of examination), head circumference, mid-upper arm circumference, and abdominal circumference will be measured at the time points specified in the schedule of assessments.

5.1.1.3. Physical Examination

A physical examination will be performed by the Investigator or qualified designee, at the time points specified in the schedule of assessments. The examination will include an assessment of the subject's general appearance, skin, head, eyes, ears, nose, and throat, heart, lungs, abdomen, extremities/joints, and neurological status. Abnormal findings at screening will be captured in the medical history electronic Case Report Form (eCRF) and abnormal findings that meet the definition of an adverse event will be captured in the AE eCRF.

Every physical examination will also include the following:

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

Information about a subject's diet prior to initiation of treatment with SBC-102 in this study and any changes in a subject's diet during treatment in this study (e.g., discontinuation of a lowfat/low-cholesterol diet and/or introduction of an unrestricted age-appropriate diet) will be recorded in the eCRF.

5.1.1.4. Laboratory Assessments

Blood and urine samples for clinical laboratory tests will be collected at the time points indicated in the schedule of assessments. [Table 2](#) lists the laboratory panels and associated tests to be performed on blood (or urine) samples. Note that not all tests are performed at the same time points due to limitations on blood volume collection that is considered acceptable in young children with very small total circulating blood volumes (see [Section 5.1.11](#) of study protocol for further details).

A central laboratory will be responsible for the analysis of all laboratory tests.

Any identified laboratory abnormalities will be specified as CS (Clinically Significant) or NCS (Not-Clinically Significant) by the Investigator or designee. Clinically significant abnormality will be recorded as AEs.

Table 2: Clinical Laboratory Tests, by Tier

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

5.1.1.5. Concomitant Medications and Treatments

Prior medications are defined as medications taken or treatments received by subjects prior to the first dose of SBC-102. Concomitant medications are defined as medications taken or treatments received by subjects during the study after first dose of SBC-102.

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).

5.1.1.6. Electrocardiogram (ECG)

Age-appropriate 12-lead ECG measurements will be obtained at Screening; and additional age-appropriate 12-lead ECGs may be obtained at subsequent study visits, if clinically indicated. ECGs will be reviewed by a qualified clinician, and any abnormalities will be specified as CS or NCS.

5.1.1.7. Anti-drug Antibodies (ADAs)

Blood samples will be obtained at the time points specified in the schedule of assessments.

5.2. Efficacy

5.2.1. Secondary Endpoint(s)

Efficacy endpoints will include the following:

- Proportion of subjects surviving to 12, 18, 24, and 36 months of age, and other time points, as data permit
- Median age at death
- The change from baseline in percentiles and z-scores, based on World Health Organization (WHO) child growth standards (WHO Multicentre Growth Reference Study Group, 2006 and 2007), for the following parameters:
 - Weight-for-age (WFA)
 - Weight-for-length (WFL) or Weight-for-height (WFH)
 - Length-for-age (LFA) or Height-for-age (HFA)
 - Head circumference-for-age (HCFA)
 - Mid-upper arm circumference-for-age (MUACFA)
- Dichotomous growth status indicators for underweight, wasting, and stunting based on WFA, WFL/WFH, and LFA/HFA, respectively (UNICEF, 2009)
- Change from baseline in Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) levels
- Normalization of hemoglobin levels without requirement for blood transfusion
- Changes from baseline in serum ferritin levels
- Change in Total and function area scores on the Denver II Development Screening Test (DDST)
- Biomarker samples will be stored for future analysis as required. Biomarkers will not be analyzed for this report.

5.2.2. Tertiary Endpoint(s)

Additional exploratory efficacy parameters include changes and percent changes from baseline in:

- Alkaline phosphatase, gamma glutamyltransferase (GGT), albumin, and bilirubin (direct, indirect, and total)
- Liver and spleen size/volume, as measured by ultrasound or magnetic resonance imaging (MRI)
- Platelet levels
- Serum lipid levels (total cholesterol, triglycerides, high density lipoprotein [HDL], and low density lipoprotein [LDL])

5.3. Pharmacokinetic Assessment

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

In all subjects:

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

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

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

Only serum sebelipase alfa concentration will be summarized and presented in listings. No other analysis is planned.

5.4. Exploratory Biomarker Assessment

Whenever feasible, based on the blood volume threshold for the subject's weight, a blood sample for serum isolation will be obtained at the time points specified in the schedule of assessments. The serum sample will be used to identify baseline disease and dynamic markers that will help better understand the pathogenesis of LAL-D, related comorbidities and response to treatment. Given the rarity of LAL-D and the paucity of information on disease characteristics, the definitive list of analytes remains to be determined.

No biomarkers are planned for analysis at this time.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

Safety and Efficacy will be examined for the Full Analysis Set (FAS).

6.1. Full Analysis Set (FAS)

The Full Analysis Set (FAS) will include all subjects who received any amount of SBC-102. This analysis set will be used for analysis of safety, efficacy, and subject health outcomes data.

6.2. Pharmacokinetic Analysis Set

This analysis set will include all available SBC-102 serum concentration data for subjects who receive at least one complete infusion of IMP.

7. STATISTICAL ANALYSIS

The Alexion Biostatistics Department or designee will perform the statistical analysis of the data derived from this trial. The analysis will be performed using the SAS® Life Science Analytics Framework version 4.7.2 or higher.

No formal inferential statistical testing will be performed. As appropriate, 95% two-sided confidence intervals (CIs) will be calculated around the estimates based on the exact binomial distribution (Clopper-Pearson method) for binomial endpoints and the t-distribution for continuous endpoints. 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 SBC-102 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 non-missing data, the mean and standard deviation (SD) of the data, and the minimum, first quartile (Q1), median, third quartile (Q3), and maximum value. Mean, median values, Q1 and Q3 will be presented with one decimal point more than the original value, SD will be displayed with two decimal points more than the original value and minimum/maximum values will have the same number of decimal points as the original 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.

7.1. Study Subjects

7.1.1. Disposition of Subjects

Subject disposition 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 signed the informed consent will be included in the summary of subject disposition. 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. In addition, the number of subjects in the FAS will be presented.

7.1.2. Protocol Deviations

Major protocol deviations will be listed by subject. Protocol deviations will be identified by the study CRAs.

7.1.3. Demographics and Medical History

All demographic and medical history information will be summarized using the FAS set.

7.1.3.1. Demographics

The following demographic variables will be summarized:

- Age (months) reported to 1 decimal place (i.e. xx.x months)
- Sex
- Race
- Ethnicity

- Whether the subject is of Japanese descent and first, second, or third generation
- Birth weight (kg)

By-patient listings of demographic information will be produced.

7.1.3.2. Disease Characteristics

The following disease characteristics will be summarized:

- Months since diagnosis
- Method of diagnosis (enzyme activity, genetic sequencing, other)
- Family members diagnosed with LAL-D (yes/no)

Further details of the family medical history, as well as details of the enzyme activity and genetic sequencing will be presented in the by subject listings.

7.1.3.3. Medical History

Medical history information will be coded to primary system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) (version 20.1 or higher). Medical histories will be summarized by system organ class and preferred term. Summaries will be presented as prior disease and concomitant disease, with the prior and concomitant status determined by whether the condition was active (yes/no) at the time of screening. By subject listings will be created for medical history which will include medical history condition, start and end date, and if ongoing. Prior and Concomitant Medications/Treatments

Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) of March 2017 or higher. Summaries will be performed using the FAS.

Summaries of prior and concomitant medications or treatments will be presented separately. The number (%) of subjects receiving each medication will be summarized using the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) Class code and generic name.

All prior and concomitant medications and treatments (pharmacological and non-pharmacological) will be provided in a data listing. The data listing will include start and end dates (or indication of ongoing), dose, unit, frequency, route, and an indication of whether the medication usage is prior, concomitant or both.

Concomitant procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 20.1 or higher). These procedures will be included in subject data listings. The listing will include the date of the procedure, procedure (including system organ class, preferred term, and reported term), indication, major findings, whether the procedure was elective (yes/no), whether the procedure was performed prior to the first dose of study drug (prior/concomitant).

7.2. Safety Analyses

No formal hypothesis testing is planned. Baseline is defined as the last available assessment prior to the first infusion of SBC-102.

Listings of all safety data will be produced.

7.2.1. SBC-102 Exposure

Number of weeks exposed to study drug and study drug infusions received will be summarized overall; and any changes in dose will be described in listings, and may also be provided in tabular summaries.

Exposure to study drug (SBC-102) will be summarized by dose and overall. The total number of infusions attempted, the number of infusions completed both without and with a rate change or infusion interruption, the number of infusions where the entire infusion volume was not administered, the number of subjects with an increase, and the number of subjects with a decrease in dosage will be presented. In addition, a summary will be provided showing the number of weeks on specific doses and the number of infusions received on specific doses.

A data listing will be presented, sorted by subject within initial dose of SBC-102, providing the dates, total planned and actual volumes of drug infused, infusion rate and duration of the each infusion along with any modification to the infusion.

7.2.2. Adverse Events and Infusion-Related Reactions

Adverse Events (AE) will be coded by primary system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) (version 20.1 or higher). AEs will be determined as occurring from the signing of informed consent and prior to the initiation of SBC-102 (pre-treatment AEs), or as on/after first dose of SBC-102 (treatment-emergent) as described in [Section 9.4.8](#). Pre-Treatment Adverse Events (PTAEs) will be presented in listings only, and Treatment-Emergent Adverse Events (TEAEs) will be presented in summary tables and listings.

Study displays for TEAEs are described below.

7.2.2.1. Overall Summary of Adverse Events

All TEAEs will be presented using summary statistics (E, and n, %), showing the number of events as well as the number and percentage of subjects with the event.

The overall summary will include but not limited to displaying TEAE, AE by severity, AE by relationship, AE requiring dose modification, AE leading to discontinuation from study, infusion associated reactions (IAR), serious AEs (SAE), and the number of subjects who died due to an AE. The overall summary will include both the number and percent of subject with an event and the number of events. These statistics will be prepared for all TEAEs and, separately, for SAEs and IARs.

The relationship of AEs requires some additional consideration:

- The relationship between an AE and the study drug will be assessed as: not related; unlikely related; possibly related; or related. The number of subjects with at least one related AE and subjects with only AEs not related to study drug will be summarized. Related AEs will include those AEs considered 'possibly related' or 'related' by the investigator; and not related AEs will include those AEs considered 'not related' or 'unlikely related'.
- The number of events (E) will be summarized as reported, with no accounting for the most extreme severity or relationship.

7.2.2.2. AEs, SAEs and IARs by System Organ Class (SOC) and Preferred Term (PT)

The frequencies of TEAEs, SAEs, IARs and percentage of patients with events will be tabulated by PT within SOC. Patients are counted once in each SOC and PT. Percentages will be based on the total number of patients in the specific analysis population. SOC's will be listed in order of frequency of occurrence.

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 SBC-102: from the start of dosing with SBC-102 in this study to 3 months after the first dose; >3 to 6 months; >6 to 12 months; >12 to

18 months; >18 to 24 months; and >24 months. The incidence of AEs leading to study discontinuation will also be summarized.

Summaries of adverse events will be summarized by anti-drug antibody (ADA) status. Subjects who developed ADA vs subjects who did not develop ADA. For subjects who developed ADA, only those AEs reported on or after the first time ADA were identified will be summarized. The number of subjects experiencing any TEAE will be presented overall and by relationship to study drug, with AE specific details presented by SOC and PT, also by relationship to study drug. This table will also be generated for all TESAEs and for all IARs.

Detailed listings of patients who experience AEs, SAEs and IARs will be presented. Detailed listings will include severity and relationship to treatment, seriousness, as well as action taken regarding study treatment, other action taken, and patient outcome. A separate listing of patients who discontinued from the study due to a treatment-emergent AE will also be provided.

7.2.2.3. Deaths

A listing of patient deaths and cause of death will be produced, if applicable.

7.2.3. Analyses for Laboratory Tests

Observed measurements and changes from Baseline to each study time point in clinical laboratory data will be summarized.

Frequencies of abnormal values relative to the laboratory normal range and clinically significant abnormal values as well as shift tables showing the change from baseline to post-baseline relative to the normal range will be summarized, if sufficient data are available for analysis.

Spaghetti plots for actual, change from baseline, and percent change from baseline will be created for the following parameters: ALT; AST; GGT; total bilirubin; albumin; alkaline phosphatase; total cholesterol; LDL-C; non-HDL-C; HDL-C; triglycerides; hemoglobin; platelets; prothrombin time (PT[INR]); partial thromboplastin time (PTT [INR]); and serum ferritin.

Plots of mean absolute change and mean percent change over time with standard deviations as error bars may be prepared for the following:

- Liver biochemical parameters: ALT/AST, GGT, bilirubin, albumin, alkaline phosphatase
- Lipids: total cholesterol, LDL-C, non-HDL-C, HDL-C, triglycerides
- Other: Hemoglobin, platelets, PT/PTT, serum ferritin
- The number of subjects contributing to each mean value will be presented in each figure

7.2.4. Physical Examination

A summary of findings including liver size, spleen size, and lymphadenopathy at Screening and follow-up will be presented for baseline and each post-baseline visit.

Summaries of liver and spleen will include the percentage of subjects with palpable and non-palpable organ, the regularity (smooth or nodular), and the sensitivity (tender or non-tender). In addition, the abdominal circumference will be summarized as observed, change from baseline, and percent change from baseline.

Summaries of lymphadenopathy will include whether any lymphadenopathy is present (yes/no) and the presence/absence and tender/non-tender status of each of five specific regions: cephalic, cervical, clavicular, axillary and inguinal.

7.2.5. Vital Signs

Within each visit (infusion), descriptive summaries of both maximum and minimum result and both maximum minimum increase from the pre-infusion assessment will be summarized.

Observed values and change from pre-infusion will be presented for the following vital sign parameters:

- Body temperature
- Pulse rate
- Blood pressure
- Respiratory rate

A listing of the vital signs measurements will be also provided.

7.2.6. Electrocardiograms (ECG)

Baseline ECG results will be summarized as the number and percentage of subjects with baseline ECGs whose ECG was normal, abnormal but not clinically significant, and abnormal and clinically significant.

A listing of ECG results, baseline and unscheduled, will be presented by subject, visit, date, and study day.

7.2.7. Denver II Developmental Screening Test (DDST)

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

DDST results will be listed. The results will also be summarized with the number of patients who had the test done and tested 'normal', 'suspect', or 'untestable' by visit for each of the categories. A shift of the change from baseline to post-baseline result will also be summarized; percentages in the shift table will be based on the number of subjects in the FAS with baseline and post-baseline results.

7.2.8. Antidrug Antibody (ADA) Titer

A subject is considered as having been ADA positive if both the initial titer and a confirmatory titer were positive at that visit.

ADA data will be summarized and include both the number and percentage of subjects who become ADA-positive and positive to neutralizing antibodies.

7.3. Efficacy Analyses

Efficacy will be examined on the FAS. For the continuous endpoints, the observed values, change from baseline and percent change from baseline at each time of assessment will be summarized, and may include 95% confidence intervals (e.g. for time points with ≥ 2 observed data points).

7.3.1. Handling of Dropouts or Missing 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 applied, are described in Section 9.

7.3.1.1. Overall Survival and Survival at 12, 18, 24 and 36 months of age

Survival will be analyzed as the proportion of subjects surviving to 12, 18, 24, and 36 months of age. A 95% exact confidence interval, calculated using the Clopper-Pearson method, will also be presented for each proportion estimate. In addition, the Kaplan-Meier estimate of median survival time and 95% confidence interval will be summarized as well as the number of deaths and the number and percentage of subjects censored. Kaplan-Meier curves of survival since birth and survival since first dose of SBC-102 will be presented. Kaplan-Meier estimates of median survival since birth (median age at death) and median survival since first dose of SBC-102 will also be provided, along with 95% CIs, if estimable.

Survival rates and median age at death derived from this study will be compared to rates/times reported in the literature and previous studies. No statistical comparisons will be performed.

7.3.1.2. Abdominal Magnetic Resonance or Abdominal Ultrasound

Change and percent change in liver and spleen volume in multiples of normal and fat content will be calculated from Baseline and tabulated for each evaluation time point. Multiples of normal are defined in Section 9.4.10. Change from baseline will only be calculated if the same mode of assessment, MRI or ultrasound, was used at baseline and post-baseline. Data will be summarized for the endpoints as continuous variables.

7.3.1.3. Clinical Laboratory Tests

Observed measurements, changes and percent changes from baseline to each study time point in serum liver biochemical parameters, serum lipids, serum ferritin, hemoglobin levels, and platelet count will be tabulated. Data will be summarized for the endpoints as continuous variables and relative to the laboratory normal range Spaghetti plots (1 line per subject) and mean plots of absolute value, change or percent change in measurements over time may also be created for selected endpoints. Also see [Section 7.2.3](#).

Transfusion-Free Hemoglobin

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

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

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

A subject who is transfusion-free beginning at Week 6 will be considered to have maintained transfusion-free normal hemoglobin if:

- regardless of baseline hemoglobin value, the subject has no abnormally low hemoglobin values beginning at Week 8 of the study and continuing for at least 13 weeks (3 months).

The proportion of subjects who have maintained transfusion-free normal hemoglobin will be summarized.

7.3.1.4. Anthropometric Parameters

Anthropometric indicators of growth 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. Summaries will include summaries of observed z-scores and percentiles at each visit and also the change from baseline and the percentage change from baseline (percentile data only). In addition, the percentages of subjects who meet criteria for underweight (< -2 standard deviations [SD] from the median for WFA), stunting (< -2 SD from the median for LFA/HFA), and wasting (< -2 SD from the median for WFL/WFH) will be tabulated for each time point.

7.3.1.5. Exploratory Efficacy Analyses

Exploratory analyses of the effect of ADAs on the efficacy of SBC-102 may be explored using stratified analyses on efficacy endpoints.

Observed values and changes and percent changes from baseline in other exploratory efficacy endpoints may be tabulated for each evaluation time point. These will include changes in

- liver and spleen size/volume, as measured by ultrasound or magnetic resonance imaging (MRI). Liver and spleen volumes will be presented in statistical outputs as multiples of normal (where normal is defined as 2.5% of body weight for liver and 0.2% of body weight for spleen); changes will be calculated if the same method was used at baseline and the post-baseline time point;

Shift tables may be used to tabulate dietary changes, including shift from low-cholesterol diet to unrestricted diet if sufficient data exist for summary.

7.4. Pharmacokinetic Analyses

7.4.1. Plasma Concentration Analysis

Plasma concentrations will be summarized by time point and by visit. The summaries will include mean, standard deviation, geometric mean and standard deviation, median, min, max and geometric CV%. Graphical displays and listings will also be created.

7.4.2. PK Analysis

Only serum sebelipase alfa concentration will be summarized and presented in listings. No other analysis is planned.

7.5. Subgroup Analysis

No subgroup analysis is planned.

7.6. Additional Exploratory Analyses

Post-hoc subgroup analyses may be performed as needed. No planned exploratory analysis is planned at this time.

7.7. Interim Analyses

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

7.8. Data Monitoring Committee

An independent Safety Review Committee (SRC) will perform periodic reviews of aggregated safety data for study LAL-CL08 on an at least semiannual basis (i.e., every 6 months) from the date of enrollment of the first patient until completion of dosing for all patients in the study. Details of SRC procedures, processes and analysis for the study are provided in an SRC Charter.

8 REFERENCES

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

9 APPENDICES

9.1 Protocol Schedule of events

Refer to the approved study protocol for a schedule of events.

9.2 Changes from Analyses Specified in the Previous Version of the SAP

Not applicable

9.3 Sample Size, Power, and Randomization

No formal sample size calculations were performed for this study; the projected enrollment is based on feasibility. Given the rarity of LAL-D, it is not expected that more than 10 patients will be treated.

9.4 Technical Specifications for Derived Variables

9.4.1 Age

Age will be presented as the number of years between date of birth and the reference date. The following age will be computed, with reference dates indicated:

Table 3: Age and reference date

AGE	REFERENCE DATE
• Age at Enrollment	• Date of Signing ICF
• Age at First Dose of SBC-102	• Date of First Dose of SBC-102

In cases where only the month and year are provided for a date, the day for the date will be imputed as 15. Missing month will be imputed as June. In cases where the day is observed but the month is missing, the date will be imputed as July 1.

9.4.2 Time to Death (from Birth)

Time to Death (months) = [(Date of Death – Date of Birth + 1)/365.25]*12;

This derived variable will be used in the calculation of Kaplan-Meier estimate of median age at death/median survival since birth. This calculation will be adjusted for subjects born prematurely; details are described in Section 7.3.1.4.

9.4.3 Time to Death (from first Infusion of SBC-102)

Time to Death (months) = [(Date of Death – Date of First SBC-102 Infusion + 1)/365.25]*12;

This derived variable will be used in the calculation of Kaplan-Meier estimate of median survival since first dose of SBC-102.

9.4.4 Time to Peak ADA Titer

Time to Peak Titer (Weeks) = (Date of Peak ADA Titer - Date of First SBC-102 Infusion + 1)/7;

This derived variable will be used in the calculation of Kaplan-Meier estimate of median time to peak ADA titer (if calculable), and probability of “no titer detected” at selected time points.

9.4.5 Time to Transfusion-Free Hemoglobin Normalization

Time to Transfusion-Free Hemoglobin (Weeks) = (Date of First Assessment in 4 week period where conditions for TFHN are satisfied* - Date of First SBC-102 Infusion + 1)/7;

*See [Section 7.3.1.3](#) for details.

9.4.6 Body Mass Index (BMI)

BMI is calculated as:

$$\text{BMI} = \text{body weight (Kg)} / [\text{Height (m)}]^2$$

BMI is expressed in Kg/m²

9.4.7 Derivation of Study Day

The date and time of first study drug infusion is the reference day for deriving study day, with study day calculated as follows:

- for measurements on or after first study drug infusion, study day is:
 - collection date – first study infusion date + 1.
- for measurements prior to first study drug infusion, study day is:
 - collection date – first infusion date -1.

9.4.8 Definition of Baseline Values and Change from Baseline

9.4.8.1 Baseline

Baseline is defined as the last available assessment prior to the start of the first infusion of sebelipase alpha.. If any Baseline laboratory analyte is evaluated at both the local and the central laboratory, then the central laboratory results will be used for analysis.

9.4.8.2 Change from Baseline

Change from baseline will be calculated as:

Change of Baseline = Assessment Value – Baseline Assessment Value.

Change from pre-infusion, at a given visit, will be calculated as the infusion or post-infusion value minus the pre-infusion value.

9.4.8.3 Percent Change from Baseline

Percent change from baseline will be calculated as:

Percent Change of Baseline = [(Assessment Value – Baseline Assessment Value)/(Baseline Assessment Value)]*100 and rounded to 2 decimal places.

Similarly, the percent change from pre-infusion, at a given visit, will be calculated as the infusion or post-infusion value minus the pre-infusion value, all divided by the pre-infusion value.

9.4.9 Adverse Events

The analysis of Adverse Events is described in detail in [Section 7.2.2](#).

9.4.9.1 Treatment-emergent Adverse Events (TEAEs)

Treatment-emergent AEs (TEAEs) are events with start dates and start times on or after the date and time of the first study drug infusion (SBC-102). All other AEs with complete start dates and start times are considered Pre-Treatment Adverse Events (PTAEs).

Percentages are based on the total number of treated patients.

9.4.9.2 Missing AE Dates

If the start date or time of an AE is partially or completely missing and the end (stop) date or time of the AE does not indicate that it occurred prior to the first dose or the end date or time does not indicate that it occurred prior to the first dose, then treatment-emergence will be determined as follows:

- If the start year is after the year of the first study drug dose, then the AE is treatment-emergent; else,
- If the start year is the same as the year of the first study drug dose and
 - the start month is missing, then the AE is treatment emergent; else if
 - the start month is present and is the same or after the month of the first study drug dose, then the AE is treatment-emergent; else.
- If the start date is completely missing, then the AE is treatment-emergent.
- If the start date is the same as the date of the first study drug dose and start time is missing, then the AE is treatment-emergent.

To be able to calculate time from first dose to AE, the following are rules to input AE start dates:

Imputation Rules for Partial Dates (D = day, M = month, Y = year)			
Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y is after Y of first dose	Set to Jan 1st
	D, M, Y	None - date is completely missing	Date of first dose of study drug

9.4.9.3 AE Duration (Days)

AE Duration (days) = Date of stop of AE – Date of start of AE + 1;

Duration will be set to 'missing' if dates are incomplete, or if the AE is ongoing.

9.4.10 Calculation of Multiples of Normal for Liver and Spleen Volume

Multiples of Normal (MN) is derived by determining the expected “normal” weight of a specific organ based on body weight.

- Liver: 2.5% of body weight in kg gives the expected “normal” liver weight in liters;
- Spleen: 0.2% of body weight in kg gives the expected “normal” spleen volume in liters

For example: a 50 kg patient would have an expected “normal” liver volume of 1.25 liters ($0.025 \times 50 = 1.25$) and an expected “normal” spleen volume of 0.10 liters ($0.002 \times 50 = 0.1$). The patient’s observed organ volume is then divided by the expected “normal” volume. Values of MN >1.0 indicate an organ volume which is larger than the expected normal volume.

9.4.11 Geometric Mean of ADA Titer

$$\text{Geometric Mean (at Time } i) = (v_1 \times v_2 \times \dots \times v_n)^{\frac{1}{n}}$$

where v_n is the titer value for the n^{th} subject at time point i (e.g. baseline), and n is the number of subjects with non-missing titer values.

9.4.12 The Z-Score (or SD Score) and Percentiles

9.4.12.1 Z-Score

Is the deviation of an individual’s observed value* from the median value of a reference population, divided by the standard deviation (SD) of the reference population.

$$\text{Z-score (or SD-score)} = \frac{\text{observed value} - \text{median value of the reference population}}{\text{standard deviation value of reference population}}$$

* Weight; Height; BMI; Head circumference etc.

9.4.12.2 Z-Scores in Growth Curves

Alternatively, the formula for the Z-score can also be expressed as:

$$Z = \frac{\left[\frac{\text{observed value}}{M} \right]^L - 1}{L * S}; \quad \text{whenever } L \neq 0$$

$$Z = \frac{\log_e \left(\frac{\text{observed value}}{M} \right)}{S}; \quad \text{whenever } L = 0$$

where L (lambda: power in Box-Cox transformation, reflecting degree of skewness), M (mu: the median) and S (sigma: the generalized coefficient of variation) are curve parameters – which vary according to the child’s sex and age (e.g. weight-for-age among boys) or according to the child’s sex and height (e.g. weight-for-height among boys) – determined from smoothed percentile curves using a series of linear and non-linear regression models and a modified LMS procedure (Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight,

height, body mass index and head circumference fitted by maximum penalized likelihood. Stat Med. 1998;17:407–429).

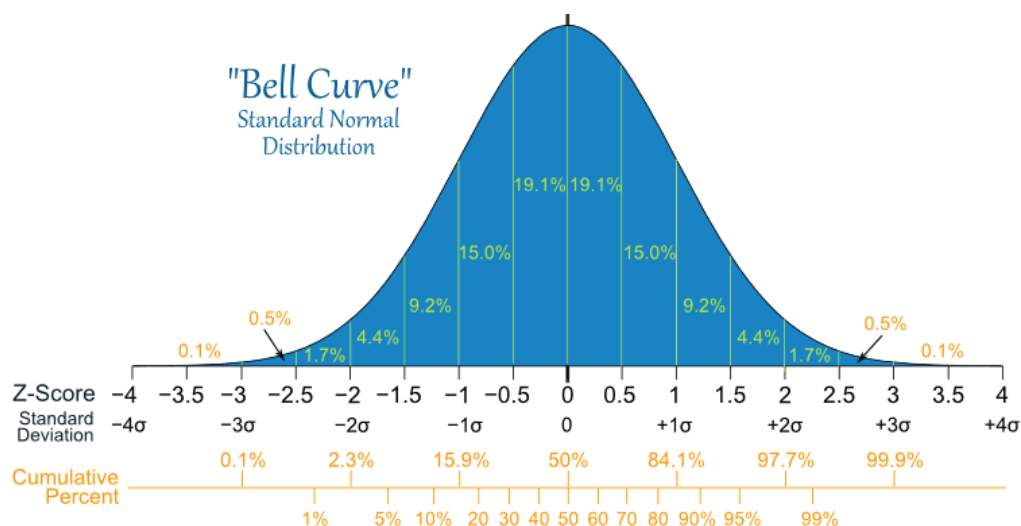
The estimates of L, S and M have been tabulated - for different anthropometric parameters - for a series of ages by WHO and CDC using datasets from surveys conducted in the United States. The estimates for these parameters are available from publicly available WHO Growth Charts (for patients ≤ 24 months of age) and CDC Growth Charts (subjects > 24 months of age to 18 years) and can be used to calculate Z-scores and percentiles for observed anthropometric parameters.

9.4.12.3 Classification of Z-Scores for malnutrition

1. Underweight:
 - Moderate: Weight-for-age < -2 SD from the international reference median value
 - Severe: Weight-for-age < -3 SD from the international reference median value
2. Stunting:
Height-for-age or Length-for-age < -2 SD from the international reference median value
3. Wasting:
Weight-for-height or Weight-for-length < -2 SD from the international reference median value

9.4.12.4 Percentiles

Percentiles are cumulative probabilities associated with z-scores using Standard Normal distribution theory. Z-scores, by definition, have a Standard Normal Distribution.



Source: Pierce, Rod. (11 Oct 2014). "Normal Distribution". Math Is Fun. Retrieved 14 Jan 2016 from <http://www.mathsisfun.com/data/standard-normal-distribution.html>

For example, a z-score of +2 would be equal to the 97.7 percentile on the standard normal curve, meaning the patient's Z-score is in the top 2.3% in comparison to his/her reference population.

9.4.12.5 Note on Z Scores and Percentiles

1. Will only be calculated for patients ≤ 18 years at informed consent

2. 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)
3. 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., 2000)

9.4.12.6 Denver II Developmental Screening Test (DDST)

The Denver II Developmental Screening Test (DDST) will be administered at the time points specified in the schedule of assessments.

The test is a standardized measure to assess development in children from 1 month to 6 years of age (Frankenberg et al., 1992). It includes performance-based and parent-reported items in 4 functional areas: fine motor-adaptive, gross motor, personal-social, and language skills with respect to the age-matched population. 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. DDST II results are expressed as Normal, Abnormal, Questionable, and Untestable. The instrument has good inter-rater and test-retest reliability (correlations ≥ 0.90 for most tests).

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

Refer to the Study Operations Manual (SOM) for further information on administration and scoring of DDST.