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

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Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: LAL-CL03

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Author: PPD

Date: December 6th, 2017

Version: Final 1.0

APPROVAL SIGNATURES

PPD

Chiltern International Limited

Date dd mmm yyyy

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Alexion Pharmaceuticals

21 DEC 2017

Date dd mmm yyyy

PPD

Alexion Pharmaceuticals

21 Dec 2017

Date dd mmm yyyy

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1. Introduction

This document provides a record of all the changes made to the LAL-CL03 statistical analysis plan (SAP) dated March 7, 2014 (version 1.1).

2. Amendments to the LAL-CL03 SAP

2.1 Summary of Amendments

The following updates have been made to the planned analysis:

- Urinalysis and ADA assessments will only be presented in the listings. Summaries will not be presented.
- For specified lab parameters, change from baseline and percent change from baseline will not displayed in spaghetti plots.
- The per protocol analysis set will not be used to summarize results.
- Adverse event will be presented for time periods spanning the entire treatment period. The periods that will be used are 0 to 12 Months, >12 to 24 Months, >24 to 36 Months, >36 to 48 Months, and >48 Months
- Denver II scores will only be presented in a listing.

STATISTICAL ANALYSIS PLAN

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

Protocol LAL-CL03

Protocol Number:	LAL-CL03
Protocol Version and Date:	Amendment 10: 24 January 2014 Amendment 9: 19 March 2013 Amendment 8: 05 February 2013 Amendment 7: 23 October 2012 Amendment 6: 05 April 2012 Amendment 5: 20 September 2011 Amendment 4: 02 June 2011 Amendment 3: 20 May 2011 Amendment 2: 19 April 2011 Amendment 1: 09 February 2011 Original: 10 January 2011
Name of Test Drug:	SBC-102 (sebelipase alfa)
Methodology:	Open Label, Multicenter, Dose Escalation
Sponsor:	Synageva BioPharma Corp. 33 Hayden Avenue Lexington, MA 02421 Tel: PPD Fax: PPD
Sponsor Representative:	PPD PPD Synageva BioPharma Corp.
Analysis Plan Date:	07 March 2014
Analysis Plan Version:	Final Version 1.1

APPROVAL SIGNATURE PAGE

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

Sponsor: Synageva BioPharma Corp.
33 Hayden Avenue
Lexington, MA 02421

Protocol Number: LAL-CL03

Document Date / Version: 07 March 2014 / Final Version 1.1

Veristat, Inc. Author:

PPD

Signature: PPD

Date: 07 Mar 2014

Veristat, Inc.
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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

Stephen Eckert, PhD
Senior Director, Biostatistics
Synageva BioPharma Corp.
33 Hayden Avenue
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Signature: PPD

Date: 07 Mar 2014 PPD

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ABBREVIATIONS

Abbreviation	Definition or Description
ADAs	Anti-drug antibodies
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AE	Adverse event
ATC	Anatomical therapeutic chemical
CDC	Center for Disease Control and Prevention
CL	Clearance
Cmax	Maximum observed plasma concentration
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical study report
DBP	Diastolic blood pressure
EMA	European Medicines Agency
FAS	Full analysis set
FDA	Food and Drug Administration
GGT	Gamma glutamyltransferase
HCFA	Head circumference-for-age
HDL	High density lipoprotein
HFA	Height-for-age
HR	Heart rate
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
IMP	Investigational medicinal product
IRR	Infusion-related reaction
LAL	Lysosomal acid lipase
LDL	Low density lipoprotein
LFA	Length-for-age
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUACFA	Mid-upper arm circumference-for-age
NCI	National Cancer Institute
PD	Pharmacodynamic(s)
PES	Primary efficacy analysis set
PK	Pharmacokinetic(s)
PPS	Per-protocol set
RR	Respiratory rate

SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Safety Committee
SOC	System organ class
TEAE	Treatment-emergent adverse event
TFHN	Transfusion-free hemoglobin normalization
TLFs	Tables, listings, and figures
WFA	Weight-for-age
WFH	Weight-for-height
WFL	Weight-for-length
WHO	World Health Organization

1. OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Synageva Biopharma Corp. protocol LAL-CL03 (An Open Label, Multicenter, Dose Escalation Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics and Pharmacodynamics of SBC-102 in Children with Growth Failure Due to Lysosomal Acid Lipase Deficiency), Amendment 10, dated 24 January 2014. This study is designed primarily to evaluate the efficacy of treatment with SBC-102, based on survival at 12 months of age, in patients with early onset LAL Deficiency presenting with growth failure prior to 6 months of age.

Pharmacokinetic (PK) analyses will be described in a separate document and are not discussed in this SAP.

2. STUDY OBJECTIVES AND ENDPOINTS

The information in this section is intended to orient the reader of this SAP to the study, and is copied from the protocol; no new information is presented.

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of the study is to evaluate the effect of SBC-102 therapy on survival at 12 months of age in children with growth failure due to LAL Deficiency.

2.1.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of SBC-102 in children with growth failure due to LAL Deficiency;
- To evaluate the effect of SBC-102 therapy on survival beyond 12 months of age in children with growth failure due to LAL Deficiency;
- To evaluate the effects of SBC-102 on growth parameters in children with growth failure due to LAL Deficiency;
- To evaluate the effects of SBC-102 on hepatomegaly, splenomegaly, and liver function in children with growth failure due to LAL Deficiency;
- To determine the effects of SBC-102 on hematological parameters in children with growth failure due to LAL Deficiency;
- To characterize the PK of SBC-102 delivered by IV infusion.

2.1.3 Exploratory Objectives

The exploratory objectives are:

- To determine the effects of SBC-102 on lipid parameters in children with growth failure due to LAL Deficiency;

- To assess the effects of SBC-102 on achievement of developmental milestones in children with growth failure due to LAL Deficiency;
- To assess the effects of SBC-102 on the ability of children with LAL Deficiency to tolerate an unrestricted diet;
- To evaluate potential disease-related biomarkers.

2.2 Efficacy Endpoints

2.2.1 Primary Endpoint

The primary efficacy endpoint is the proportion of subjects in the Primary Efficacy Set surviving to 12 months of age.

2.2.2 Secondary Endpoints

Secondary efficacy endpoints are:

- proportion of subjects surviving at 18 and 24 months of age;
- median age at death;
- changes from baseline in percentiles and/or z-scores as determined from WHO criteria for
    - Weight-for-Age (WFA),
    - Weight-for-Length (WFL) and/or Weight-for-Height (WFH),
    - Length-for-Age (LFA) and/or Height-for-Age (HFA)
    - head circumference-for-age (HCFA)
    - mid-upper arm circumference-for-age (MUACFA);
- dichotomous growth status indicators of underweight, wasting, and stunting.
- changes from baseline in
    - alanine aminotransferase (ALT)
    - aspartate aminotransferase (AST)
    - serum ferritin
- normalization of hemoglobin levels without requirement for blood transfusion;

2.2.3 Exploratory Endpoints

Exploratory efficacy endpoints are:

- changes and/or percent changes from baseline (or first available measurement if baseline data are unavailable) in
    - alkaline phosphatase, gamma glutamyltransferase (GGT), albumin, and direct (conjugated), indirect (unconjugated), and total bilirubin levels;
    - liver and spleen size/volume, as measured by ultrasound or magnetic resonance imaging (MRI);
    - hepatomegaly and/or splenomegaly (abdominal girth, liver size, and spleen size) by physical examination;
    - platelet levels;

  - serum lipid levels (total cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL).
- Dietary changes, including discontinuation of a low-fat/low-cholesterol diet and/or introduction of an unrestricted age-appropriate diet.
- Denver II developmental screening test: four functional area scores (fine motor-adaptive, gross motor, personal-social, and language skills).
- The impact of anti-SBC-102 antibodies (ADAs) on efficacy endpoints will also be explored.

2.3 Safety Endpoints

The safety endpoints are:

- Incidence of adverse events (AEs), serious adverse events (SAEs), and infusion related reactions (IRRs);
- Changes from baseline in clinical laboratory results (chemistry, hematology and urinalysis);
- Changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature) during and post-infusion relative to pre-infusion values;
- Physical examination findings;
- ECG findings
- Use of concomitant medications/therapies;
- Characterizations of anti-drug antibodies (ADAs)
  - seroconversion rate,
  - time to seroconversion,
  - median and peak immunoglobulin G (IgG) ADA titer,
  - time to peak IgG ADA titer, and tolerization.

Further characterization of ADAs, including inhibitory ADAs, may be performed, if appropriate.

3. STUDY METHODS

The information in this section is intended to orient the reader of this SAP to the study, and is copied from the protocol; no new information is presented.

Note that one subject was originally enrolled in study LAL-CL05 following initiation of treatment under compassionate use due to the need for emergent therapy, and that LAL-CL05 was merged with the current study. This subject from LAL-CL05 will be included in the analyses.

3.1 Overall Study Design and Plan

This is an open-label, multicenter (up to 10 centers globally), dose escalation study to evaluate the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of SBC-102 in children with growth failure due to LAL Deficiency. Given the rarity of subjects with this condition, approximately 8-10 subjects will be enrolled. Eligible subjects will receive qw IV infusions of SBC-102 for up to 4 years, as described below. All subjects will be evaluated for safety, tolerability, and efficacy. Where feasible, given

blood volume thresholds based on subject weight, blood samples will also be collected for analyses of the PK and PD of SBC-102 and for an exploratory analysis of potential disease-related biomarkers in this patient population.

See Figure 1 for a Study Flow Chart.

All subjects will initiate treatment with SBC-102 at a dose of 0.35 $mg \cdot kg^{-1}$ qw. After receiving 2 infusions at this starting dose, a subject will receive a dose increase to 1 $mg \cdot kg^{-1}$ qw, contingent upon acceptable safety and tolerability of preceding infusions. A further dose escalation to 3 $mg \cdot kg^{-1}$ qw may be considered for a subject who has received at least 4 infusions at a dose of 1 $mg \cdot kg^{-1}$ qw and exhibits a suboptimal response to treatment, as defined in section 3.1.1 of the protocol, contingent upon acceptable safety and tolerability of preceding infusions.

An independent safety committee (SC) will oversee safety in this study. The SC will review available safety data for each subject:

(1) Following the first 2 infusions at a dose of 0.35 $mg \cdot kg^{-1}$ qw to determine the acceptability of escalating the dose to 1 $mg \cdot kg^{-1}$ qw; and
(2) Following the first 2 infusions at a dose of 1 $mg \cdot kg^{-1}$ qw to determine the acceptability of continuing treatment at this dose level.

In addition, for subjects who exhibit a suboptimal treatment response at a dose of 1 $mg \cdot kg^{-1}$ qw and are escalated to a dose of 3 $mg \cdot kg^{-1}$ qw, the SC will review their safety data following the first 2 infusions at a dose of 3 $mg \cdot kg^{-1}$ qw to determine the acceptability of continuing treatment at this dose level.

The remainder of the safety data for all subjects will be reviewed during at least biannual periodic meetings of the SC and on an ad-hoc basis as needed in the event of unanticipated safety findings.

Details on the dose escalation can be found in the protocol.

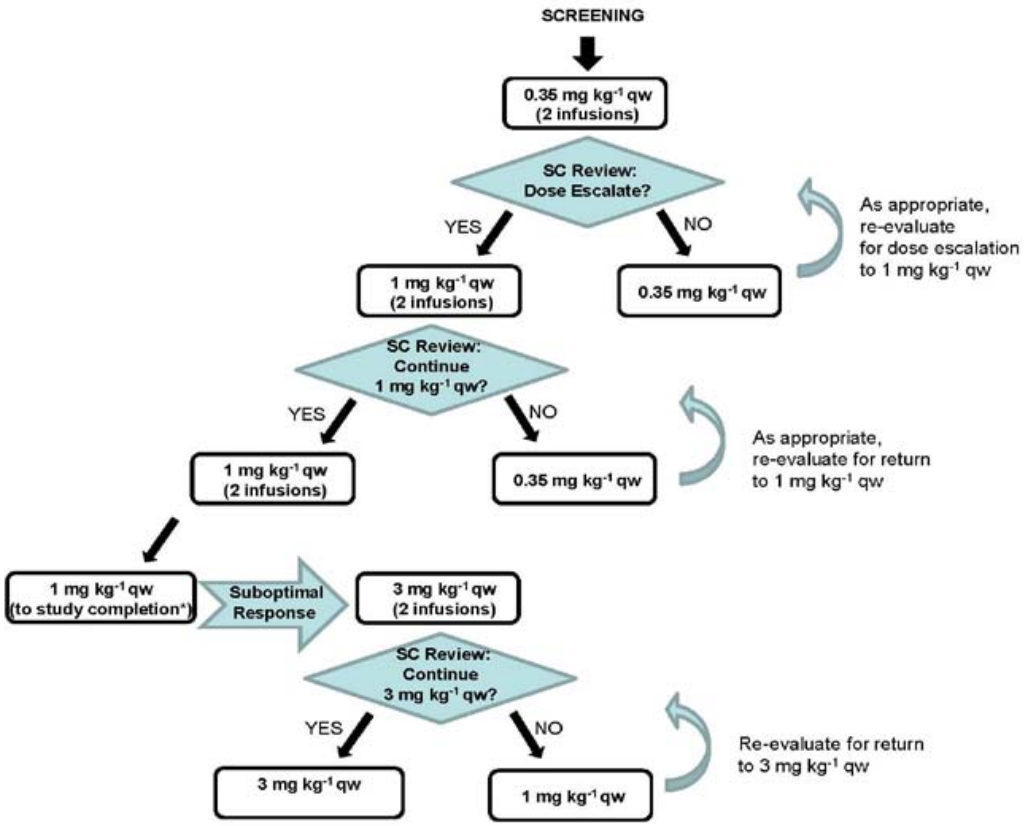
Given the severity and life-threatening nature of LAL Deficiency in this population, it is likely that these subjects will be hospitalized during the first several weeks on study. For the subjects who are stable enough to be treated on an outpatient basis, safety follow-up assessments for AEs will be conducted by telephone 24 hours following the first 2 infusions of 0.35 $mg \cdot kg^{-1}$ qw, 1 $mg \cdot kg^{-1}$ qw, as well as 3 $mg \cdot kg^{-1}$ qw, if needed. Additional details about the SC review process can be found in Section 7.6 of the study Protocol LAL-CL03. Refer to Appendix A in the study Protocol LAL-CL03 for the full Schedule of Assessments.

Subjects who appear to have an acute illness (e.g., upper respiratory infection or febrile illness) should have their scheduled infusions postponed by up to 2 days (5 days if subject is on a qow infusion schedule) to allow for resolution. If the illness persists for longer than 2 days (5 days if subject is on a qow infusion schedule), the infusion schedule should reset to a new weekly schedule following the first infusion after the subject's recovery. The Investigator may conduct an unscheduled visit at any time during the study at his/her discretion. Assessments performed at this unscheduled visit should be

symptom directed. Safety laboratory testing may be performed if the Investigator considers it necessary. Repeat laboratory testing may be needed based on results from the unscheduled laboratory testing.

If the subject is discontinued from study treatment at a scheduled visit or at an unscheduled visit, the subject should return no earlier than 7 days after the last dose of SBC-102 for an End of Study assessment.

Figure 1 Study Flow Chart



Notes:

- All dose increases are contingent upon acceptable safety and tolerability during preceding infusions.
- Dose reductions are permitted in the event of poor tolerability, or in clinically stable subjects who have received SBC-102 at a dose of 3 $mg \cdot kg^{-1}$ for at least 18 months. See Protocol Section 3.1 for details.

- Subjects will receive a dose of 1 $mg \cdot kg^{-1}$ qw until study completion, except where a subject's treatment response after at least 4 infusions of 1 $mg \cdot kg^{-1}$ qw is considered suboptimal (see definition in section 3.1.1 of the protocol) and a dose increase to 3 $mg \cdot kg^{-1}$ qw is approved.

3.2 Selection of Study Population

See study protocol for inclusion/exclusion conditions.

3.3 Method of Treatment Assignment and Randomization

This study is open label and there is no randomization scheme employed; study entry will be sequential.

3.4 Treatment Masking (Blinding)

This is an open-label study and no study treatments are blinded or masked.

4. ANALYSIS AND REPORTING

4.1 Interim Analysis

No formal statistical interim analyses are planned. The Safety Committee will review interim safety data as specified in the protocol. Data may also be summarized as required for regulatory submissions.

4.2 Final Analysis

All final, planned analyses as identified in this SAP will be performed following database lock and prior to completion of the final CSR.

Post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in the CSR.

5. SAMPLE SIZE DETERMINATION

Approximately 8 to 10 subjects will be enrolled in this study. No formal sample size calculation has been performed.

Approximately 8 subjects who meet the requirements for inclusion in the Primary Efficacy Analysis Set (i.e., subjects whose first dose of study medication is on or before the age of 8 months) will be enrolled in this study. Additional subjects who meet the same entry criteria, but are between 8 and 24 months on the date of first dose of study medication, may be enrolled and followed for safety information.

This sample size was selected to facilitate comparison with natural history study (LAL-1-NH01) in patients with early onset LAL Deficiency. An analysis of preliminary data from study LAL-1-NH01, which was ongoing at the time of the creation of this SAP, shows that, of the 18 patients who met growth failure criteria and had known date of death, only one patient survived past 12 months of age. (Note: Of these 18 patients, 5 had received a hematopoietic stem cell transplant and one had received a liver transplant.) An exact 95%

CI for survival past 12 months of age in these patients is (0.14%, 27.29%). An analysis of survival, beginning on the date that growth failure criteria were met, indicated no relationship between age at onset of growth failure and survival past onset of growth failure. Thus, assuming that the final data from LAL-1-NH01 are consistent with these preliminary data and if the lower limit of an exact 95% CI for the 12-month survival rate in the current study is greater than 27.29%, there would be statistical evidence that the rate of 12-month survival in the current study is superior to that in study LAL-1-NH01 for a similar patient population. For the current study, if 8 subjects are included in the Primary Efficacy Analysis Set and 6 of these subjects survive to 12 months of age, the exact 95% CI for 12-month survival would be (34.91%, 96.81%), with the lower limit exceeding the upper limit of the CI for study LAL-1-NH01.

6. ANALYSIS SETS

The following analysis sets are planned for this study:

- **Full Analysis Set (FAS):** This analysis set consists of all subjects who received any amount of SBC-102.
- **Primary Efficacy Analysis Set (PES):** This set will include subjects in the FAS who were no older than 8 months of age on the date of the first infusion of SBC-102.
- **Per-Protocol Analysis Set (PPS):** This set will include subjects in the PES who, in addition, receive at least 4 complete infusions of SBC-102.

7. GENERAL ISSUES FOR STATISTICAL ANALYSIS

7.1 General Statistical Methodology

All data will be presented in patient data listings. Descriptive summaries and/or graphics will be provided where appropriate for each of the analysis variables.

Continuous quantitative variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation, minimum, first quartile (Q1), median, third quartile (Q3), and maximum.

Shift tables and/or frequencies and percentages will be produced for categorical variables. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the group, unless otherwise specified.

Listings with the potential for multiple timepoints per topic (eg, labs) will have Dosing Regimen at Time of Xxxx. Dosing Regimen at Time of the assessment/event/etc will be the dose that preceded the assessment (ie, not necessarily the dose given on the day of the assessment). Vital Signs and AEs/IRRs occurring during or following an infusion should have the dose associated with the infusion – ie, the dose administered during the infusion.

7.1.1 Handling of Missing Data

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

7.2 Derived and Computed Variables

The following derived and computed variables have been initially identified as important for pre-specified and exploratory analyses. It is expected that additional computed variables will be required to aid in analysis. The SAP will not be amended to describe additional variables used as computational aids.

Chronological age at first dose will be reported in months to one decimal using the formula:

age at first dose = (date of first dose - birth date)/30.4375.

Table 1
Computation of Age-Adjusted Endpoints (Per WHO Growth Standards)

Endpoint	Computation Methods, Notes, or Equation(s)
Z-score for weight	$$Z = \begin{cases} \dfrac{(X/M)^L - 1}{LS}, & L \neq 0 \\ \dfrac{\ln(X/M)}{S}, & L = 0 \end{cases}$$ There are three parameters required to transform weight (in kg), height (in cm), and BMI (kg/m^2) to Z-scores: *L*, *M*, and S. Values for these parameters can be found at the US Centers for Disease Control website http://www.cdc.gov/growthcharts/who_charts.htm
Z-score for height	
Z-score for head circumference	
Percentile for normalized weight	
Percentile for normalized height	
Percentile normalized head circumference	
Percentile for mid upper arm circumference	
Note: In this table, the word "height" refers to either length (for subjects ≤2 years of age) or height (for subjects >2 years of age).	

8. STUDY SUBJECTS AND DEMOGRAPHICS

8.1 Disposition of Subjects

All subjects who provide informed consent will be accounted for in this study. The number and percentage of subjects enrolled overall and in each analysis set, as well as those subjects who completed the study, and those who discontinued from the study, along with reasons for discontinuation, will be presented.

Data for the subjects who provide informed consent but were not treated will be provided in a listing and in a disposition table but will not be included in other output.

8.2 Protocol Deviations

Protocol deviations will be listed for all subjects. The final decision regarding inclusion/exclusion of subjects from the per-protocol analysis set will be determined during the data review meeting before database lock with input from Clinical and Biostatistics team members and approved by the Sponsor.

8.3 Demographics

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

Medical history will be summarized by body system. Details will be listed for all subjects.

Prior medications/therapies will be coded using the World Health Organization (WHO) Drug Dictionary and summarized. Details will be listed for all subjects.

9. EFFICACY ANALYSES

Efficacy will be analyzed for the PES. If at least one subject in the PES is excluded from the PPS (i.e., if the PES is not identical to the PPS) then all the efficacy analyses will also be run for the PPS. If there are subjects in the FAS who are not in the PES, a subset of efficacy analyses may be re-run for the FAS, as appropriate.

9.1 Efficacy Endpoint Analysis

The primary endpoint is the proportion of subjects surviving to 12 months of age. A 95% exact confidence interval, calculated using the Clopper-Pearson method [Clopper and Pearson, 1934], will also be presented.

It is not anticipated that subjects will be lost to follow-up prior to 12 months of age; however, subjects in the PES who are not confirmed to have survived to 12 months of age will not be considered to have met the primary endpoint. As a complementary analysis, Kaplan-Meier survival curves of survival since birth and survival since first dose of SBC-102 will be presented. A Kaplan-Meier estimate, with 95% CI if appropriate, of median survival post first dose of SBC-102 will also be provided.

The proportion of subjects surviving to 18 and 24 months of age will also be analyzed as described for the primary endpoint (i.e., percent of subjects in the PES surviving to 18 and 24 months). These proportions will also be estimated by Kaplan-Meier (product-

limit) methodology if there are subjects whose survival times are censored prior to 18 or 24 months.

The median age at death will be calculated and presented in a summary table. The median will also be estimated by Kaplan-Meier (product-limit) methodology.

Estimated survival rates and median age at death derived from these analyses will be compared to rates/times reported in the literature, and will be discussed in conjunction with information derived from the natural history study in a similar patient population (study LAL-1-NH01). Further, a separate Kaplan-Meier survival curve for survival from birth will be constructed for the patient population in LAL-1-NH01.

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

For anthropometric indicators of growth, age will be adjusted for prematurity if gestational age is <37 weeks and the subject is under 12 months of age. The adjustment will be made such that corrected age in months = chronological age in months minus the number of months premature.

Change and percent change from baseline in AST, ALT, and serum ferritin will be tabulated for each evaluation timepoint.

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

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

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

A subject who is transfusion-free beginning at Week 6 will be considered to have maintained transfusion-free normal hemoglobin if, regardless of baseline hemoglobin value, the subject has no abnormally low hemoglobin values beginning at Week 8 of the

study and continuing for at least 13 weeks (3 months). The proportion of subjects who have maintained transfusion-free normal hemoglobin will be summarized.

Denver II scores will be summarized with the number of patients who had the test done and tested 'normal', 'suspect', 'untestable' by visit for each of the categories. Additionally this data will be listed.

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

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

- alkaline phosphatase
- gamma glutamyltransferase (GGT)
- albumin
- direct (conjugated), indirect (unconjugated), and total bilirubin levels;
- 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).
- hepatomegaly and/or splenomegaly (abdominal girth, liver size, and spleen size) by physical examination;
- platelet counts;
- serum lipid levels including
  - total cholesterol,
  - triglycerides,
  - high density lipoprotein (HDL),

10. LOW DENSITY LIPOPROTEIN (LDL). SAFETY AND TOLERABILITY ANALYSIS

The safety analysis will be performed on the FAS. The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data.

- Adverse Events
  - Adverse Events (AEs), serious adverse events (SAEs), and infusion related reactions (IRRs)
  - AEs leading to withdrawal
  - Deaths
- Safety Laboratory Tests (Serum chemistries, CBC/Hematology, Urinalysis, Liver function tests, Anti-drug antibody, Coagulation studies)
- Vital Signs (systolic and diastolic blood pressure, heart rate (HR), respiratory rate (RR), body temperature)
- Physical Examination findings

- Concomitant Medications/Therapies/Procedures
- Study Drug Exposure

10.1 Adverse Events

This SAP specifies standard tabular summaries for adverse events. If the number of any particular type of event is small, the data may be presented in listing format, rather than as a tabular summary.

All AEs will be coded using the MedDRA for the study (version 9.1 or higher).

The severity of AEs will be graded on a 5 point scale according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 or higher.

For the purpose of this study, an IRR will be defined as any AE that occurs during the 2-hour IMP infusion or within 4 hours after the IMP infusion and is assessed by the Investigator as at least possibly related to IMP.

TEAEs are defined as AEs occurring or worsening with an onset at the time of or following the start of treatment with study medication and up to 30 days after the last dose of SBC-102 (completion of the follow-up visit).

Attempts will be made to resolve any missing or partial AE dates with the site; however, if these cannot be resolved, to handle the missing or partial AE start/end date, the following rules will be implemented:

If the start date and time of an AE are partially or completely missing, the AE will be assumed to be treatment-emergent if it cannot be definitely shown that the AE did not occur or worsen during the treatment emergent period (worst case approach). Missing dates and times will not be imputed, but will be shown on listings as incomplete.

Thus, the following approach will be taken:

- If the start time of an AE is missing, but the start date is complete, an AE will only be excluded from treatment-emergent AEs if the start day is before day of first treatment or the start day is after end day of the treatment-emergent period.
- If the start time and day are missing but the start month is complete, an AE will only be excluded from treatment emergent AEs if the start month is before month of first treatment or the start month is after end month of treatment-emergent period or if the stop date/time is before the start of first treatment.
- If the start day and month are missing but the start year is complete, an AE will only be excluded from treatment-emergent AEs if the start year is before year of first treatment or if the start year is after end year of treatment-emergent period or if the stop date/time is before the start of first treatment.
- If the start date is completely missing, an AE will not be excluded from treatment-emergent AEs unless the stop date/time is before the start of first treatment.

An Overall AE summary table will be presented and will include the number of subjects with:

- All treatment-emergent AEs
- IRRs
- SAEs
- Treatment-emergent AEs related to SBC-102
- Treatment-emergent AEs leading to discontinuation from the study

Summaries of number of events and incidence rates (frequencies and percentages of subjects) of AEs by MedDRA SOC and Preferred Term will be prepared. Such summaries will also be displayed for all AEs by intensity and by relationship to study drug.

Each subject will be counted only once within each level of the summary. If a subject experiences more than one AE within a level, only the AE with the strongest relationship or the maximum intensity, as appropriate, will be included in the summaries of relationship and intensity.

No inferential statistical tests will be performed.

In addition, frequency of AEs, SAEs, and IRRs 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.

All AEs will be listed. Separate listings of SAEs, IRRs, AEs leading to study discontinuation, and AEs leading to discontinuation of SBC-102 will also be provided.

As appropriate, a summary of numbers of events and incidence rates (frequencies and percentages or subjects) of IRRs, and AEs leading to withdrawal from the study by SOC and Preferred Term will be prepared for the FAS. No inferential statistical tests will be performed.

10.1.1 Serious Adverse Events

A summary of numbers of events and incidence rates (frequencies and percentages of subjects) of SAEs by SOC and Preferred Term will be prepared for the FAS. No inferential statistical tests will be performed. SAEs will also be tabulated by severity and relationship to SBC-102.

A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF.

10.1.2 Dosing and Exposure

All dosing information will be presented in a listing.

The number of weeks in the study and number of study infusions received by subjects will be summarized. The total number of infusions attempted, the number of infusions

completed both without and with a rate change or infusion interruption and the number of infusions where the entire infusion volume was not administered will be presented.

A listing will be provided that summarizes SBC-102 exposure by subject, and date of first and last dose and total number of doses (by dose level) of SBC-102.

10.1.3 Prior and Concomitant medication data

Concomitant medications and treatments are defined as any medication or treatment taken after first dosing with SBC-102 and up to 30 days after last dose with SBC-102. Any prior or concomitant medication(s), treatment(s), and therapy(ies) data will be coded using the WHO-DRUG dictionary. All data will be listed, and the percentages of subjects receiving each coded concomitant medication/treatment will be tabulated.

10.2 Safety Laboratory Evaluations

In general, laboratory evaluations will be displayed in SI units. For some labs (e.g., plasma lipids and serum ferritin), labs will also be displayed in conventional units.

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

Spaghetti plots for actual, change from baseline, and percent change from baseline will be created for the following parameters: ALT, AST, GGT, total bilirubin, direct bilirubin, indirect bilirubin, albumin, alkaline phosphatase, total cholesterol, LDL-C, HDL-C, triglycerides, hemoglobin, platelets, PT, PTT, and serum ferritin.

IgG antibody titer values will be tabulated at each assessment time point using summary statistics appropriate to the data. The percentage of subjects who seroconvert, the time to seroconversion, the median and peak IgG antibody titer, the time to peak IgG antibody titer, and the percentage of subjects who tolerize will also be summarized. A further characterization of ADAs, including neutralizing ADAs, may be performed as a separate pooled analysis across studies, and will be reported separately.

10.3 Vital Signs

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

Baseline will be defined as the non-missing assessment attained before and closest to the date/time of first dose of SBC-102.

A listing of all vital signs data will also be prepared by subject.

10.4 Physical examination

A listing of all physical examination results will be created by subject. Abnormal findings for Physical Examinations will also be listed separately. Summaries of percentages of subjects with hepatomegaly and splenomegaly may be created as appropriate.

Measurements observed at screening visit will be considered as baseline.

10.5 ECGs

Baseline and any abnormal findings/values for ECGs will be listed.

11. OTHER PLANNED ANALYSIS

The pharmacokinetic (PK) analyses will be described in a separate document and are not discussed in this SAP.

12. APPENDIX

Changes to the appendix are not considered amendments to, or violations of, this SAP.

12.1 Analysis Set Summary Conventions

- Analysis sets represented on the tables will be clearly identified at the end of the table title and will be identical in name to that identified in the protocol or SAP: (Full Analysis Set), (Primary Efficacy Analysis Set), and (Per-Protocol Analysis Set).
- In general, all data recorded will be included in data listings. For listings that include screen failure data, the screen failure subject IDs will be sorted at the end of each listing.
- Consistent terminology will be used to define and identify a population. Common nomenclature may include (a) Full Analysis Set (FAS) (b) Total Sebelipase Alfa
- Subpopulation(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (eg, ITT Females, PP Males greater than 60 years of age) used for analysis in a table or figure.
- Population sizes may be presented as the total in the column header as (N=xx) where appropriate.
- Population sizes shown with summary statistics are the sample sizes (n) of patients with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the patients may have had a response. If no subject is counted in a category, the count of 0 will be displayed. Percentages corresponding to null categories (cells) will be suppressed.
- All percentages are rounded to the nearest percent and reported without decimal points (xx %). A percentage of 100% will be reported as 100%. If an output displays both count and percent contiguously (e.g. “5 (50%)” where n=10), and the count is 0, then “0%” will not be displayed, only the count of “0” will be displayed. If the count is not presented, only the percentage, then “0%” will be displayed.
- Population summaries that include p-values will report the p-value to 3 decimal places with a leading zero (0.001). All p-values reported on default output from statistical software may be reported at the default level of precision; p-values less than 0.001 will be reported as “<0.001,” not “0.000.”

13. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

1. The four functional area scores of the Denver II developmental screening test will each be summarized, but no Total score.

14. REFERENCES

Clopper, C.; Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". *Biometrika* **26**: 404–413.

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.

15. TABLES, LISTINGS, AND FIGURES

The planned tables, listings, and figures to accompany this SAP will be contained in a SAP addendum.