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

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Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: **LAL-CL04**

An Open Label Multicenter Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of SBC-102 in Adult Subjects with Liver Dysfunction Due to Lysosomal Acid Lipase Deficiency Who Previously Received Treatment in Study LAL-CL01

Author: PPD

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Chiltern International Limited

PPD

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Alexion Pharmaceuticals

PPD

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Alexion Pharmaceuticals

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation Definition

ADA	Antidrug Antibodies
AE	Adverse Event
ATC	Anatomic Therapeutic Class
AUC0-t	The Area Under the Concentration curve from the start of the infusion to the last measurable level at Weeks 24, 52, and 104/end of study
AUCtau	The Area Under the Concentration curve from the start of the infusion to the end of the dosing interval.
AUC0-∞	The Area Under the Concentration curve from the start of the infusion extrapolated to infinity (∞) on Day 0
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CI	Confidence Interval
CL	Total body clearance
CLDQ	Chronic Liver Disease Questionnaire
C_{max}	The maximum serum level observed over the dose interval
C_{min}	The minimum serum level observed over the dose interval
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
ECG	Electrocardiogram
EMA	European Medicines Agency
ERT	Enzyme Replacement Therapy
ESR	Erythrocyte Sedimentation Rate
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRR	Infusion Related Reaction
IAR	Infusion Associated Reaction
IV	Intravenous

z	Apparent terminal rate constant calculated from the regression analysis (slope) from the log-transformed measured concentrations on the terminal phase of the time-point concentration curve
LAL	Lysosomal acid lipase

Abbreviation	Definition
LOQ	Limit of Quantification
MCS	Mental Component Summary (SF-36)
MedDRA®	Medical Dictionary for Regulatory Activities
MEGE	Multi-Echo Gradient Echo
MEOI	Medical Events of Interest
NCA	Noncompartment analysis
PCS	Physical Component Summary (SF-36)
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-Protocol
PT	Preferred Term
QOW	Every other week dosing
QTc	QT-interval for ECG corrected for heart rate
QW	Once a week dosing
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Safety Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
t½	Apparent terminal half-life
TEAE	Treatment-Emergent Adverse Event
t_{max}	The time to reach the C_{max}
V_z	Volume of distribution after IV infusion
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WNL®	WinNonlin®

1. OVERVIEW

This Statistical Analysis Plan (SAP) describes the final planned analysis Protocol LAL-CL04 (An Open Label Multicenter Extension Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of SBC-102 in Adult Subjects with Liver Dysfunction Due to Lysosomal Acid Lipase Deficiency Who Previously Received Treatment in Study LAL-CL01).

The planned analysis identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Any post hoc, or unplanned, exploratory analysis performed for the CSR will be clearly identified in the final CSR.

In addition to the study protocol and amendments, the following documents were reviewed in preparation of this SAP:

- Case report forms (CRFs) for Protocol LAL-CL04.
- Clinical Research Protocol LAL-CL01 and associated documents.
- ICH Guidance on Statistical Principles for Clinical Trials (E9).

Readers of this SAP are encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Any statements about patient intervention or trial design are for reader convenience; and are not intended to modify protocol instructions. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of SBC102 in patients with liver dysfunction due to Lysosomal acid lipase (LAL) Deficiency.

2.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate the long-term efficacy of SBC-102 in patients with liver dysfunction due to LAL Deficiency.
- To characterize repeat-dose pharmacokinetics (PK) of SBC-102 delivered by intravenous (IV) infusion.
- To determine the effect of SBC-102 on pharmacodynamic (PD) biomarkers.

2.1.3 Exploratory Objectives

The exploratory objectives are:

- To determine the effect of SBC-102 on Health-Related Quality of Life (HRQOL) outcome measures.
- To evaluate the acceptability of an every other week dosing regimen of SBC-102.
- To evaluate liver histology.

2.2 Study Endpoints

2.2.1 Safety Endpoints

This study is designed primarily to evaluate the safety and tolerability of long-term treatment with SBC-102, administered as weekly (qw) and biweekly (qow) IV infusions. The primary safety endpoints in this study will include:

- The incidence of:
  - Adverse events (AEs).
  - Serious adverse events (SAEs).
  - Infusion Associated reactions (IARs).
- Change/shift from baseline in:
  - Vital signs.
  - Physical examination findings.
  - Clinical laboratory tests.
  - 12-lead ECG parameters.
  - Use of concomitant medications/therapies.
- Characterization of anti-drug antibodies (ADAs) including:
  - Antibody positive rate.
  - Time to first antibody positive result.
  - Median and peak ADA titer.
  - Time to peak ADA titer.

A further characterization of ADAs, including neutralizing ADAs, may be performed as a separate pooled analysis across studies, and will be reported separately.

2.2.2 Efficacy Endpoints

The following efficacy measures will be utilized to investigate the effect of SBC-102 on hepatic dysfunction in LAL Deficiency

- Liver and spleen volumes by magnetic resonance imaging (MRI)
- Liver and spleen fat content by multi-echo gradient-echo MRI and ^{1}H- magnetic resonance spectroscopy (MRS) (if available)

- Histologic assessment of liver disease by biopsy in subjects who agree to the optional procedure.

2.2.3 Pharmacokinetic Endpoints

The PK endpoints are the multiple-dose (Weeks 24, 52, and 104) parameters estimated from the PK sampling times and serum SBC-102 concentrations for each dose profiled.

2.2.4 Pharmacodynamic Endpoints

The PD endpoints include observed values, change from baseline and percent change from baseline for hepatic transaminases, serum lipids and acute phase reactants at each time of assessment, overall and by dosing cohort. The percentage of subjects with abnormal transaminases at each time point will also be summarized overall and by dosing cohort.

Exploratory disease-related biomarkers, which may be identified, based on emerging information from the SBC-102 development program and scientific literature will be analyzed by changes or percent changes from baseline if the assessments are continuous.

2.2.5 Health-Related Quality of Life (HRQOL)

As there are no validated tools to assess HRQOL in LAL Deficiency, HRQOL will be assessed using tools developed for other diseases. Evidence of SBC-102 treatment benefits will be assessed by changes in scores for the following:

- Chronic Liver Disease Questionnaire (CLDQ).
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue).
- The Short Form 36 Health Survey (SF-36®).

3. STUDY METHODS

3.1 Overall Study Design and Plan

This section of the SAP is intended to orient the reader to the study design. All information in this section is either copied or summarized from the protocol.

This Phase 2, open-label, extension study will evaluate the long-term safety, tolerability, and efficacy of SBC-102 in adult patients with liver dysfunction due to LAL Deficiency who previously received 4 doses of SBC-102 in the Phase 1/2 repeat-dose, dose escalation study (Study LAL-CL01). The study will consist of a screening period, treatment period, and follow-up period.

Subjects who successfully receive all 4 doses of SBC-102 in study LAL-CL01 and wish to continue treatment with SBC-102 in the extension study will undergo screening assessments to determine study eligibility (Note: assessments performed in study LAL-CL01 within a defined

time period may not need to be repeated at the screening visit; see Appendix A: Schedules of Assessments in the study protocol for details).

Eligible subjects will initiate treatment in the current extension study at least 4 weeks after their last dose of SBC-102 in study LAL-CL01 and continuing for up to 3 years. Each subject will initiate treatment in the extension study at the same once-weekly dose of SBC-102 that he/she received during the fourth infusion in study LAL-CL01 (i.e., 0.35 mg/kg qw, 1 mg/kg qw, or 3 mg/kg qw). After the 4th infusion under this protocol, all subjects will move to an every other week (qow) dosing regimen of 1 or 3 mg/kg.
Subsequent modifications to the dose and dosing frequency will be undertaken for individual subjects as outlined below based on observed safety and tolerability and/or clinical response to treatment. After a minimum of 12 weeks of treatment in study LAL-CL04, a subject may be considered for a dose escalation, either from 1 mg kg-1 qow to 3 mg kg-1 qow or from 3 mg kg-1 qow to 3 mg kg-1 qw, if the subject exhibits an inadequate clinical response (see below). Prior to considering a dose increase, the subject should be evaluated for other potential causes of any clinical manifestations that are thought to reflect a suboptimal response. Other causes could include:

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

Inadequate clinical response is defined as:

- Clinically important manifestations of LAL Deficiency on either clinical examination, laboratory assessment, liver biopsy or imaging which have either: a) not improved from baseline,

    b) improved and plateaued but have not normalized, or
    (Note: the definition of a plateauing of effect requires consideration of a minimum of 3 assessments.)

    c) failed to normalize within 12 months of initiation of treatment.

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

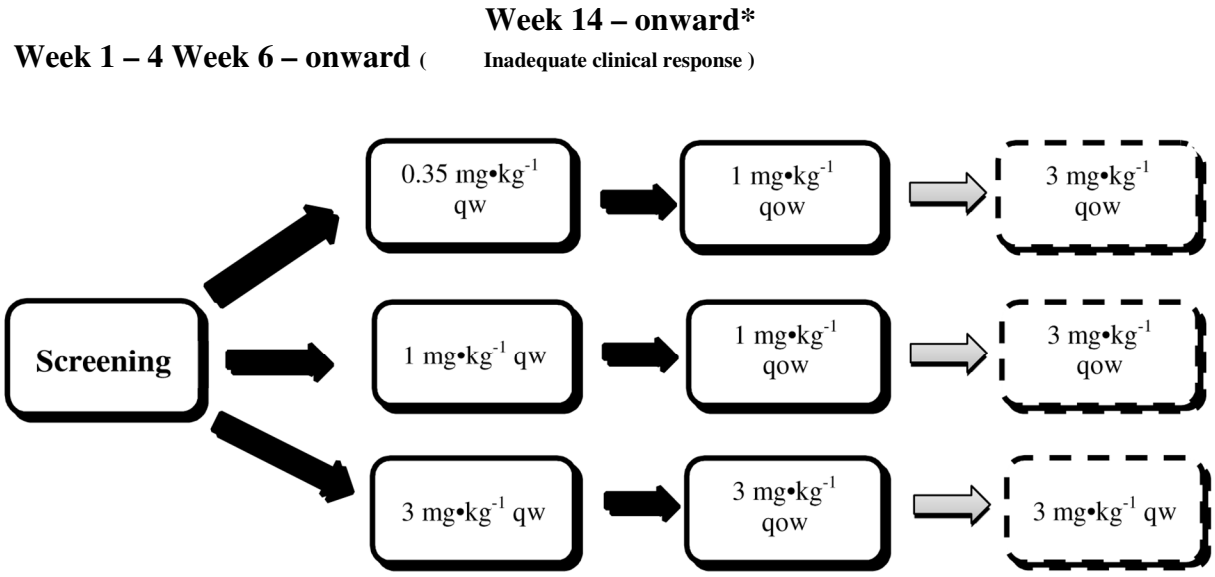
All such decisions will be made jointly by the Investigator and Sponsor.

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

Safety, tolerability, and efficacy assessments will be conducted at regular intervals throughout the extension study according to Appendix A: Schedules of Assessments in the study protocol. In addition, blood samples will be obtained at selected time points for analysis of SBC-102 PK and biomarkers of SBC-102 PD activity. Blood and urine samples will also be collected for an exploratory analysis of potential disease-related biomarkers in these subjects, and HRQOL measures will be assessed through subject questionnaires.

A follow-up visit will be conducted for all subjects at 30 (+7) days after the last dose of SBC102.

Figure 1: LAL-CL04 Study Flow Diagram



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

3.2 Selection of Study Population

The target population for this study is male and female subjects (≥ 18 years of age) with liver dysfunction due to LAL Deficiency who received treatment with SBC-102 in study LAL-CL01.

3.2.1 Inclusion Criteria

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

1. Subject understands the full nature and purpose of the study, including possible risks and side effects, and is willing and able to comply with all study procedures and provide informed consent.
2. Subject received all 4 scheduled doses of SBC-102 in study LAL-CL01 with no lifethreatening or unmanageable study drug toxicity.
3. Female subjects have a negative serum pregnancy test at screening, and are not breastfeeding.
4. Female subjects of childbearing potential are willing and able to use a highly effective and approved contraceptive method(s) from the date of informed consent until 30 days after last dose of IMP. A highly effective method of contraception is defined as fulfilling at least one of the following: a) Strict abstinence; b) Bilateral tubal ligation;

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

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

3.2.2 Exclusion Criteria

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

1. Clinically significant concurrent disease, serious inter-current illness, concomitant medications, or other extenuating circumstances that, in the opinion of the Investigator, would either interfere with study participation or the interpretation of the effects of SBC-102.
2. Clinically significant abnormal values on laboratory screening tests, other than liver function or lipid panel tests. Subjects with an abnormal laboratory value that is of borderline significance may be allowed to undergo repeat testing once within a 30-day period.

3.3 Treatment Masking (Blinding)

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

4. ANALYSIS AND REPORTING

4.1 Analysis of Available Data for Regulatory Filing

A CSR of available data may be produced to support regulatory filing(s). Such report of available data would likely include listings, summary tables, and graphs of safety, efficacy, PK and PD data available by a designated cutoff date prior to the regulatory filing(s). Select descriptive p-values to guide clinical judgment and interpretation of the data would be presented without adjustment for multiplicity.

4.2 Safety Data Summaries

The Safety Committee (SC) will perform periodic reviews of aggregate safety data from study LAL-CL04 on at least a biannual basis (i.e., every 6 months) from the date of enrollment of the first subject until completion of dosing for all subjects in the study. Ad-hoc reviews of safety data will also be performed by the SC on an as needed basis in the event of emerging safety signals of clinical concern in one or more subjects, including potential safety risks that meet the

pre-defined stopping rules for study treatment (see Section 7.6 of the protocol). Following each periodic and ad-hoc review of safety data, the SC will indicate whether dosing of SBC-102 may continue (or be resumed) for all subjects or a subset of subjects in the study.

4.3 Final Analysis

All final, planned analyses identified in the protocol and in this SAP will be performed after the last subject has completed the final follow-up visit and all relevant study data have been processed and integrated into the analysis database.
Any changes from the planned study analysis as described in the protocol are listed in Section 14 of this SAP. Any post hoc, exploratory analysis completed to support planned study analysis, which were not identified in this SAP, will be described in the CSR. Any results from these unplanned analyses (post hoc) will also be clearly identified in the text of the CSR.

4.4 Data Reporting by Cohort

For this study, results will be reported by cohort and overall. A subject's dose cohort will be defined by the dose of longest duration, i.e., by the subject's every-other-week dose.

4.5 Sample Size Determination

Sample size for the study was based on the number of treated subjects in LAL-CL01 who were eligible and willing to participate in this extension study.

5. STATISTICAL ANALYSIS

5.1 General Statistical Methodology

All data will be provided in listings sorted by cohort and subject study number, and, if applicable, date of assessment. Dates will be provided in the ISO8601 yyyy-mm-dd format (eg, 2013-01-01). Where a time component is included (24 hour clock with hour and minute) the format will be yyyy-mm-dd:hh:mm (eg, 2012-01-01:16:32). Included in all listings will be the dosing cohort for each subject. Select listings will also include the dosing regimen that each subject was on at the onset of the event.

Tabulations will be prepared using the following descriptive statistics:

- Continuous, quantitative variable summaries will include the number of subjects with non-missing values (n), mean, standard deviation (SD), minimum, median, and maximum. In addition, the percent coefficient of variation (CV%) will be provided for PK parameters.
- Categorical, qualitative variable summaries will include the frequency and percentage of subjects who are in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the analysis set for the cohort. Shift tables comparing data observed at baseline to that observed after the initiation of dosing will be prepared as noted for specific endpoints.

95% two-sided confidence intervals (CI) may be calculated around the estimates based on the exact binomial distribution for categorical endpoints and the t-distribution for continuous endpoints. Confidence intervals will be based on a 2-sided alpha of 0.05 and are intended to guide clinical judgment and interpretation of the data. Effect of anti-drug antibodies may be examined for efficacy, safety, and PK endpoints. Additional exploratory analyses may be conducted in other subgroups of interest.

Baseline values are defined as the last measurement prior to the first infusion of SBC-102 in study LAL-CL04.
For select continuous efficacy, safety, and HRQOL endpoints that are computed as changes from baseline, change from the CL04 Baseline will be presented. All tabulations will present data overall and by dosing cohort.

Subjects who miss infusions do not "make up" those infusions, rather, they continue with the procedures stated in the protocol as if they had not missed the infusions. If a subject misses more than 3 consecutive planned infusions, laboratory data for that subject will not be included in summaries, beginning with the first of the multiple missed doses. Adverse event summaries will, however, include any events reported for such a subject.

P-values and confidence intervals are considered descriptive and are not adjusted for multiplicity.

5.2 Analysis Sets

The following analysis sets are defined for this study:

- **Full Analysis Set (FAS):** This analysis set consists of all subjects who received at least one complete infusion of SBC-102 in the extension study, and have at least one post-treatment measurement in the extension study. This analysis set will be used for analysis of efficacy, PD, and patient health outcomes data.
- • Safety Analysis Set (SAFETY)**: This analysis set consists of all subjects who received any amount of SBC-102 in the extension study.** Note: if the FAS and SAFETY consist of the same subjects, then results will be reported as "Full Analysis Set" results, and separate displays for the Safety Analysis Set will not be generated. **Per-Protocol Set (PPS):** This analysis set will consist of all subjects in the FAS who have no protocol deviations that could potentially confound the interpretation of serum transaminase or lipid results.
    - o The list of subjects to be included in the per-protocol analysis set will be determined before database lock (i.e. locking of data elements for analysis). If all subject**s** in the FAS are also in the PPS, then separate analyses for the PPS will not be performed.
- **Pharmacokinetic (PK) 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 in the extension study and will be used for all PK analyses.

5.3 Handling of Missing Data

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

6. STUDY SUBJECTS AND DEMOGRAPHICS

6.1 Subject Disposition and Withdrawals

The frequency and percentage of subjects who completed or prematurely discontinued participation in LAL-CL04, will be presented by dosing cohort and overall. A listing, sorted by cohort and subject number, including dose of SBC-102 first administered on the LAL-CL04 study, age, gender, date of informed consent, date of first dose of SBC-102 in the LAL-CL01 study, date of the first dose of SBC-102 in the LAL-CL04 study, date of completion or premature discontinuation from the LAL-CL04 study, whether the subject completed the study or terminated early along with any reason for early termination, and inclusion in the various analysis sets will be provided for all subjects.

6.2 Protocol Deviations

Protocol deviations will be listed by subject, as applicable.

6.3 Demographics and Other Baseline Characteristics

Descriptive summaries for subjects in the Safety Analysis Set and data listings for all subjects, of demographic and other baseline characteristics will be presented by dosing cohorts and overall. The following data will be included:

- Demographics (age, gender, race, ethnicity).
- Investigator and investigational site locations (data listing only).
- Height, weight and BMI (derived as (weight in kg)/(height in m)^2.
- Medical history as reported in LAL-CL04
- Summaries of lipid-lowering medications will be provided.
- Years since LAL diagnosis and age at LAL diagnosis as reported in LAL-CL01.
- Frequency of abnormal transaminases at the LAL-CL04 Baseline.
- Physical examination at LAL-CL04 Baseline, including clinical significance of findings, size and characteristics of the liver, spleen and lymph nodes, and palpability of the tibialis and pedis pulse.

Body Mass Index (BMI) will be summarized as both continuous variable and as a categorical variable with values of Underweight (<18.5), Normal (18.5-24.9), Overweight (25.0-29.9), and Obese (≥30). Abnormal transaminases (at Baseline) are defined as ALT or AST at Baseline is greater than 1.5×ULN. The LAL diagnosis information will be obtained from study LALCL01

from the manual review of medical history data in "Gastrointestinal System" subcategory conducted in that study.

Prior medications/therapies, as reported in LAL-CL04 will be coded using the World Health Organization (WHO) Drug Dictionary, and will be tabulated and listed overall and by dosing cohort.
Medical history and physical examination will be summarized by body system. Details will be listed for all subjects.

7. EFFICACY ANALYSES

Liver and spleen volumes by magnetic resonance imaging (MRI) will be summarized as multiples of normal (where normal is defined as 2.5% of body weight for liver and 0.2% of body weight for spleen). Analysis of efficacy endpoints will include a summary of observed values, absolute change and percent change from baseline for each post-baseline time point in liver and a listing for spleen fat content by multi-echo gradient-echo MRI and H magnetic resonance spectroscopy (MRS) (if available). The protocol also specified analysis of liver cholesteryl ester signature by ^{13}C-magnetic resonance spectroscopy, if feasible; the test proved infeasible at participating sites. MEGE and MRS liver fat content will be summarized for the right lobe of the liver; both right and left lobe liver fat content will appear in listings. Descriptive statistics along with 95% CIs will be displayed by dosing cohort and overall. Descriptive pvalues based on the Wilcoxon sign-rank test, unadjusted for multiplicity, may be presented as an assessment change from baseline relative to the observed variability in these measures. These p-values are not considered confirmatory.

An assessment of hepatic histopathology will also be conducted in those subjects who agree to an optional liver biopsy. Biopsy results will be provided in listings and may be summarized if sufficient data are available. ADA data will be listed.

8. PHARMACOKINETIC ANALYSES

A secondary objective of this study is to characterize repeat-dose pharmacokinetics of SBC-102 delivered by IV infusions [pre and post infusion at Weeks 24, 52, and 104].

Pharmacokinetic parameter estimates for each subject are derived from serum concentration variables.

8.1 Plasma Concentration Data

8.1.1 PK Serum Sample Collection Times

PK samples for measurement of SBC-102 serum levels at Weeks 24, 52, and 104/end of study will be collected:

- Immediately pre-dose (within 30 minutes of the start of the infusion).
- At 10(±1), 15(±1), 20(±1), 40(±2), 60(±2) and 90(±2) minutes from the beginning of the infusion and at the end of the infusion (approximately 120 minutes).

- At 5(±1), 10(±1), 20(±1), 30(±1), 40(±2), 60(±2) and 120(±2) minutes after completion of the infusion.

8.1.2 PK Serum Sample Elapsed Time

The elapsed time from the start of the infusion to the sampling time will be calculated from the recorded clock time. It will be used to characterize each sample in data listings and for PK parameter estimation. However, the scheduled times will be used to summarize concentration data and mean figures. These new elapsed scheduled times would only be used for the post infusion times. They would add the infusion time (approximately 120 minutes) to the scheduled times after the infusion resulting in 125, 130, 140, 150, 180, and 240 minutes from the beginning of the infusion.

8.1.3 PK Input File Creation

The PK analysis dataset will be created from SBC-102 serum levels provided by the bioanalysis laboratory combined with study database records of the actual dose amounts and infusion start times and actual sampling times. The actual elapsed time for each sample will be calculated from the actual clock time of infusion start to the actual clock sample time. The actual clock time for each sample will be compared with the scheduled time for each sample to determine the time difference to be reported in minutes.

8.1.4 PK Serum Sample Presentations

PK concentration data will be listed as received from the bioanalytical laboratory along with dosing dates and times, scheduled sampling times, elapsed time from start of the infusion, lab reported concentration, and deviation from the scheduled sampling times in minutes.

PK concentration data will be summarized by dose at the time of the infusion (rather than cohort) and profile week (24, 52, and 104) using the modified sampling schedule times.

Observed values of SBC-102 concentrations will be summarized by dosing regimen and plotted over time. Descriptive statistics will include mean, SD, minimum, median, maximum, CV% and geometric mean. SBC-102 concentrations at pre-dose times will be set to zero and a footnote added if this situation occurs.

Figures will be provided for each subject's concentration-time data and for mean data at each dose and profile week. Individual concentration-time figures will contain Weeks 24, 52, and 104 profiles plotted in the same figure with origin for both lines being the start of the infusion. Mean concentrations will be illustrated in 3 figures (Weeks 24, 52, and 104) with different plots for different doses (since subjects may be changing doses during the study, there may be up to 3 dose levels. All figures will be presented in linear and semi-log scale.. Based on a review of the final data, some adjustments may be made to the graphical presentations and additional figures may be created to more fully present the data.

8.2 Pharmacokinetic Parameters

Individual PK parameters will be computed for samples obtained for PK characterization (multiple-dose parameters at Weeks 24, 52, and 104/end of study). Profile intervals will begin at the time of the start of the infusion and continue to the last sample collected on that infusion period. PK parameters will be estimated by standard non-compartment analysis (NCA) methods.

A summary of calculated PK parameters will be presented. All SBC-102 concentrations and calculated PK parameters will be included in data listings. Descriptions and calculations of the PK parameters are presented in the table below.

Parameters for PK Analysis

Parameter	Unit	Description of Parameter
C_{max}	ng/mL	The maximum serum level observed in units of concentration. Observed for each subject-dose profiled.
t_{max}	hr	The time to reach the Cmax in hours to hundredths of the hour. Observed for each subject-dose profiled.
AUC0-t	hr×ng/mL	The Area Under the Concentration curve from the start of the infusion to the last measurable level at weeks 24, 52, and 104/end of study. Trapezoidal rule used for estimation.
AUCtau	hr×ng/mL	The Area Under the Concentration curve from the start of the infusion to the end of the dosing interval. Trapezoidal rule used for estimation but with linear extrapolation to end of dosing interval if needed.
AUCO-∞	n	The Area Under the Concentration curve from the start of the infusion extrapolated to infinity (∞) on Day 0. AUC0-t + [Ct/ z)] where Ct is the last measurable level of a prof iled dose interval.
z	1/hr	Apparent terminal rate constant calculated from the regression analysis (slope) from the log-transformed measured concentrations on the terminal phase of the time-point concentration curve. Based on slope from linear regression of terminal phase.
t½	hr	Apparent terminal half-life. t½ = ln(2)/ z.
CL	mL/hr/kg	Total body clearance. CL =dose/AUC0-t (Weeks 24, 52, and 104/end of study).
Vz	mL/kg	Volume of distribution after IV infusion. Vz = MRTiv x CL where MRTiv = mean residence time.

For PK parameter estimation, analyte concentrations that are below the limit of quantification (BLQ) will be assigned a value of zero when they precede the first quantifiable sample. BLQ

values embedded between 2 quantifiable data points will be treated as missing. BLQ values occurring after the last quantifiable concentration will be treated as missing data. When consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by assigning them a value of missing, unless otherwise warranted by the concentration-time profile. No linear interpolation for these missing concentration values will be completed.

Individual PK parameters will be estimated for each subject in the PK analysis set and will be provided in a listing. Actual elapsed sampling time from the start of the infusion will be used for all parameter estimation. Descriptive summaries such as mean, SD, geometric mean, CV%, median, minimum, and maximum of the PK parameters will be presented by dosing cohort.

9. PHARMACODYNAMIC ANALYSIS

Analysis of pharmacodynamic endpoints will include summaries of liver biochemical parameters (ALT, AST, GGT, total bilirubin, bilirubin, albumin, and alkaline phosphatase), serum lipids (serum total cholesterol, LDL, HDL, and triglycerides), serum ferritin, hsCRP, and platelets which will be tabulated overall and by dosing cohort. Observed values, change from baseline and percent change from baseline at each time of assessment will be summarized, and will include 95% confidence intervals. P-values may be calculated if there are a minimum of 6 subjects across all cohorts available for analysis at a particular timepoint; if presented, these will be computed using Wilcoxon-sign-rank statistics on change from baseline.

Serum lipids, serum ferritin, and hsCRP will be presented by-subject and tabulated in both SI and Conventional units; all other laboratory data will be presented as SI units only. In addition, the proportion of subjects with abnormal transaminases, serum lipids, serum ferritin and hsCRP will be displayed by cohort and overall.

Shift tables comparing the percentages of subjects (pooled across dosing cohorts) with normal/abnormal values for each pharmacodynamic parameter at each time of assessment relative to the CL04 baseline will be presented.

Graphical displays may be created to illustrate the time course of these lab parameters, including spaghetti plots and mean plots. Graphical displays may also be used to investigate differences in lipid results from assessments taken one week after infusion versus those taken 2 weeks after infusion.

Change from baseline analyses for PD endpoints will be performed using CL01 and CL04 baselines.

10. PATIENT HEALTH-RELATED QUALITY OF LIFE (HRQOL) OUTCOMES ANALYSES

Observed scores and changes from the CL01 and CL04 baseline will be summarized for HRQOL measures including the 36-item Short Form Health Survey (SF-36), Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue) scale, and Chronic Liver Disease Questionnaire (CLDQ). All score data will be presented by study visit in data listings.

For SF-36 scores, scores for the 8 subscales (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health) as well as the Physical Component Summary (PCS) and Mental Component Summary (MCS) will be derived and summarized. Both transformed scores (0 – 100 scoring) and norm-based scores will be presented. The FACIT-Fatigue Total Score, Total CLDQ score, and the 6 subscales of the CLDQ (Abdominal Symptoms, Fatigue, Systemic Symptoms, Activity, Emotional Functions and Worry) will also be listed and tabulated. Observed measurements and changes and/or percent changes from baseline to study time points will be summarized overall and by dosing cohort including 95% confidence intervals.

These analyses will be based on the FAS.

11. SAFETY AND TOLERABILITY ANALYSIS

The analysis of safety and tolerability will include the following data:

- SBC-102 exposure.
- Adverse events. ○ AEs (i.e., treatment-emergent AEs), including related AEs and SAEs. ○ AEs causing study discontinuation.
  ○ Infusion related reactions.
- Clinical laboratory investigations.
- Vital signs (body temperature, pulse rate, respiratory rate, blood pressure).
- Physical exam.
- 12-Lead ECG.
- Concomitant medications and therapies.
- Antidrug antibody formation.

These analyses will be based on the Safety Analysis Set.

11.1 SBC-102 Exposure

Exposure to study drug (SBC-102) will be summarized by dose. 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 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.

11.2 Adverse Events

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

Severity of AEs will be graded on a 5-point scale (mild, moderate, severe, life-threatening and death) according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 13.1 or higher.

In AEsummaries, subjects will only count in one column.

For counting events, if a subject experiences the same AE multiple times, each occurrence of this event will be counted toward the frequency of events; but for counting subjects, each subject will be counted only once within each PT and each SOC. If a subject experiences more than one AE within a PT or SOC, only the AE with the strongest relationship or the greatest severity, as appropriate, will be included in the summaries of relationship and severity, respectively.

A data listing of all AEs reported in the study will be presented.

Additionally a data listing of deaths and AEs leading to study discontinuation will be provided.

11.2.1 Serious Adverse Events

Summaries of the numbers of SAEs and incidence rates (frequencies and percentages of subjects), by PT within SOC, overall and by dosing cohort, will be prepared for the Safety Analysis Set.

A data listing of SAEs will be provided.

11.2.2 InfusionAssociated Reactions

Infusion reactions will be considered Medical Events of Interest (MEOI). An AE will be considered an IAR if the Investigator checks “Yes” to the question “Is AE an IAR?” on the AE CRF. In addition, for the purpose of this study, an AE (diagnosis and/or symptom) that occurs from the start of the infusion, up to 4 hours after the infusion and is assessed by the Investigator as at least possibly related to SBC-102 will be considered an IAR. Note that several AEs may be associated with one IAR observed with SBC-102 administration; each AE is captured as a separate event. The number and percentage of subjects who experience any IAR (any subject who experiences an IAR is only counted once regardless of the number of associated events) and the number of IARs reported over the course of the study (i.e., subjects may be counted more than once if IARs occur on more than one dosing day) will be summarized.

Summaries of AEs that comprise an IAR will be presented in a similar manner to AEs in Section 11.2.

A data listing of all AEs reported as IARs during the study will be presented.

IMP infusions in which the rate was slowed or which were discontinued due to IAR will also be detailed in data listings along with an indication of whether the subject developed one or more antidrug antibodies during the course of the study.

11.3 Clinical Laboratory Evaluations

Observed measurements and changes/percent changes from the CL01 and CL04 baseline to study time points in clinical chemistry, hematology, and urinalysis will be summarized by dosing cohort and overall. All laboratory values will be classified as normal, above normal, or below normal based on normal ranges provided by the laboratory. All laboratory values will be presented in data listings. Results will be flagged to indicate if they were abnormal (high, low) and/or clinically significant. Frequencies of abnormal values relative to the laboratory normal range will also be summarized via shift tables.

Information relating to development of anti-drug antibodies will be provided in listings.

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, HDL-C, triglycerides, hemoglobin, platelets, PT, PTT, and serum ferritin. Plots will include a line for each subject with line color to indicate cohort plus a black line for the overall mean.

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, HDL, triglycerides
- Other: Hemoglobin, platelets, PT/PTT, serum ferritin

Change from baseline analyses will be performed using CL01 and CL04 baselines.

11.4 Vital Signs

Observed values and change from pre-dose will be presented for the following vital sign parameters, where applicable:

- Body temperature.
- Pulse rate.
- Blood pressure.

- Respiratory rate.

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

11.5 Electrocardiograms

Change from CL01 and CL04 baseline in the ECG parameters will be provided, where applicable. Categorical summaries (e.g. normal, abnormal, abnormal clinically significant) will also be presented. A listing of ECG results will be provided.

11.6 Physical Examination

Summaries of physical examination findings by body system as well as summaries of clinical significance of findings, size and characteristics of the liver, spleen and lymph nodes, and palpability of the tibialis and pedis pulse will be summarized at baseline and post baseline.

A summary of findings including liver size, spleen size, lymphadenopathy and arterial disease at Screening and follow-up will be presented.

11.7 Concomitant Medications and Therapies

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. The name of the medication or therapy, reason for use, start date, stop date, dose and route of administration (if applicable), and frequency of administration will be reported as in the eCRF.

Prior medications and concomitant medication/treatment data will be coded using the WHODRUG dictionary (March 2011 edition). All data will be listed, and the number and percentage of subjects receiving each prior and concomitant medication/treatment by ATC class and/or preferred term as appropriate will be tabulated.

All prior medications and concomitant medications and treatments (pharmacological and nonpharmacological) received by the subject from the last assessment in LAL-CL01 until completion of the follow-up visit approximately 30 days after the last does of SBC-102 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.

11.8 Antidrug Antibody Titer

The proportion of subjects with measurable antibodies to SBC-102 will be displayed overall and by cohort. A data listing will be provided.

12. TREATMENT GROUP ANALYSIS

This is a Phase 2 drug safety and PK/PD study. No formal statistical hypothesis testing is planned to compare between cohort (treatment group) effects.

13. SUBGROUP ANALYSES

If there is a sufficient number of subjects with presents of one or more anti-SBC-102 antibodies versus those subjects without presence of any anti-SBC-102 antibodies then efficacy analysis will be performed separately for each group.

Post-hoc subgroup analyses may be performed as needed.

14. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

1. Liver cholesteryl ester signature (as measured by ^{13}C MRS) will not be analyzed.
2. Listings will be sorted by cohort then subject, rather than only by subject.
3. ADA, seroconversion data will be listed only.
4. Tabulations will be presented overall and by cohort, where cohort is defined by the dose of longest duration, i.e., by the subject's every-other-week dose.
5. The protocol states that 'For endpoints that are computed as changes from baseline, a comparison between change from Baseline and change from the CL01 Study Baseline will be performed, as appropriate'. This comparison will be a text description, rather than an additional analysis.
6. Liver cholesteryl ester signature (as measured by ^{13}C MRS) in a subset of subjects receiving treatment at sites with access to this imaging technology. This will not be analyzed.

15. REFERENCES

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
2. ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999. http://www.amstat.org/about/ethicalguidelines.cfm
3. RSS. (1993) The Royal Statistical Society: Code of Conduct, April 1993. http://www.rss.org.uk/main.asp?page=1875.

16. APPENDICES

16.1 Calculation of Multiples of Normal for Liver and Spleen Volume

Multiples of Normal (MN) are 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 subject would have an expected "normal" liver volume of 1.25 liters (0.025*50=1.25) and an expected "normal" spleen volume of 0.10 liters (0.002*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.

16.2 Health-Related Quality of Life Questionnaires

16.2.1 The Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale

The FACIT-Fatigue instrument consists of 13 items, with each item rated on a 4-point ordinal scale ranging from 0 (Not at all) to 4 (Very Much).

		Not at all	A little bit	Somewhat	Quite a bit	Very Much
1	I feel fatigue	0	1	2	3	4
2	I feel weak all over	0	1	2	3	4
3	I feel listless ("washed out")	0	1	2	3	4
4	I feel tired	0	1	2	3	4
5	I have trouble starting things because I am tired	0	1	2	3	4
6	I have trouble finishing things because I am tired	0	1	2	3	4
7	I have energy	0	1	2	3	4
8	I am able to do my usual activities	0	1	2	3	4
9	I need to sleep during the day	0	1	2	3	4
10	I am too tired to eat	0	1	2	3	4
11	I need help doing my usual activities	0	1	2	3	4
12	I am frustrated by being too tired to do things I want to do	0	1	2	3	4
13	I have to limit my social activity because I am tired	0	1	2	3	4

Scoring of FACIT-Fatigue: The total score ranges from 0-52. Higher scores suggest better quality of life for the subject. All items, except Items #7 and #8, are reversed scored.

	Reverse Item?		Item Response	Item Score
1	4	-		=
2	4	-		=
3	4	-		=
4	4	-		=
5	4	-		=
6	4	-		=
7	0	+		=
8	0	+		=
9	4	-		=
10	4	-		=
11	4	-		=
12	4	-		=
13	4	-		=

Total Score: (sum of Item Scores) * 13 and divide by the number of items answered.

Missing Data: The total FACIT-Fatigue Scale can be calculated as long as more than 50% of the items were answered (e.g. a minimum of 7 of 13 items).

16.2.2 The Chronic Liver Disease Questionnaire (CLDQ)

CLDQ is a 29-item instrument to measure quality of life in 6 domains: abdominal symptoms; fatigue; systemic symptoms; activity; emotional function; and worry. Each item is rated on a 7-point ordinal scale ranging from 1 (All of the time) to 7 (none of the time).

Domains of the CLDQ:

Abdominal Symptoms (AB):	Items 1, 5, 17
Fatigue (FA):	Items 2, 4, 8, 11, 13
Systemic Symptoms (SY):	Items 3, 6, 21, 23, 27
Activity (AC):	Items 7, 9, 14
Emotional Function (EM):	Items 10, 12, 15, 16, 19, 20, 24, 26
Worry (WO):	Items 18, 22, 25, 28, 29;

Scoring of CLDQ:
Single domains and overall score range from 1-7. Higher scores implicate a better quality of life.

Single domain = (Sum individual item scores) x (number of scheduled items per domain) and divide by number of items answered.

Total score = (Sum single domains) divide by 6.

Total score can only be calculated if each single domain score is available.

Missing data:
Single domain scores can be calculated as long as more than 50% of the items were answered (e.g. a minimum of 2 of 3 items, 3 of 5 items, 4 of 8 items)