FINAL

CLINICAL STUDY REPORT

AN OPEN-LABEL MULTICENTER STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SBC-102 IN ADULT PATIENTS WITH LIVER DYSFUNCTION DUE TO LYSOSOMAL ACID LIPASE DEFICIENCY

Sponsor:	Synageva BioPharma Corp. 128 Spring Street Suite 520 Lexington, MA 02421 United States of America (USA)
Protocol Number:	LAL-CL01
EudraCT Number:	2010-024068-16
IND Number:	108460
Indication:	Lysosomal Acid Lipase Deficiency
Phase:	1/2
Design:	Open-label, repeat-dose
Study Initiation Date:	25 April 2011
Study Completion Date:	06 January 2012
Report Date:	04 June 2012
Sponsor Signatory and Responsible Medical Officer:	Anthony Quinn, MB ChB, PhD, FRCP Chief Medical Officer Synageva BioPharma Corp. Tel: +1-781-357-9900 Fax: +1-781-357-9901

This study was conducted and reported in accordance with the principles of Good Clinical Practice (GCP) as stated in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and all applicable government regulations and institutional policies and procedures, including the archiving of essential documents.

Synopsis

<table>
<tr><td>NAME OF COMPANY
Synageva BioPharma Corp.
128 Spring Street
Suite 520
Lexington, MA 02421
USA

NAME OF FINISHED PRODUCT
SBC-102

NAME OF ACTIVE INGREDIENT
recombinant human lysosomal acid lipase</td><td>SUMMARY TABLE
Referring to Part …… of the Dossier:

Volume:

Page:</td><td>FOR NATIONAL AUTHORITY USE ONLY:</td></tr>
<tr><td colspan="3">Title of Study: An Open-label Multicenter Study to Evaluate the Safety, Tolerability and Pharmacokinetics of SBC-102 in Adult Patients with Liver Dysfunction Due to Lysosomal Acid Lipase Deficiency</td></tr>
<tr><td colspan="3">Investigator(s): A total of 7 Principal Investigators participated in this study. The Coordinating Investigator for the study was Manisha Balwani, MD, MS.</td></tr>
<tr><td colspan="3">Study Site(s): The study was conducted at a total of 7 sites in the United States (US), United Kingdom (UK), France, and the Czech Republic.</td></tr>
<tr><td colspan="3">Publication(s): There are no publications as of the date of this report.</td></tr>
<tr><td colspan="2">Study Period:
Study Initiation Date: 25 April 2011

Study Completion Date: 06 January 2012</td><td>Phase of Development:
1/2</td></tr>
<tr><td colspan="3">Objectives:
The primary objective was to evaluate the safety and tolerability of SBC-102 in patients with liver dysfunction due to lysosomal acid lipase (LAL) Deficiency (vital signs, physical examination, clinical laboratory tests, immunogenicity tests, adverse event [AE] assessment, and concomitant therapies).

The secondary objective was to characterize the pharmacokinetics (PK) of SBC-102 delivered by intravenous (IV) infusion after single and multiple doses (pre- and post-infusion Day 0 and 21).

The exploratory objectives were:
• To examine the onset, magnitude of change, and reversibility of changes in transaminases [screening, pre-infusion Day 0, 7, 14, 21 and Day 28, 35 and 52]
• To evaluate the onset, magnitude of change, and reversibility of changes in total serum cholesterol, triglycerides, low density lipoprotein (LDL), and high density lipoprotein (HDL) [Days 0, 28 and 52]
• To provide information on the overall health of patients with liver dysfunction due to LAL Deficiency relative to reference populations using baseline patient health outcomes assessments:
o 36-item short form (SF-36™)
o Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue).
o Chronic liver disease questionnaire (CLDQ)</td></tr>
<tr><td colspan="3">Methodology:
This open-label study evaluated the safety, tolerability and PK of 3 dose levels of SBC-102 following administration as once-weekly (qw) IV infusions in adult patients with liver dysfunction due to LAL Deficiency. Pharmacodynamic (PD) markers and pre-treatment patient health outcomes were also evaluated on an exploratory basis. The study comprised a screening period, a treatment period, and a</td></tr>
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post-treatment follow-up period (including an End of Study visit).

Screening assessments were conducted 7 to 28 days prior to the start of dosing. Eligible subjects were treated in 3 sequential dose cohorts: 0.35 $mg \cdot kg^{-1}$ (Cohort 1), 1 $mg \cdot kg^{-1}$ (Cohort 2), and 3 $mg \cdot kg^{-1}$ (Cohort 3). In each cohort, subjects were administered qw infusions of SBC-102 on Day 0, Day 7, Day 14, and Day 21. Subjects were monitored for safety for at least 4 hours after the completion of each infusion. In addition, all subjects had a 24-hour inpatient stay after the first infusion with a safety assessment at 24 hours post-infusion, and a telephone contact at 24 hours after the second, third, and fourth infusions. Following the fourth infusion, subjects continued to be monitored at follow-up visits conducted at approximately 7 days and 14 days (optional) post-infusion. An End of Study visit was conducted at 30 days after the fourth infusion or, for subjects who prematurely withdrew from the study, no sooner than 7 days after their last infusion.

Within each cohort, one subject was initially dosed and, if SBC-102 was deemed safe and well tolerated in this subject after at least 24 hours of monitoring, dosing was allowed to be initiated for the remaining subjects in the cohort. Initiation of dosing in the next cohort occurred only after all subjects in the preceding cohort had been monitored for at least 5 days after the second infusion, and an independent Safety Committee had reviewed cumulative safety data and provided their recommendation on the acceptability of beginning dosing in the next cohort. The Safety Committee also provided additional general oversight of subject safety through its ongoing review of available safety data, and could make recommendations regarding continuation, modification, or suspension of dosing for an individual subject, a dose cohort, or all subjects in the study.

Number of Subjects (Planned and Analyzed):
Nine subjects (3 subjects per cohort) were planned, treated, and analyzed.

Diagnosis and Main Criteria for Inclusion:
Male or female subjects, 18 to 65 years of age, inclusive, who had documentation of either decreased LAL activity (relative to the normal range of the lab performing the assay) or molecular genetic testing confirming a diagnosis of LAL Deficiency, and had hepatomegaly on clinical examination and/or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1.5x upper limit of normal [ULN] (but not persistently >3x ULN), were eligible to participate in this study. Subjects could not be Child Pugh Class C and could not have previously received a hematopoietic bone marrow or liver transplant or enzyme replacement therapy, nor could they have participated in a study employing another investigational drug within 30 days prior to Screening. Subjects were excluded from this study if they had clinically significant laboratory abnormalities (other than liver enzymes or lipids), a clinically significant concurrent disease, serious inter-current illness, or concomitant medications that might interfere with study participation or data interpretation, an Alcohol Use Disorders Identification Test (AUDIT) score ≥8, or a hypersensitivity to eggs. Female subjects could not be pregnant or breast-feeding. Excepting women who were not of childbearing potential, all subjects had to continue using an approved contraceptive method until at least 30 days after the last dose of investigational medicinal product (IMP).

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Test Product, Dose and Mode of Administration, Batch Numbers:
Subjects received 4 IV infusions of SBC-102, administered qw at a dose of 0.35 $mg \cdot kg^{-1}$ (Cohort 1), 1 $mg \cdot kg^{-1}$ (Cohort 2), or 3 $mg \cdot kg^{-1}$ (Cohort 3). SBC-102 was provided by Synageva BioPharma Corp. in single-dose 10-mL glass vials, each containing a 10.5 mL (including 5% overfill) of a buffered 2 $mg \cdot mL^{-1}$ solution of SBC-102 as a clear liquid. The lots of SBC-102 used in this study were #102-09-006, #102-09-007, and #102-09-008.

Reference Therapy, Dose and Mode of Administration, Batch Numbers:
No reference therapy was administered in this study.

Duration of Treatment:
Each subject received treatment for 4 weeks in this study.

Criteria for Evaluation:

Efficacy:
Not applicable.

Safety:
Safety was evaluated based on medical review of reported AEs, changes and/or shifts in clinical laboratory tests (including hematology, serum chemistry, urinalysis, and anti-SBC-102 antibody), vital signs, 12-lead electrocardiograms (ECGs), and physical examinations, and use of concomitant medications/therapies.

Pharmacokinetics:
Single- and multiple-dose PK parameters for SBC-102 were derived from serum concentration versus time data, and included maximum observed serum concentration (C_{max}), time of maximum observed serum concentration (T_{max}), area under the serum concentration-time curve (AUC) from the start of the infusion to the time of the last quantifiable concentration ($AUC_{(0\text{-last})}$), AUC from the start of the infusion extrapolated to infinite time ($AUC_{(0\text{-}\infty)}$), apparent terminal rate constant (λ_z), apparent terminal half-life ($t_{1/2}$), total body clearance (CL), and volume of distribution (V_z).

Pharmacodynamics:
Changes in liver enzymes (ALT, AST, gamma glutamyl transferase [GGT]), serum lipid parameters (total cholesterol, triglycerides, LDL, and HDL), serum ferritin, and high-sensitivity C-reactive protein (hsCRP) were evaluated as markers of SBC-102 biological activity.

Patient Health Outcomes:
Pre-treatment SF-36v2, CLDQ, and FACIT-Fatigue scores for the subjects in this study were compared with scores previously reported in relevant reference populations.

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Statistical Methods:

Power and Sample Size:
Sample size was not determined on the basis of statistical considerations. Given the low prevalence of LAL Deficiency, a sample size of 9 subjects was thought to provide a reasonable estimation of the overall safety and tolerability of SBC-102 across the range of doses used in the study.

Analysis Sets:
The Safety Analysis Set included all subjects who received any full or partial dose of SBC-102 in this study. Of these subjects, those with at least one measurable SBC-102 serum level composed the PK Analysis Set and those with at least one post-baseline assessment of liver enzymes, serum lipids, and serum ferritin composed the PD Analysis Set. All 9 subjects were included in the Safety Analysis Set, PK Analysis Set, and PD Analysis Set.

A Per-Protocol Analysis Set was to be used for a secondary assessment of PD endpoints, in the event that there were subjects with major protocol deviations affecting data interpretability. As this was not the case, separate analyses were not performed for the PP Analysis Set.

Efficacy:
Not applicable.

Safety:
All safety data were listed. Treatment-emergent AEs (TEAEs), serious AEs (SAEs), infusion-related reactions (IRRs), and TEAEs leading to discontinuation of IMP, displayed by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) within system organ class (SOC), were tabulated overall and by dose cohort. As applicable, TEAEs, SAEs, and IRRs were also tabulated by categories of severity or causality. Shift tables (normal/abnormal low/abnormal high) and descriptive summaries of observed values and changes and/or percent changes from baseline to each study visit and from Visit 7 (Day 28) to Visit 8 (Day 52) (for parameters measured at each time point), presented overall and by dose cohort, were generated for all laboratory parameters except erythrocyte sedimentation rate (ESR), coagulation parameters, and urinalysis parameters. The number and percentage of subjects receiving each medication/therapy, classified by World Health Organization (WHO) Drug Dictionary (DD) Anatomical Therapeutic Classification (ATC) classes and preferred terms, were summarized overall and by dose cohort.

Pharmacokinetics:
SBC-102 concentration data and PK parameters were listed and descriptively summarized by dose and profile day (Day 0 or Day 21). Individual and mean concentration-time profiles were also plotted by dose and profile day, on both linear and semi-logarithmic scales.

Pharmacodynamics:
In addition to the shift tables and descriptive summaries described above for clinical laboratory tests, the proportion of subjects with abnormal results for liver enzymes (ALT, AST, and GGT), serum lipids (total cholesterol, LDL, HDL, and triglycerides), serum ferritin, or hsCRP was tabulated overall and by dose.

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Spaghetti plots were produced for hepatic transaminases, serum lipids, serum ferritin, and hsCRP.

Patient Health Outcomes:
Pre-treatment scores for SF-36v2, CLDQ, and FACIT-Fatigue were listed and descriptively summarized overall and by dose cohort.

Summary of Results:

Disposition, Demographic, and Baseline Characteristics:
All 9 (100%) subjects treated in the study (3 subjects per cohort) completed the study as planned.

All subjects were Caucasian and two-thirds were male. Mean age at the time of enrollment was 32 ± 11 years. Mean body mass index (BMI) was 26.8 ± 6.3 kg m^{-2}, and all subjects except one were non-obese (i.e., BMI <30.0 kg m^{-2}). Selected demographic and baseline disease characteristics are summarized in Table 1.

Table 1: Baseline Disease Characteristics

Parameter Category/Statistic	**Cohort 1: 0.35 mg·kg^{-1} N=3**	**Cohort 2: 1 mg·kg^{-1} N=3**	**Cohort 3: 3 mg·kg^{-1} N=3**	**Total N=9**
Age at Diagnosis, years				
Mean (SD)	16.3 (19.4)	31.9 (17.2)	7.20 (4.5)	18.5 (17.0)
Range	4.1, 38.6	12.1, 42.4	4.5, 12.4	4.1, 42.4
PBMC LAL Activity[a]				
Median	42	46	24	42
Range	33, 42	10.4, 57	19, 42	10.4, 57
Liver Dysfunction (Study Entry Criteria)				
Hepatomegaly Present on Physical Examination, n (%)	3 (100)	2 (66.7)	3 (100)	8 (88.9)
1.5x ULN < AST or ALT <3x ULN[b]	0	1 (33.3)	1 (33.3)	2 (22.2)
Any Abnormal Serum Lipids[c] n (%)	3 (100)	2 (66.7)	3 (100)	8 (88.9)
Receiving Lipid-Lowering Medications, n (%)	2 (66.7)	3 (100)	2 (66.7)	7 (77.8)
BMI, kg m^{-2}				
Mean (SD)	23.6 (3.76)	30.3 (10.48)	26.4 (1.11)	26.8 (6.31)
Range	20.5, 27.8	23.5, 42.4	25.2, 27.4	20.5, 42.4

[a] Normal range = 350 to 2000 µmol/g/h.
[b] ULN is 73 U/l (males) and 50 U/l (females) for GGT, 50 U/l for AST and 67 U/l for ALT.
[c] ULN is 232 mg/dL for total cholesterol, 199 mg/dL for triglycerides, and 162 mg/dL for LDL, and the lower limit of normal (LLN) is 35 mg/dL for HDL.

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Efficacy:
Not applicable.

Safety:
There were no deaths or treatment-emergent SAEs in this study. Most (86.4%) TEAEs were unrelated to IMP, and all but one TEAE was Grade 1 (86.4% events) or Grade 2 (11.4% events) in severity. No subject experienced an IRR or developed anti-SBC-102 antibodies. Treatment was not modified or discontinued in any subject due to a TEAE. Table 2 summarizes TEAEs reported by more than one subject in the study.

Table 2: Summary of TEAEs, Regardless of Causality, Reported by More Than One Subject

	Cohort 1: 0.35 mg·kg^{-1} N=3		**Cohort 2: 1 mg·kg^{-1} N=3**		**Cohort 3: 3 mg·kg^{-1} N=3**	
System Organ Class Preferred Term	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
Any TEAE	4	1 (33.3)	23	3 (100)	17	3 (100)
Gastrointestinal						
Diarrhea	1	1 (33.3)	3	2 (66.7)	0	0
Nausea	3	1 (33.3)	0	0	1	1 (33.3)
Nervous system						
Headache	0	0	3	1 (33.3)	4	2 (66.7)

There were no clinically important changes in vital signs or ECG parameters, and no clinically relevant trends in physical examination findings. With the exception of increases in total cholesterol, triglycerides, and LDL (see below), there were no trends in any laboratory parameters that presented a potential safety concern for SBC-102 treatment.

Increases in total cholesterol, LDL and triglycerides were observed between baseline and Day 28 at all doses of SBC-102 evaluated in this study, and are consistent with the mechanism of action of SBC-102. These lipid elevations occurred irrespective of whether a subject was receiving concomitant statin therapy, and were most pronounced in Cohort 3, with increases of lesser and comparable magnitude in the 2 lower dose cohorts. The maximum increases from baseline in serum lipids were observed for 2 subjects in Cohort 3, one having the greatest increase in total cholesterol (from 220 mg/dL to 772 mg/dL [5.70 to 19.99 mmol/L]) and LDL (from 143 mg/dL to 674 mg/dL [3.70 to 17.46 mmol/L]), and the other the greatest increase in triglycerides (from 80 mg/dL to 351 mg/dL [0.90 to 3.97 mmol/L]). In one of the 2 subjects, the observed increases in total cholesterol and triglycerides were considered by

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the Investigator to be a clinically significant worsening from baseline, and were reported as TEAEs of Grade 4 hypercholesterolemia and Grade 2 hypertriglyceridemia that were possibly related to IMP. While the elevation in total cholesterol was assessed as a Grade 4 event based on the specific Common Terminology Criteria for Adverse Events (CTCAE) cut-off for Grade 4 laboratory toxicity (total cholesterol >500 mg/dL), the Investigator, the Sponsor, and the independent Safety Committee did not consider this event to be life threatening or to require urgent intervention. Lipid levels in this subject decreased within a week and returned to normal range (and below baseline levels) by Day 52, without additional medical treatment. A similar reversibility of total cholesterol, triglycerides, and LDL after discontinuation of SBC-102 therapy was observed for the other 4 subjects in Cohorts 2 and 3 who had increases in serum lipids during treatment, and by Day 52, 5 of the 6 subjects in these 2 cohorts had total cholesterol, triglyceride, and LDL levels that were below those at baseline. Reversibility of serum lipids was not assessed for Cohort 1 due to an oversight in the protocol schedule of assessments.

Pharmacokinetics:

Based on visual examination of median AUC and C_{max} values, the increase in SBC-102 exposure was reasonably dose-proportional from 0.35 $mg \cdot kg^{-1}$ to 1 $mg \cdot kg^{-1}$ and more than dose-proportional from 1 $mg \cdot kg^{-1}$ to 3 $mg \cdot kg^{-1}$ (i.e., a 10-fold increase in exposure for a 3-fold increase in dose) after both the first infusion and the fourth infusion. Small mean increases in $AUC_{(0\text{-last})}$ from Day 0 to Day 21, ranging from 13.4% to 16.9%, were dose-independent and pharmacokinetically unimportant, and there was no evidence of accumulation in the Day 21 pre-infusion sample.

SBC-102 was rapidly eliminated at all doses, although median $t_{1/2}$ at Day 21 was slightly longer for the 0.35 $mg \cdot kg^{-1}$ dose (0.78 hours) compared to the 1 $mg \cdot kg^{-1}$ dose (0.11 hours) and 3 $mg \cdot kg^{-1}$ dose (0.13 hours). Median serum clearance at Day 21 was similar for the 0.35 $mg \cdot kg^{-1}$ dose (665.07 mL/h/kg) and 1 $mg \cdot kg^{-1}$ dose (541.22 mL/h/kg), and 4- to 5-fold lower for the 3 $mg \cdot kg^{-1}$ dose (135.50 mL/h/kg). The $t_{1/2}$ and serum clearance were both reasonably consistent between Day 0 to Day 21 within each dose cohort.

The apparent volume of distribution (V_z) decreased with increasing dose after both the first and fourth infusions. The estimated median V_z was higher at 0.35 $mg \cdot kg^{-1}$ (788.18 mL/kg at Day 21) compared with the 1 and 3 $mg \cdot kg^{-1}$ dose cohorts (70.01 mL/kg, and 22.05 mL/kg, respectively, at Day 21). A marked decrease in Vz was also apparent between Day 0 and Day 21 for the 0.35 $mg \cdot kg^{-1}$ and 1 $mg \cdot kg^{-1}$ dose cohorts, with respective decreases of 47% and 54%.

Pharmacodynamics:

Liver Enzymes

ALT and/or AST were elevated (>ULN) in 6 subjects at baseline, including 4 subjects with elevations in both transaminases. Following initiation of treatment with SBC-102, ALT and AST decreased rapidly (within 2 weeks) in 7 of the 9 subjects, regardless of whether their baseline levels were within or above the normal range, and transaminase levels continued to decline through Day 28. In the two other subjects, ALT and AST either fluctuated around baseline levels (413-02001, Cohort 1) or increased transiently and then returned to near baseline levels (416-05001, Cohort 2). Of note, subject 416-05001

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had a medical history of cirrhosis, a low baseline ALT, and pre-treatment ALT and AST values that were notable for the variability between Screening (50 U/l and 124 U/l, respectively) and baseline (22 U/l and 67 U/l, respectively).

By Day 28, transaminases had normalized in 4 (66.7%) of 6 subjects with abnormal baseline AST levels and all 6 (100%) subjects with abnormal baseline ALT levels. For all 9 subjects, the mean decreases from baseline to Day 28 were 18.2 ± 15.0 U/l (31.8% decrease) for AST and 38.7 ± 25.6 U/l (43.1% decrease) for ALT.

During the post-treatment follow-up period, a reversal (increase) in AST and ALT levels was observed in all 8 subjects who demonstrated an improvement (decrease) in transaminases during treatment with SBC-102. By Day 52, AST and ALT were at or approaching baseline levels in all subjects.

There was no evidence of a dose-related effect in the time to onset or magnitude of the reduction in AST and ALT, or in the reversal of that effect after discontinuation of treatment.

GGT was elevated in 2 subjects at baseline and decreased markedly in one of these subjects during treatment (from 203 to 96 U/l) but did not otherwise show any clinically meaningful changes either during or after treatment with SBC-102.

Serum Lipids: Total Cholesterol, Triglycerides, and LDL

At baseline, 5 of 9 subjects had elevated levels (>ULN) in total cholesterol, triglycerides, and/or LDL. By the next assessment at Day 28, total cholesterol and triglycerides had increased in 8 subjects, with 7 of these subjects also having increases in LDL at that time point. At Day 28, shifts from normal to abnormal lipid levels were reported for 3 of 7 subjects with normal baseline total cholesterol, 1 of 6 subjects with normal baseline triglycerides, and 3 of 7 subjects with normal baseline LDL. One other subject (418-07001, Cohort 2) had serum lipids that were normal and did not increase from baseline through Day 28.

Mean increases from baseline to Day 28 in total cholesterol, triglycerides, and LDL were more marked in Cohort 3 (127.7%, 136.8%, and 171.6%) than in Cohort 2 (41.2%, 28.6%, 69.3%) or Cohort 1 (41.0%, 40.0%, 21.2%). The more marked increase in serum lipids in Cohort 3 was due to pronounced lipid elevations in 2 of the 3 subjects in this dose cohort (see Safety results for further details).

During the post-treatment follow-up period, a reversal (decrease) in total cholesterol, triglycerides, and LDL levels was observed for the 5 subjects in Cohorts 2 and 3 who had elevations in serum lipids during treatment. By Day 52, 5 of the 6 subjects in these two dose cohorts had normal serum lipid levels that were below their baseline values (including the one subject who had no increase in serum lipids), and one subject had serum lipids that were normal or borderline abnormal and approaching baseline values. Reversibility was not evaluated for subjects in Cohort 1 due to an oversight in protocol schedule of assessments.

Serum Lipids: HDL

HDL levels were abnormal (<LLN) in 4 subjects at baseline. There were no meaningful changes in HDL

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levels in any dose cohort between baseline and Day 28. During the post-treatment follow-up period, HDL levels increased from baseline by >25% for all subjects in Cohort 3 (26.5%, 30.2%, and 50.0%), a trend that was not apparent for any subject in Cohort 2 (-2.2%, 0%, and 8.7%). Post-treatment assessments of HDL were not available for subjects in Cohort 1 due to an oversight in protocol schedule of assessments.

Serum Ferritin and hsCRP

Serum ferritin levels were normal in 8 of the 9 subjects at baseline, and decreased in all 9 subjects by the next assessment at Day 28. Mean decreases in serum ferritin were comparable for Cohort 2 (42.7 ± 8.6%) and Cohort 3 (49.4 ± 9.0%), and appeared slightly lower in Cohort 1 (29.0 ± 14.6%). No consistent trends were observed in serum ferritin during the post-treatment follow-up period, or in hsCRP during either the treatment period or post-treatment follow-up period.

Patient Health Outcomes:

The mean norm-based SF-36v2 scores for the Physical Component Summary (PCS) and Mental Component Summary (MCS) for the subjects in this study, prior to treatment with SBC-102, were 52.5 ± 10.0 and 43.0 ± 15.0. By comparison, the general US population norm was represented by 50.0 ± 10.0, and the respective mean norm-based PCS and MCS scores were 45.2 ± 10.9 and 47.6 ± 11.0 in patients with non-alcoholic fatty liver disease (NAFLD), and 44.5 ± 11.0 and 47.5 ± 10.9 in patients with non-alcoholic steatohepatitis (NASH) (David et al., 2009).

The mean per-item CLDQ score for the subjects in this study was 5.26. By comparison, the mean per-item CLDQ score in a healthy population was approximately 6, and the mean per-item CLDQ scores in patients with Hepatitis C, Hepatitis B, and NAFLD ranged from approximately 5.1 to 5.5 (Mahmood et al., 2008).

The mean total FACIT-Fatigue score for the 9 subjects in this study was 37.4 ± 12.3. By comparison, the mean total FACIT-Fatigue score in a general US population was 43.6 ± 9.4, and mean FACIT-Fatigue scores in non-anemic cancer patients and anemic cancer patients were 40.0 ± 9.8 and 23.9 ± 12.6, respectively (Cella et al., 2002).

As expected, there was considerable individual variability in norm-based scores for the SF-36v2 PCS (range: 31.3 to 61.7) and MCS (range: 13.7 to 59.0), the CLDQ per-item score (range: 3.7 to 6.7), and the FACIT-Fatigue total score (range: 12 to 52).

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Conclusions:

All 3 doses of SBC-102 (0.35, 1 and 3 $mg \cdot kg^{-1}$ qw) were well tolerated by the adult patients with late onset LAL Deficiency treated in this study. No safety concerns were identified that would preclude further development of SBC-102.

SBC-102 AUC and C_{max} increased proportional to dose from 0.35 to 1 $mg \cdot kg^{-1}$ and more than proportional to dose from 1 to 3 $mg \cdot kg^{-1}$.

All 3 doses of SBC-102 were biologically active, as evidenced by decreases in ALT and AST and increases in serum lipids (total cholesterol, triglycerides, and LDL), which were observed within 2 and 4 weeks, respectively, and were reversible following discontinuation of SBC-102 therapy.

Effects on serum lipids appeared more pronounced in the 3 $mg \cdot kg^{-1}$ dose cohort, whereas effects on ALT and AST appeared to be independent of dose.

The general health, quality of life, and level of fatigue in patients with late onset LAL Deficiency, prior to treatment in this study, appeared to be impaired. Patient health outcomes scores in these patients were similar to those described in other patient populations with recognized impairment of health.

Date of Report:
04 June 2012

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1 List of Abbreviations and Terms

AE	adverse event
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	area under the concentration-time curve
$AUC_{(0\text{-last})}$	area under the concentration-time curve from the start of the infusion to the time of the last quantifiable concentration
$AUC_{(0\text{-}\infty)}$	area under the concentration-time curve from the start of the infusion extrapolated to infinite time
$AUMC_{(0\text{-}\infty)}$	area under the first moment curve extrapolated to infinite time
AUDIT	Alcohol Use Disorder Identification Test
BLQ	below the limit of quantification
BMI	body mass index
BMT	bone marrow transplant
CDC	Centers for Disease Control and Prevention
CL	total body clearance
CLDQ	Chronic Liver Disease Questionnaire
C_{max}	maximum observed serum concentration
CS	clinically significant
DD	Drug Dictionary
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
ERT	enzyme replacement therapy
ESR	erythrocyte sedimentation rate
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
GlcNAc	N-acetylglucosamine
GGT	gamma glutamyl transferase
GI	gastrointestinal
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
hsCRP	High-sensitivity C-reactive protein
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
IV	intravenous
λ_z	apparent terminal rate constant

LAL	lysosomal acid lipase
LDL	low density lipoprotein
LLN	lower limit of normal
LSD	lysosomal storage disorder
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MMR	macrophage mannose receptor
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NCS	not clinically significant
PBMC	peripheral blood mononuclear cells
PCS	Physical Component Summary
PD	pharmacodynamics
PK	pharmacokinetics
PP	per protocol
PT	prothrombin time
PT	preferred term
PTT	partial thromboplastin time
QC	quality control
qw	once-weekly
rhLAL	recombinant human lysosomal acid lipase
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF-36v2	36-item Short-Form (version 2)
SOC	system organ class
$t_{1/2}$	apparent terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed serum concentration
ULN	upper limit of normal
UK	United Kingdom
URTI	upper respiratory tract infection
US	United States
V_{ss}	volume of distribution at steady state
V_z	volume of distribution
WHO	World Health Organization

2 Ethics

2.1 Independent Ethics Committee or Institutional Review Board

The protocol, amendments, and subject informed consent were reviewed and approved by an institutional review board (IRB) or independent ethics committee (IEC) prior to initiation of the study at each site. The letter or certificate of approval from the IRB or IEC was received by the Sponsor prior to delivery of investigational medicinal product (IMP) to the site. The IRBs/IECs consulted during this study are listed in Appendix 16.1.3.

2.2 Ethical Conduct of the Study

This study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation, and the ethical principles in the Declaration of Helsinki. The applicable laws and regulatory requirements of all countries participating in this study were adhered to.

2.3 Subject Information and Consent

The Investigators were responsible for ensuring that subjects were provided full and adequate oral and written explanations of the objectives, procedures, anticipated benefits, and potential risks of the study, and that written informed consent was obtained from each subject prior to performing any study-related procedures. Subjects were free to withdraw from the study at any time for any reason or could have been withdrawn, if necessary, to protect their health or the integrity of the study. A sample informed consent form is provided in Appendix 16.1.3.

3 Investigators and Study Administrative Structure

A total of 7 Principal Investigators at 7 centers in the United States (US), United Kingdom (UK), France, and Czech Republic participated in this study. The coordinating investigator for the study was Manisha Balwani, MD, MS. A list of all Principal Investigators and their affiliations and curricula vitae is provided in Appendix 16.1.4. The signature of the Coordinating Investigator is provided in Appendix 16.1.5.

An independent Safety Committee was responsible for additional oversight of subject safety in this study. The Safety Committee made recommendations regarding initiation of dosing in the second and third dose cohorts (1 $mg \cdot kg^{-1}$ and 3 $mg \cdot kg^{-1}$) based on review of cumulative safety data for all subjects dosed in previous cohorts. As per its Charter, the Safety Committee could also recommend suspension of dosing in an individual subject, a dose cohort, or all subjects due to poor tolerability or potential safety risks noted in its periodic or ad-hoc reviews of safety data. The Safety Committee Charter outlining the composition, responsibilities, and operations of this committee is provided in Appendix 16.1.9.

The following regulatory obligations were transferred by the Sponsor to Premier Research Group, Ltd., Philadelphia, PA, US:

Description	21 CFR Reference
Ensuring that all participating Investigators in this trial are promptly informed of significant new adverse effects or risks with respect to the investigational medicinal product	§312.55(b)
Reviewing and evaluating the evidence relating to safety and efficacy of the investigational medicinal product as it is obtained from the investigator	§312.56(c)
Retaining records and reports	§312.57(c)

In addition to pharmacovigilance and medical monitoring functions, Premier Research Group also supported data management, clinical programming, and statistical analysis activities for this study.

All study-related laboratory evaluations were conducted by central laboratories, with the exception of erythrocyte sedimentation rate (ESR), coagulation and urinalysis parameters, and urine pregnancy tests. The central laboratories for this study are listed below.

- CBC/hematology, serum chemistry (including liver and lipid panels), serum β-hCG, serum ferritin, high-sensitivity C-reactive protein (hsCRP), and autoimmune and viral hepatitis screens: MEDTOX, St. Paul, MN, US (US sites) or INTERLAB, Munich, Germany (UK, France, and Czech Republic sites);
- Lysosomal acid lipase (LAL) enzyme activity: Willink Biochemical Genetics Unit, Manchester, UK;

- SBC-102 serum concentrations and anti-SBC-102 antibody: Synageva BioPharma Corp., Athens, GA, US

Pharmacokinetic analyses were performed by GBPK Consulting Ltd., Nottingham, UK.

Monitoring of study data was performed by Synageva BioPharma Corp. and clinical research associates contracted to Synageva BioPharma Corp. in each study region.

Additional details regarding the study administrative structure are provided in Appendix 16.1.4.

4 Introduction

This clinical study report presents the results of the first clinical study of SBC-102, a recombinant human lysosomal acid lipase (rhLAL; sebelipase alfa), in patients with late onset LAL Deficiency.

LAL Deficiency is a rare autosomal recessive lipid storage disorder in which a marked decrease in the lysosomal enzyme, LAL, leads to lipid accumulation (predominately cholesteryl esters and triglycerides) in a number of tissues. Although a single disease, LAL Deficiency presents as a clinical continuum with 2 major phenotypes: early and late onset. The early onset phenotype (also referred to as Wolman Disease) is characterized by malabsorption, growth failure, and hepatic failure and is usually fatal within the first year of life (Anderson et al., 1999; Assmann & Seedorf, 2001; Mayatepek et al., 1999; Surve et al., 2005). In the late onset phenotype (also referred to as Cholesteryl Ester Storage Disease), liver and cardiovascular involvement dominate the clinical picture, with marked hepatomegaly, elevation of transaminases, liver fibrosis, type II hyperlipidemia, and accelerated atherosclerosis (Beaudet et al., 1977; Anderson et al., 1999; Elleder et al., 2000).

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

SBC-102 has the appropriate glycan characteristics for targeting the key cells affected in LAL Deficiency. The lipid accumulation observed in patients with LAL Deficiency is most marked in cells of the reticuloendothelial system. These cells express the macrophage mannose/N-acetylglucosamine receptor (also known as macrophage mannose receptor [MMR] or CD206), which mediates the binding, cell uptake, and lysosomal localization of proteins with N-acetylglucosamine (GlcNAc) or mannose terminated N-glycans and provides a pathway for the potential correction of the enzyme deficiency in these key cells (Stahl et al., 1978). SBC-102 contains predominantly GlcNAc and mannose terminated N-linked glycan structures.

Nonclinical studies with SBC-102 support its potential therapeutic utility in patients with LAL Deficiency. In *in vitro* studies, SBC-102 demonstrated uptake and localization to lysosomes of macrophages, in addition to producing a dose-dependent correction of LAL activity in enzyme deficient human fibroblasts. In a rat model of LAL Deficiency, restoration of enzyme activity after intravenous (IV) administration of SBC-102, as evidenced by reduction in abnormal lysosomal lipid content in the liver and other key target tissues, was associated with improvements in weight gain, organ size, serum transaminase levels, and decreased tissue burden of LAL substrates, relative to placebo-treated animals.

This first clinical study with SBC-102 was designed to provide initial data on the safety, tolerability, and pharmacokinetics (PK) of SBC-102 following a 4-week regimen of once-weekly (qw) IV infusions of SBC-102 at doses of 0.35 $mg \cdot kg^{-1}$, 1 $mg \cdot kg^{-1}$, and 3 $mg \cdot kg^{-1}$ in adult patients with liver dysfunction due to late onset LAL Deficiency. The study also investigated the

pharmacodynamics (PD) of SBC-102 in this patient population, and the overall health of these patients relative to reference populations.

5 Study Objectives

5.1 Primary Objective

The primary objective was to evaluate the safety and tolerability of SBC-102 in patients with liver dysfunction due to LAL Deficiency (vital signs, physical examination, clinical laboratory tests, immunogenicity tests, adverse event (AE) assessment, and concomitant therapies).

5.2 Secondary Objectives

The secondary objective was to characterize the pharmacokinetics of SBC-102 delivered by IV infusion after single and multiple doses (pre and post infusion Day 0 and 21).

5.3 Exploratory Objectives

The exploratory objectives were:

- To examine the onset, magnitude of change, and reversibility of changes in transaminases (Screening, pre-infusion Day 0, 7, 14, 21 and Day 28, 35 and 52)
- To evaluate the onset, magnitude of change, and reversibility of changes in total serum cholesterol, triglycerides, low density lipoprotein (LDL), and high density lipoprotein (HDL) (Days 0, 28 and 52)
- To provide information on the overall health of patients with liver dysfunction due to LAL Deficiency relative to reference populations using baseline patient health outcomes assessments:
    - 36-item short form (SF-36™)
    - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
    - Chronic liver disease questionnaire (CLDQ)

6 Investigational Plan

6.1 Overall Study Design and Plan

This open-label study evaluated the safety, tolerability, and PK of 3 dose levels of SBC-102 following administration as qw IV infusions in adult patients with liver dysfunction due to LAL Deficiency. Pharmacodynamic markers and pre-treatment patient health outcomes were also evaluated on an exploratory basis. The study comprised a screening period, a treatment period, and a post-treatment follow-up period (including an End of Study visit).

Screening assessments were conducted 7 to 28 days prior to the start of dosing. Eligible subjects were treated in 3 sequential dose cohorts: 0.35 $mg \cdot kg^{-1}$ (Cohort 1), 1 $mg \cdot kg^{-1}$ (Cohort 2), and 3 $mg \cdot kg^{-1}$ (Cohort 3). In each cohort, subjects were administered qw infusions of SBC-102 on Day 0, Day 7, Day 14, and Day 21. Subjects were monitored for safety for at least 4 hours after the completion of each infusion. In addition, all subjects had a 24-hour inpatient stay after the first infusion with a safety assessment at 24 hours post-infusion, and a telephone contact at 24 hours after the second, third, and fourth infusions. Following the fourth and final infusion, subjects also had additional safety follow-up visit(s) at 7±1 days and 14±1 days (optional) post-infusion. An End of Study visit was conducted at 30±1 days after the fourth infusion or, for subjects who prematurely withdrew from the study, no sooner than 7 days after their last infusion.

Within each cohort, one subject was initially dosed and, if SBC-102 was deemed safe and well tolerated in this subject based on at least 24 hours of monitoring, dosing was allowed to be initiated for the remaining subjects in the cohort. Initiation of dosing in the next cohort occurred only after all subjects in the preceding cohort had been monitored for at least 5 days after the second infusion, without any evidence of significant safety signals, and an independent Safety Committee had reviewed the cumulative safety data and provided their recommendation on the acceptability of beginning dosing in the next cohort.

The Safety Committee also provided additional general oversight of subject safety through its ongoing review of available safety data, and could make recommendations regarding continuation, modification, or suspension of dosing for an individual subject, a dose cohort, or all subjects in the study.

6.2 Discussion of Study Design, Including Choice of Control Group

This first clinical study was designed primarily to evaluate the safety and tolerability of SBC-102 in patients with LAL Deficiency across a range of doses that were anticipated to be of potential clinical benefit and for which there was an adequate safety margin based on nonclinical studies. The rationale for selection of the doses administered in this study is discussed in further detail in Section 6.4.4. There was no control group in this study.

The planned enrollment was 9 subjects, with each dose cohort comprising 3 subjects who received up to 4 infusions of SBC-102. This sample size and dosing strategy was chosen to

provide a reasonable estimation of the safety and tolerability of SBC-102 , while enabling the study to be recruited and completed within a reasonable timeframe given the low prevalence of late onset LAL Deficiency.

Dosing was staggered within and between cohorts, as described in Section 6.1, to mitigate potential safety risks to study subjects. Decisions regarding dose continuation and initiation of dosing in successive dose cohorts were informed by recommendations from an independent Safety Committee, which reviewed safety data on an ongoing basis. As ERTs have a short plasma half-life and biological activity is primarily driven by enzyme concentrations in the target tissue, SBC-102 plasma concentrations were measured only to characterize SBC-102 PK, and were not routinely used for decisions regarding dose continuation or initiation of dosing in successive dose cohorts.

A post-treatment follow-up period was included in this study to assess the reversibility of the effects of SBC-102 on liver enzymes and serum lipids, in accordance with the study objectives.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

Subjects were required to meet all of the following criteria to be eligible for this study:

1. Subject understood the full nature and purpose of the study, including possible risks and side effects, and was willing and able to comply with all study procedures and provide informed consent.
2. Male or female subjects ≥18 and ≤65 years of age.
3. Documented decreased LAL activity relative to the normal range of the lab performing the assay or documented result of molecular genetic testing confirming diagnosis of LAL Deficiency.
4. Evidence of liver involvement based on clinical presentation (hepatomegaly) and/or laboratory test results (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥ 1.5x upper limit of normal [ULN]).
5. If on a statin or ezetimibe, had to be on a stable dose for at least 4 weeks prior to screening.
6. All women had to have a negative serum pregnancy test at screening and could not be breast feeding.

7. Female subjects of childbearing potential had to agree to use a highly effective and approved contraceptive method(s) for the duration of the study and continue to use for 30 days after last dose of investigational medicinal product (IMP). A highly effective method of contraception was defined as:
    a. strict abstinence;
    b. bilateral tubal ligation;
    c. combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives on a stable dose for at least 1 month prior to the Screening visit;
    d. hormonal intra-uterine device inserted at least 1 month prior to the Screening visit;
    e. vasectomized partner for at least 3 months prior to the Screening visit.

    Male subjects and their partners had to be using, and continue to use for 30 days after last dose of IMP, an acceptable method of birth control. Women considered not of childbearing potential had to be surgically sterile (total hysterectomy, bilateral salpingo-oophorectomy) or post-menopausal, defined as a complete cessation of menstruation for at least one year after the age of 45 years.

6.3.2 Exclusion Criteria

Subjects who met any of the following criteria were 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 was of borderline significance could be allowed to undergo repeat testing once within a 30 day period.
3. Subject participated in a study employing an investigational drug within 30 days of the screening.
4. Child-Pugh Class C or AST and/or ALT persistently elevated >3x ULN at screening (2 or more occasions).
5. Previous hematopoietic bone marrow or liver transplant.
6. Subject received prior treatment with enzyme replacement therapy.
7. Subject had a total score of 8 or more on a screening Alcohol Use Disorders Identification Test (AUDIT).
8. Subject had a known hypersensitivity to eggs.

6.3.3 Removal of Subjects from Treatment or Study

Subjects were free to withdraw consent and discontinue participation in the study at any time, and without prejudice to further treatment.

The Investigator and Sponsor could, at their discretion, also discontinue a subject's participation in the study at any time. Justifiable reasons for discontinuation included but were not restricted to the following:

- Intercurrent illness
- Adverse events including severe infusion reactions
- Pregnancy
- Protocol violation or non-compliance
- Termination of the study by the Sponsor

Recommendations could be made by the independent Safety Committee to discontinue treatment in an individual subject, a dose cohort, or the study. The final decision on whether to discontinue treatment was at the discretion of the Sponsor.

For each subject discontinuing treatment in the study, the date and reason(s) for discontinuation were recorded in the electronic case report form (eCRF). Information on any AEs was also recorded. Whenever possible, follow-up and End of Study visit procedures were completed prior to withdrawing the subject from the study.

6.4 Treatments

6.4.1 Treatments Administered

Subjects received 4 IV infusions of SBC-102, administered qw at a dose of 0.35 $mg \cdot kg^{-1}$ (Cohort 1), 1 $mg \cdot kg^{-1}$ (Cohort 2), or 3 $mg \cdot kg^{-1}$ (Cohort 3).

The dose of SBC-102 (mg) was calculated based on a subject's weight at screening. The required volume of SBC-102 was diluted in 0.9% sodium chloride for injection to a total volume of 100 mL (Cohorts 1 and 2) or 250 mL (Cohort 3), and administered over approximately 2 hours at a constant rate. After emptying the infusion bag, a 25-mL sodium chloride (0.9%) flush was administered at the same rate. The end of the infusion was documented as the time of completion of the flush. Detailed instructions on the calculation of dose and preparation and administration of the infusion were provided to the study investigators in an IMP Instruction Manual.

6.4.2 Identity of Investigational Medicinal Product(s)

SBC-102 is a rhLAL produced in transgenic G*allus*.

SBC-102 was provided by Synageva BioPharma Corp. in single-dose 10-mL glass vials, each containing a 10.5 mL (including 5% overfill) of a buffered 2 $mg \cdot mL^{-1}$ solution of SBC-102 as a clear liquid. The lots of SBC-102 used in this study are listed by subject in Appendix 16.1.6.

Sodium chloride (0.9%) for injection was sourced locally by the study center.

6.4.3 Method of Assigning Subjects to Treatment

Sites pre-identified potentially eligible subjects, and the Sponsor approved these subjects to initiate screening. To minimize potential bias in this process, the Sponsor only had access to the subject's pre-screening identifier at the time of approving subjects for screening. A sequential enrollment number was assigned by the site after receiving Sponsor approval to initiate screening.

Eligible subjects were allocated to a dose cohort sequentially. No randomization schemes were employed (Appendix 16.1.7). As soon as subject eligibility was confirmed, the Investigator or designee notified the Sponsor to request a written dose cohort assignment. Eligible subjects were identified throughout the study using a 5-digit subject identification number in which the first 2 digits denoted the site and the last 3 digits denoted the sequential order of subject treatment at that site. In all data listings, a 3-digit hyphenated prefix was added to each subject identification number, and represents the site identifier used by the contract research organization responsible for data management, clinical programming, and statistical analysis activities (see Section 3).

6.4.4 Selection of Doses Used in the Study

The doses for this study were chosen to span the anticipated therapeutic dose range for SBC-102, and all doses were within the safety margin indicated by the nonclinical toxicology results.

A dose of 0.35 $mg \cdot kg^{-1}$ was selected as the starting dose because this was the minimally effective dose in a highly relevant nonclinical model of LAL Deficiency. In this model, a dose of 0.2 $mg \cdot kg^{-1}$ every other week showed no evidence of effect on a number of disease-related abnormalities including reduced weight gain and organomegaly, whereas evidence of biological effect was observed at a dose of 0.35 $mg \cdot kg^{-1}$ qw. The dose was increased in approximately 3-fold increments, to 1 $mg \cdot kg^{-1}$ and then to a top dose of 3 $mg \cdot kg^{-1}$, to allow assessment of safety and tolerability over an approximately 9-fold dose range. In the rat model of LAL Deficiency, the PD effects of SBC-102 were broadly comparable at the 2 highest qw doses evaluated, 3 $mg \cdot kg^{-1}$ and 5 $mg \cdot kg^{-1}$. Thus, it was not anticipated that doses greater than 3 $mg \cdot kg^{-1}$ qw would be required in humans.

All doses of SBC-102 administered in this study were anticipated to be safe and well tolerated in the absence of human data based upon the following:

- The IMP has an amino acid sequence identical to the natural enzyme with no engineering of enhancements in biological activity.
- Knowledge of the biochemistry of LAL Deficiency and the mode of action of SBC-102 did not raise concerns for unexpected toxicity in humans.
- There were no meaningful toxicological findings in 4-week repeated dose toxicology studies in the Sprague-Dawley rat and Cynomolgus monkey at doses up to 50 $mg \cdot kg^{-1}$. Based on the human equivalent doses in rats (8.1 $mg \cdot kg^{-1}$) and monkeys (16.1 $mg \cdot kg^{-1}$), this represented a 23.1- to 46.0-fold safety margin relative to the starting dose in the current study (0.35 $mg \cdot kg^{-1}$) and a 2.7- to 5.4-fold safety margin relative to the proposed top dose (3 $mg \cdot kg^{-1}$). Additionally, the qw administration of SBC-102 for 6 months was well-tolerated in the Cynomolgus monkey at the high dose level of 30 $mg \cdot kg^{-1}$ (human equivalent dose = 9.7 $mg \cdot kg^{-1}$).
- In general for LSDs, the enzymatic activities and mechanisms for lysosomal targeting are conserved across species. Toxicological studies of this class of therapy consistently demonstrate low systemic toxicity (Andrews and O'Callaghan, 2008).

6.4.5 Selection and Timing of Dose for Each Subject

Subjects were assigned to a dose cohort as described in Section 6.4.3. In each subject, infusions were administered 7 $\pm$ 1 days relative to the preceding infusion. Dosing was staggered across subjects, both within each cohort and between cohorts, as described in Section 6.1.

6.4.6 Blinding

This was an open-label study.

6.4.7 Prior and Concomitant Therapy

Medications and therapies were recorded by site personnel at each study visit from screening through study completion.

Prior medications/therapies were those received by the subject within 30 days prior to the date of informed consent until the start of first IMP infusion in this study. Prohibited prior medications/therapies included enzyme replacement therapy and hematopoietic bone marrow or liver transplant procedures, as well as other IMPs used within 30 days prior to the date of informed consent for this study. Statins and ezetimibe were permitted only if a subject was on a stable dose for at least 4 weeks prior to screening.

Concomitant medications/therapies were those received by the subject on or after the start of the first IMP infusion in this study, including any medications/therapies initiated prior to the first IMP infusion and continued during the study. Concomitant medications included prescription and over-the-counter medications, herbal and dietary supplements, prophylactic and therapeutic vaccines, and vitamins. Concomitant therapies included diagnostic, palliative, or interventional

procedures, e.g., ambulatory aids, prescribed diets or exercise regimes, oxygen, transfusions, dialysis, or physical therapy.

All prior and concomitant medications were coded using the World Health Organization (WHO) Drug Dictionary (WHO-DD).

6.4.8 Treatment Compliance

All infusions of SBC-102 were administered under controlled conditions by qualified site personnel in accordance with the study protocol, IMP Instruction Manual, and applicable institutional standards and local regulations. Reasons for any missed or incomplete infusions were clearly documented in the eCRF. In addition, the Investigator or designee maintained accountability records for all IMP received, dispensed, returned, and/or destroyed. Therefore, no additional measures of treatment compliance were required.

6.5 Study Variables

Table 1 presents the schedule of assessments for each study visit from Screening through study completion.

Table 1: Schedule of Assessments for Study LAL-CL01

Assessments	Screening	Active Phase								Post Active Phase		
	Visit 1	Visit 2	Visit 3	Visit 4	TC	Visit 5	TC	Visit 6	TC	Visit 7	Visit 7.1[1]	Visit 8
	(Day -28 to -7)	(Day 0)	(Day 1)	(Day 7±1)	Day 8	(Day 14±1)	Day 15	(Day 21±1)	Day 22	(Day 28±1)	(Day 35±1)	(Day 52±1)
Informed Consent	X											
Inclusion/Exclusion Criteria	X	X										
Demographic Information	X											
Patient Health Outcomes	X											
Medical History (including AUDIT)	X											
12-lead ECG	X											X
Physical Examination	X[2]	X						X		X[2]		X
Vital Signs[3]	X	X[3]	X	X[3]		X[3]		X[3]		X		X
Urinalysis	X	X[p]	X[p]	X		X		X		X		X
Pregnancy Test[4]	X	X[p]						X[p]				X
CBC/Hematology and Chemistry Panel	X	X[p]	X[p]	X[p]		X[p]		X[p]		X		X
Liver Panel	X	X[p]	X[p]	X[p]		X[p]		X[p]		X	X	X
Lipid Panel	X	X[p]								X	X[6]	X[6]
Acute Phase Reactants	X	X[p]								X		X
Coagulation Tests	X											X
Viral & Autoimmune Hepatitis Screens	X											
DNA sample	X											
Blood PBMC LAL activity	X							X[p]				X
Anti-SBC-102 Antibody	X	X[p]								X		X
Exploratory Biomarker Sample	X	X[p]								X	X	X
PK Sample[5]		X						X				
SBC-102 Dosing		X		X		X		X				
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapies	X	X	X	X	X	X	X	X	X	X	X	X

TC = Telephone Call; P = Pre-dose
[1] Visit 7.1 was optional.
[2] Including height and weight.
[3] Pre-dose, every 15 minutes during infusion, every 15 minutes for the 2 hours after the infusion and every 30 minutes for hours 2 to 4 after the infusion
[4] Serum at Visit 1 and Visit 8; urine at Visit 2 and Visit 6.
[5] Pre-dose, 10, 15, 20, 40, 60, 90 minutes during the infusion, at the end of the infusion (approximately 120 minutes), and at 5, 10, 20, 30, 40, 60 and 120 minutes after the infusion.
[6] Lipids were assayed at these time points only for subjects in Cohorts 2 and 3, using excess serum from samples collected for the liver panel, as described in Section 6.8.1.3.

6.5.1 Efficacy Assessments

Not applicable.

6.5.2 Safety Assessments

6.5.2.1 Adverse Events

An AE was defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject, whether or not causally related to administration of IMP. Adverse events were obtained through spontaneous reporting or elicited by specific questioning or examination of the subject, and were recorded from the time of informed consent until completion of the last scheduled visit at approximately 30 days after the last infusion of IMP. In addition, any serious adverse event (SAE) occurring after completion of the last scheduled visit and considered to be at least possibly related to IMP was also recorded.

Treatment-emergent adverse events (TEAEs) were defined as AEs that had an onset or increased in severity or relatedness to IMP on or after the time of the first infusion of SBC-102. For data analysis and reporting purposes, a recurring TEAE was counted only once within the preferred term (PT) and system organ class (SOC) (by greatest severity and relationship to IMP) when tabulating subjects, but each occurrence of the recurring TEAE was counted when tabulating events.

For this first clinical study, all AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA), version 13.1.

6.5.2.1.1 Infusion-Related Reaction

Infusion-related reactions (IRRs) were considered medical events of interest in this study based on clinical experience with other ERTs, and were defined as any immunologically-mediated AE that was at least possibly related to the infusion of IMP.

The Investigator made the initial determination as to whether an AE was an IRR. To assist the investigator, guidance was provided in the study protocol regarding the signs and symptoms of a possible IRR, including both acute and delayed reactions.

In addition, any AE that occurred between the start of the infusion and 4 hours after completion of the infusion and was assessed by the Investigator as at least possibly related to IMP was also considered an IRR, irrespective of whether the Investigator reported the event as an IRR in the eCRF.

6.5.2.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations included CBC/hematology, serum chemistry, liver function tests, lipid parameters, coagulation parameters, acute phase reactants, urinalysis, pregnancy tests, anti-SBC-102 antibody, and autoimmune and viral hepatitis screens. A list of all clinical

laboratory tests performed in this study is provided in Section 5.1.9 of the study protocol (Appendix 16.1.1).

Subjects were required to fast overnight prior to collection of samples at screening, Day 0 (baseline), and Day 28. ESR, coagulation and urinalysis parameters, and urine pregnancy tests were assayed by local laboratories. All other clinical laboratory tests were performed by a central laboratory as indicated in Section 3. Reference ranges were provided by the clinical laboratory performing the testing. All laboratory abnormalities were reviewed by the Investigator and assessed as clinically significant (CS) or not clinically significant (NCS). All laboratory data were standardized to SI units; serum lipids, serum ferritin, and hsCRP were also reported in conventional units.

Results for liver enzymes (ALT, AST, gamma glutamyl transferase [GGT]), lipid parameters (total cholesterol, triglycerides, HDL, LDL), serum ferritin and hsCRP, in addition to being evaluated for safety, were also analyzed as PD biomarkers in this patient population.

6.5.2.3 Vital Signs

Pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature were measured during each scheduled vital sign assessment. Pulse rate and blood pressure were measured after the subject has been in a semi-supine position for at least 5 minutes. On dosing days, vital signs were recorded pre-infusion, every 15 minutes (±5) during infusion, every 15 minutes (±5) from 0 to 2 hours after the infusion, and every 30 minutes (±10) from 2 to 4 hours after the infusion.

6.5.2.4 Electrocardiograms

12-lead electrocardiograms (ECGs) were obtained at Screening and Day 52 after the subject had been supine for at least 5 minutes. The Investigator reviewed each ECG and assessed any identified abnormalities as clinically significant (CS) or not clinically significant (NCS).

6.5.2.5 Physical Examinations

Physical examinations included (but were not limited to) evaluation of cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight were measured as part of the physical examinations at Screening and Day 28. The Screening physical examination also included a clinical assessment of liver size, regularity, and sensitivity, characterization of lymphadenopathy (if present), measurement of bilateral posterior tibialis and dorsalis pedis pulses, and calculation of ankle brachial indices, as described in Section 5.1.5 of the study protocol (Appendix 16.1.1).

In addition to the protocol-scheduled physical examinations, the Investigator or designee assessed a subject's clinical status prior to each study infusion to confirm the acceptability of dosing.

6.5.3 Pharmacokinetic Assessments

Samples for determination of SBC-102 serum concentrations were collected on Day 0 (first infusion) and Day 21 (fourth infusion) according to the sampling schedule provided in Section 5.1.11 of the study protocol (Appendix 16.1.1).

SBC-102 concentrations in human serum were analyzed by Synageva BioPharma Corp. (Athens, GA, US) using a validated enzymatic assay (SOP, LAB-2-021-002; Validation Report, VAL-SBC-102-2012-001) during the period of known analyte stability.

Single- and multiple-dose PK parameters for SBC-102 were derived from serum concentration versus time data, and included the following:

C_{max}	Maximum observed serum concentration
T_{max}	Time of maximum observed serum concentration
$AUC_{(0\text{-last})}$	Area under the serum concentration-time curve from the start of the infusion to the time of the last quantifiable concentration
$AUC_{(0\text{-}\infty)}$	Area under the serum concentration-time curve from the start of the infusion extrapolated to infinite time
λ_z	Apparent terminal rate constant
$t_{1/2}$	Apparent terminal half-life
CL	Total body clearance
V_z	Volume of distribution

Individual subject PK parameter values were derived by standard non-compartmental methods using Phoenix WinNonlin version 6.2 (Pharsight Corporation). Actual elapsed sampling times were used for estimation of PK parameters, and scheduled elapsed sampling times were used for summaries and plots of concentration data. Elapsed times were determined relative to the start of the infusion.

For PK parameter estimation, analyte concentrations below the limit of quantification (BLQ) were imputed as zero if they preceded the first quantifiable sample, and were otherwise treated as missing. Quantifiable concentrations reported after consecutive BLQ concentrations in the terminal portion of the concentration curve were excluded from the PK analysis by assigning them a value of missing, unless otherwise warranted by the concentration-time profile. No linear interpolation for missing concentration values was conducted.

C_{max} and T_{max} were recorded directly from experimental observations. $AUC_{(0\text{-last})}$ was calculated by log- and linear-trapezoidal summations using the mixed log-linear method. Apparent terminal rate constant was calculated by regression analysis (slope) of the log-transformed concentrations on the terminal phase of the concentration curve. The absolute values of λ_z were used to estimate the $t_{1/2}$, where $t_{1/2} = \ln(2)/\lambda_z$. The $AUC_{(0\text{-}\infty)}$ was estimated by summing $AUC_{(0\text{-last})}$ and the extrapolated area, which was computed as the quotient of the last measurable concentration and λ_z. Clearance was computed as the quotient of the actual dose administered and either ($AUC_{(0\text{-}\infty)}$ (on Day 0) or $AUC_{(0\text{-last})}$ (on Day 21). V_z was computed as CL/λ_z.

6.5.4 Pharmacodynamic/Biomarker Assessments

Liver enzymes (ALT, AST, GGT), lipid parameters (total cholesterol, triglycerides, HDL, LDL), serum ferritin, and hsCRP, which were assayed as part of the standard clinical laboratory evaluations (see Section 6.5.2.2), were analyzed as PD biomarkers in this study.

In addition, blood samples for an exploratory serum biomarker analysis were collected from subjects who consented to this additional sampling. Written approval from the IEC/IRB and, where required, the applicable regulatory agency, was obtained prior to samples being acquired at each investigational site, and this approval clearly specified the collection of samples for exploratory biomarker analysis. These samples will be used to identify baseline and dynamic markers of LAL Deficiency (and related comorbidities) and response to treatment. Results of this exploratory biomarker analysis will be presented in a separate report.

6.5.5 Other Assessments

6.5.5.1 PBMC LAL Enzyme Activity

While most subjects had LAL activity testing done prior to enrolling in the study, each subject had their LAL activity tested at 3 pre-specified time points during the study. Whole blood samples were collected in EDTA vacutainer tubes, gently inverted 6 to 8 times, and shipped the same day at ambient temperature to Willink Biochemical Genetics Unit (Manchester, UK) where PBMCs were isolated and assayed for LAL enzyme activity.

6.5.5.2 DNA Sample

A blood sample for pharmacogenetic analyses was collected from subjects who consented to this additional sampling. Written approval from the IEC/IRB and, where required, the applicable regulatory agency, was obtained prior to samples being acquired at each investigational site, and this approval clearly specified the collection of samples for pharmacogenetic research.

Whole blood samples were collected in BD Vacutainer CPT™ tubes with sodium citrate and processed in accordance with the manufacturer's instructions to isolate mononuclear cells. Cell pellets were then shipped to the central laboratory, where they are currently stored in a secure controlled environment. The Sponsor will extract deoxyribonucleic acid (DNA) from these samples for a future pooled analysis to determine the spectrum of LAL (LIPA) mutations and explore how genetic variations in LAL (LIPA) and other genes may affect clinical parameters associated with SBC-102 treatment (e.g., safety, efficacy) and acid lipase biology. Results of any such pharmacogenetic analysis will be presented in a separate report.

6.5.5.3 Patient Health Outcomes

Patient health outcomes were assessed at Screening to permit an evaluation of the overall health of patients with liver dysfunction due to LAL Deficiency relative to reference populations given the paucity of data on the impact of LAL Deficiency on patient health. In the absence of validated tools to assess health outcomes in patients with LAL Deficiency, the following questionnaires developed for other diseases were completed by the subjects in this study:

- The SF-36 was developed for the Medical Outcomes Study to measure generic physical and mental health concepts relevant across age, disease, and treatment groups. Version 2 of the SF-36 (SF-36v2) was administered in this study. Norm-based scores are reported for the Physical Component Summary (PCS) and its 4 subscales (physical functioning, role-physical, bodily pain, and general health) and the Mental Component Summary (MCS) and its 4 subscales (vitality, social functioning, role-emotional, and mental health). To obtain norm-based scores, linear transformation was used to standardize raw scores to a mean of 50.0 and SD of 10.0 in the general US population (Ware et al., 2000). The minimally important difference in norm-based scores is typically considered to be a difference of 5 units (i.e., 0.5 standard deviations) (David et al., 2009; Sloan et al., 2005). Subscales are also presented according to the original 0-100 summed ratings method. For both the norm-based and original scaling, a lower value denotes worse health. In addition to the 2 summary component scores and the 8 subscales, responses to the 5-category Reported Health Transition are presented.
- The 13-item FACIT-Fatigue scale was developed to measure levels of fatigue in people living with a chronic disease. Version 4 of the FACIT-Fatigue was administered in this study. A total score is reported. Scores range from 0 to 52, where a lower value denotes greater fatigue.
- The 29-item CLDQ is a disease-specific instrument designed to assess health-related quality of life in subjects with chronic liver disease. The version dated December 28, 1998 was administered in this study. A total score is reported. A lower value denotes a worse quality of life.

6.5.6 Appropriateness of Measurements

The safety assessments performed in this study are standard measures that are widely used and generally recognized as reliable, accurate, and relevant. SBC-102 serum concentrations, anti-SBC-102 antibodies, and all other clinical laboratory tests were obtained using validated analytical methods.

Patient health outcomes were assessed using tools that are not validated for patients with LAL Deficiency (as no such tools are currently available), and are therefore considered exploratory.

6.6 Data Quality Assurance

Each clinical site was evaluated by a representative of the Sponsor or its designee to confirm their suitability for this study. Site initiation meetings were held to prepare Investigators and their staff for the study and to standardize performance. Additional instruction was provided to each Investigator via written laboratory, IMP, and study operations manuals. During the study, clinical study monitors from the Sponsor or its designee conducted periodic on-site visits to ensure adherence to the protocol, review eCRFs and site source documents for accuracy and completeness of information, examine site records for documentation of investigational product receipt and administration, observe the progress of the study, and review Investigator files for required documents.

Study-related laboratory tests were conducted by central laboratories, with the exception of ESR, coagulation and urinalysis parameters, and urine pregnancy tests (see Section 3 for details). Central laboratory data was provided by electronic data transfer between the external laboratory and the Sponsor's designee for data management activities, Premier Research Group, Ltd (Philadelphia, PA, US). Inter-laboratory standardization was performed, as appropriate (Appendix 16.1.10).

All other clinical study data were entered into eCRFs by authorized site personnel, each of whom had received training on the electronic data capture system used for this study, and accessed this system through a unique user account. Any changes made after initial data entry were captured via an electronic audit trail. The Sponsor's designee (Premier Research Group, Ltd, Philadelphia, PA, US) performed a quality assurance (QA) check of all eCRF data entered by the site. On an ongoing basis, when necessary, requests for clarifications or corrections were sent to the Investigators via data queries. After all queries were resolved, corrections were made to the database, and the database was considered clean. Database dictionaries were used to classify responses and to check spelling and accuracy of terms reported on concomitant medication and AE forms. All study data underwent a comprehensive, cross-functional quality control (QC) review by relevant Sponsor departments. Database lock occurred after resolution of any findings from this QC review, and after all decisions concerning the inclusion or exclusion of subject data for analysis were made and documented by appropriate clinical and statistical personnel.

This clinical study report underwent a complete review by the Sponsor to ensure the accuracy of the data presented herein. There has been no audit of this study to date (Appendix 16.1.8).

6.7 Statistical Methods

6.7.1 Statistical and Analytical Plans

The statistical methods used in the analysis of data from this study are described below and are specified in further detail in the Statistical Analysis Plan (SAP) provided in Appendix 16.1.9.

6.7.1.1 Demographics and Baseline Characteristics

Demographics (age, gender, race, ethnicity, height, weight, BMI) and baseline disease characteristics (age at diagnosis, years since diagnosis, abnormal liver enzymes) were listed and descriptively summarized overall and by dose cohort. Frequencies and percentages were provided for gender, race, ethnicity, and abnormal liver enzymes. Summary statistics (e.g., number of subjects [N], mean, standard deviation [SD], median, minimum, maximum) were provided for all other variables.

Other baseline characteristics were also listed and summarized overall and by dose cohort. Frequency distributions were presented for medical history (by body system) and prior medications, and summary statistics were presented for patient health outcomes and AUDIT scores.

Information on investigator sites/locations and LAL enzyme activity was listed.

6.7.1.2 Disposition

The disposition of all enrolled subjects and analysis populations were listed and summarized overall and by dose cohort.

6.7.1.3 Treatment Compliance and Extent of Exposure

Details of each IMP infusion were listed. The number of infusions was summarized overall and by dose cohort for all infusions and those that were incomplete or involved a rate change or interruption.

6.7.1.4 Efficacy Analyses

Not applicable.

6.7.1.5 Safety Analyses

6.7.1.5.1 Adverse Events

The numbers and incidence rates of TEAEs, SAEs, IRRs, and TEAEs leading to discontinuation of IMP, displayed by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) within system organ class (SOC), were tabulated overall and by dose cohort. As applicable, TEAEs, SAEs, and IRRs were also tabulated by categories of severity or causality. Listings of all AEs, treatment-emergent SAEs, IRRs, and AEs leading to discontinuation of IMP were also provided.

6.7.1.5.2 Clinical Laboratory Evaluations

All laboratory parameters were listed. Shift tables (normal, abnormal low, abnormal high) and descriptive summaries of observed values and changes and/or percent changes from baseline to each study visit and from Visit 7 (Day 28) to Visit 8 (Day 52) (for parameters measured at each time point), presented overall and by dose cohort, were generated for all laboratory parameters except ESR, coagulation parameters, and urinalysis parameters. Additional analyses of liver enzymes, serum lipids, serum ferritin, and hsCRP are described in Section 6.7.1.7.

A listing of anti-SBC-102 antibody test results was provided.

6.7.1.5.3 Other Safety Data

Listings were provided for vital sign measurements, 12-lead ECG data, and physical examination findings at screening (including liver size, lymphadenopathy, and arterial disease assessments) and after screening.

Prior and concomitant medications and therapies were listed, and the number and percentage of subjects receiving each medication/therapy, classified by WHO-DD Anatomical Therapeutic Classification (ATC) classes and preferred terms, were summarized overall and by dose cohort.

6.7.1.6 Pharmacokinetic Analyses

SBC-102 concentration data and PK parameters were listed and descriptively summarized by dose and profile day (Day 0 or Day 21). Descriptive summaries included median, minimum, and maximum for T_{max}; and mean, SD, median, minimum, maximum, geometric mean, and %CV for concentration data and all other PK parameters. Individual and mean concentration-time profiles were also plotted by dose and profile day, on both linear and semi-logarithmic scales.

6.7.1.7 Pharmacodynamic/Biomarker Analyses

Liver enzymes (ALT, AST, and GGT), serum lipids (total cholesterol, LDL, HDL, and triglycerides), serum ferritin, and hsCRP were analyzed as PD markers. In addition to the shift tables and descriptive summaries described in Section 6.7.1.5.2, the proportion of subjects with abnormal results for any PD parameter was tabulated overall and by dose. Liver enzymes were tabulated in SI units, and other PD parameters were tabulated in SI and conventional units. Spaghetti plots were produced for hepatic transaminases, serum lipids, serum ferritin, and hsCRP.

6.7.1.8 Other Analyses: Patient Health Outcomes

Scores for SF-36v2, CLDQ, and FACIT-Fatigue were listed and descriptively summarized overall and by dose cohort.

6.7.2 Determination of Sample Size

Sample size was not determined on the basis of statistical considerations. In light of the low prevalence of LAL Deficiency, a sample size of 9 subjects was thought to provide a reasonable

estimation of the overall safety and tolerability of SBC-102 across the range of doses used in the study.

6.7.3 Statistical Issues

6.7.3.1 Handling of Dropouts or Missing Data

All available data are summarized in each analysis. No imputation was performed.

6.7.3.2 Interim Analyses and Data Monitoring

No interim analyses were planned or conducted.

Listings and summary tables were provided to an independent Safety Committee for interim evaluations of safety, as outlined in Section 6.1, and included safety data, subject disposition, demographics and other baseline characteristics, IMP exposure, and concomitant medications, as appropriate.

6.7.3.3 Multiple Comparisons/Multiplicity

Statistical hypothesis testing was not performed for this study report.

6.7.3.4 Subgroup Analyses

No subgroup analyses were planned or conducted.

6.8 Changes in the Conduct of the Study or Planned Analyses

6.8.1 Protocol Amendments

There were 2 amendments to the study protocol. The major changes to study conduct implemented under each protocol amendment are summarized below. The original protocol, protocol amendments, and corresponding summary of change documents are provided in Appendix 16.1.1.

6.8.1.1 Protocol Amendment 1

Protocol Amendment 1, dated 09 February 2011, was implemented at the 6 sites in the US, UK, and Czech Republic. This amendment included the following major changes:

- Extended the inpatient period after each subject's first infusion from 4 hours to 24 hours.
- Added that if safety signals were observed during dosing in any subject, the Safety Committee would review data from all subjects through the fourth infusion, rather than through at least 2 infusions, to determine the acceptability of beginning dosing in the next cohort.
- Changed the AE grading system from DAIDS to CTCAE, version 4.
- Updated the "draft" dose modification and stopping rules to (a) add study-wide stopping criteria, and (b) add language that in the event of a study-wide pause in dosing, dosing would only be resumed after review and agreement by required regulatory authorities.

These updated dose modification and stopping rules were presented as "final" in the amended protocol.

- Indicated that Visit 8 (Day 52, End of Study Visit) procedures would also be performed for a subject who prematurely discontinued treatment in the study.
- Identified the laboratories that would be performing the PK and LAL enzyme activity assays.
- Added that the Sponsor would produce a clinical study report after study completion, and indicated the criteria for identifying the coordinating investigator who would be designated to review and sign this report.
- The publication plan was updated to indicate that study results would be published regardless of outcome. Details of the Sponsor's policy for approval of Investigator-initiated publications was removed from the protocol.

After finalization of this amendment, an error was noted in requirements for fasting prior to clinical laboratory evaluations. A note to file was distributed to all sites indicating that fasting should be done prior to blood sampling for the lipid panel at Screening, baseline (Day 0), and Visit 7 (Week 5, Day 28), rather than at baseline (Day 0), Week 4 (Day 21), and the End of Study visit (Day 52).

6.8.1.2 Protocol Amendment 2

Protocol Amendment 2, dated 23 May 2011, was implemented at one site in France. This amendment included all changes in Protocol Amendment 1, as well as the following additional major changes:

- Per regulatory feedback, it was clarified that participating Investigators would be notified "immediately" of any AE associated with the use of the drug that is both serious and unexpected.
- Corrected the infusion rate from 60 to 50 $mL \cdot hr^{-1}$ for Cohorts 1 and 2, and from 150 to 125 $mL \cdot hr^{-1}$ for Cohort 3.
- Corrected an error in the requirements for fasting prior to clinical laboratory evaluations, as per the note to file mentioned in Section 6.8.1.1.

6.8.1.3 Other Changes in the Conduct of the Study

After the study was initiated, it was noted that the protocol schedule of assessments had inadvertently omitted post-treatment assessments of serum lipids (total cholesterol, triglycerides, LDL, and HDL), which were needed to evaluate reversibility of the treatment effect, an objective of the study. At the time that this error was noted, follow-up testing could no longer be performed for subjects in Cohort 1. For subjects in Cohorts 2 and 3, serum lipid parameters were assayed using excess serum from samples collected for measurement of liver enzymes at Day 52 and, if available, at the optional visit at Day 35.

6.8.2 Changes in the Planned Analyses

The following changes were made to the analyses pre-specified in the SAP:

- For the analysis of SBC-102 PK
  - Volume of distribution (V_z) was reported instead of volume of distribution at steady state (V_{ss}), because the derivation of V_{ss} returned physiologically impossible negative values for some subjects. Briefly, the area under the first moment curve from the start of the infusion extrapolated to infinite time ($AUMC_{(0-\infty)}$) was very close to $AUC_{(0-\infty)}$, resulting in a ratio near unity which, when corrected by subtracting half the infusion length (60 minutes) in accordance with the calculation of V_{ss}, occasionally returned a negative value. Under these conditions, V_z provides a better characterization of PK.
  - $AUC_{(0-\infty)}$ was reported for Day 21, as well as Day 0.
- For clinical laboratory parameters:
  - Descriptive summaries and shift tables from Visit 7 to Visit 8 were provided for selected standard hematology and serum chemistry parameters, in addition to the PD markers.
  - Serum ferritin and hsCRP were presented in conventional units, as well as SI units.
  - Anti-SBC-102 antibody data were not summarized, as all results were negative.
  - A listing of LAL enzyme activity was provided.

7 Study Subjects

7.1 Disposition of Subjects

Nine subjects met study eligibility criteria and were allocated to one of the 3 dose cohorts (3 subjects per cohort), and all 9 (100%) subjects completed the study as planned (Table 14.1.2). The dates of each subject's participation in the study are listed in Appendix 16.2.1. A listing of the clinical sites where subjects were enrolled and treated is provided in Appendix 16.2.2.3.

One additional subject underwent screening procedures, but was ineligible to participate in the study because there was no evidence of hepatomegaly and ALT and AST were <1.5x ULN (Appendix 16.2.2.1).

7.2 Protocol Deviations

All but one of the reported protocol deviations were considered minor, and none were considered to affect the validity or interpretation of study results. No subject was excluded from any analysis of study data due to protocol deviations.

One subject (416-05001) had a missed ECG assessment at the End of Study visit (Visit 8, Day 52), which was considered a major protocol deviation because it pertained to the evaluation of safety. The ECG was not performed because the subject was unable to travel to the study site for her End of Study Visit. Other Visit 8 procedures were conducted in the subject's home, but were delayed.

Minor protocol deviations were reported for all 9 subjects in the study, and most often involved assessments that were missing or conducted outside of protocol-specified time windows. Three subjects had minor deviations pertaining to IMP administration (see Section 7.6 for details). A listing of all protocol deviations reported in this study is provided in Appendix 16.2.2.2.

7.3 Analysis Sets

All 9 (100%) treated subjects were included in each of the following analysis sets (Table 14.1.1; Appendix 16.2.1):

- The **Safety Analysis Set** included all subjects who received any full or partial dose of SBC-102 during the study.
- The **PK Analysis Set** included all subjects in the Safety Analysis Set who had at least one measurable SBC-102 serum level.
- The **PD Analysis Set** included all subjects in the Safety Analysis Set who had at least one post-baseline assessment of liver enzymes, serum lipids, and serum ferritin.
- The **Per-Protocol (PP) Analysis Set** included all subjects in the Safety Analysis Set who completed the study and had no major protocol deviations (defined as deviations from eligibility criteria and/or study procedures that could potentially have a negative effect on the scientific validity of the study). The PP Analysis Set was to be used for a secondary assessment of PD endpoints, if this analysis set differed from the PD Analysis Set.

As the PP Analysis Set was identical to the Safety Analysis Set (i.e., there were no major protocol deviations affecting data interpretability), separate analyses were not performed for the PP Analysis Set.

7.4 Demographic and Other Baseline Characteristics

7.4.1 Demographics

Table 2 summarizes the demographic characteristics of the 9 subjects treated in this study. All subjects were Caucasian and two-thirds were male. Mean age at the time of enrollment was 32 ± 11 years. Dose cohorts were similar with respect to the numbers of male and female subjects and subject age. All subjects except one were non-obese (i.e., body mass index [BMI] <30.0 $kg \cdot m^{-2}$).

Demographic characteristics are listed for each subject in Appendix 16.2.4.1.

Table 2: Demographic Characteristics of Subjects Treated in Study LAL-CL01

Parameter Category/Statistic	Cohort 1: 0.35 mg·kg^{-1} N=3	Cohort 2: 1 mg·kg^{-1} N=3	Cohort 3: 3 mg·kg^{-1} N=3	Total N=9
Age at Enrollment, years				
Mean (SD)	32 (8)	35 (14)	27 (12)	32 (11)
Range	27, 41	19, 45	19, 41	19, 45
Gender, n (%)				
Male	2 (66.7)	2 (66.7)	2 (66.7)	6 (66.7)
Female	1 (33.3)	1 (33.3)	1 (33.3)	3 (33.3)
Race, n (%)				
White	3 (100)	3 (100)	3 (100)	9 (100)
Ethnicity, n (%)				
Not Hispanic or Latino	3 (100)	3 (100)	3 (100)	9 (100)
Weight, kg				
Mean (SD)	69.9 (11.5)	86.9 (33.1)	79.9 (11.4)	78.9 (19.9)
Range	57.8, 80.8	64.0, 124.8	68.4, 91.2	57.8, 124.8
BMI, kg m^{-2}				
Mean (SD)	23.6 (3.76)	30.3 (10.48)	26.4 (1.11)	26.8 (6.31)
Range	20.5, 27.8	23.5, 42.4	25.2, 27.4	20.5, 42.4
BMI Category, n (%)				
Underweight (<18.5)	0	0	0	0
Normal (18.5 to 24.9)	2 (66.7)	1 (33.3)	0	3 (33.3)
Overweight (25.0 to 29.9)	1 (33.0)	1 (33.3)	3 (100)	5 (55.6)
Obese (≥30.0)	0	1 (33.3)	0	1 (11.1)

Source: Table 14.1.3.1
BMI= body mass index

7.4.2 Baseline Disease Characteristics

Table 3 summarizes the baseline disease characteristics of the 9 subjects treated in this study.

The age of subjects at the time of diagnosis of LAL Deficiency was variable (range 4.1 to 42.4 years), as was the time between diagnosis and enrollment in this study (0.8 to 36.3 years). All 9 subjects had liver involvement, as evidenced by hepatomegaly on the screening physical examination (8 subjects) and/or AST or ALT ≥1.5x ULN (but <3x ULN) (2 subjects), as per study eligibility criteria. An additional 6 subjects had elevations in AST or ALT that were >ULN but <1.5x ULN (Appendix 16.2.6.1). Eight of the 9 subjects also had lipid abnormalities (Appendix 16.2.6.2.2), and 7 subjects were receiving lipid-modifying medications at the time of enrollment (Appendix 16.2.9.1).

Levels of peripheral blood mononuclear cell (PBMC) LAL activity measured at Screening were consistent with the diagnosis of LAL Deficiency in all 9 study subjects. PBMC LAL (acid esterase) activity ranged from 10.4 to 57 µmol/g/h at Screening, corresponding to approximately 3% to 16% of the normal activity in the reference population (laboratory normal range = 350 to 2000 µmol/g/h). Beta-galactosidase was assayed concurrently as a control lysosomal enzyme, and its levels were within the normal range in all 9 subjects at Screening (109 to 233 µmol/g/h; normal range = 100 to 400 µmol/g/h).

Information pertaining to diagnosis of LAL Deficiency is listed for each subject in Appendix 16.2.4.1, and results for LAL enzyme activity, liver enzymes, and lipid parameters are presented in Appendix 16.2.4.6, Appendix 16.2.6.1, and Appendix 16.2.6.2.2, respectively.

Table 3: Baseline Disease Characteristics of Subjects Treated in Study LAL-CL01

Parameter Category/Statistic	Cohort 1: 0.35 mg·kg^{-1} N=3	Cohort 2: 1 mg·kg^{-1} N=3	Cohort 3: 3 mg·kg^{-1} N=3	Total N=9
Age at Diagnosis, years				
Mean (SD)	16.3 (19.4)	31.9 (17.2)	7.20 (4.5)	18.5 (17.0)
Range	4.1, 38.6	12.1, 42.4	4.5, 12.4	4.1, 42.4
Time from Diagnosis to Study Enrollment[a], years				
Mean (SD)	16.1 (11.8)	3.4 (3.1)	19.8 (14.6)	13.1 (12.1)
Range	2.4, 22.9	0.8, 6.9	8.6, 36.3	0.8, 36.3
PBMC LAL Activity[b]				
Median	42	46	24	42
Range	33, 42	10.4, 57	19, 42	10.4, 57
Liver Dysfunction (Study Entry Criteria)				
Hepatomegaly Present on Physical Examination, n (%)	3 (100)	2 (66.7)	3 (100)	8 (88.9)
1.5x ULN ≤ AST or ALT <3x ULN[c]	0	1 (33.3)	1 (33.3)	2 (22.2)
Abnormal Liver Enzymes[c], n (%)				
ALT >ULN	2 (66.7)	2 (66.7)	2 (66.7)	6 (66.7)
AST >ULN	2(66.7)	3 (100)	1 (33.3)	6 (66.7)
GGT >ULN	0	1 (33.3)	1 (33.3)	2 (22.2)
Abnormal Serum Lipids[d], n (%)				
Any Lipid Parameter	3 (100)	2 (66.7)	3 (100)	8 (88.9)
Total Cholesterol >ULN	2 (66.7)	0	0	2 (22.2)
Triglycerides >ULN	1 (33.3)	0	2 (66.7)	3 (33.3)
HDL <LLN	1 (33.3)	2 (66.7)	1 (33.3)	4 (44.4)
LDL >ULN	2 (66.7)	0	0	2 (22.2)
Receiving Lipid-Lowering Medications, n (%)	2 (66.7)	3 (100)	2 (66.7)	7 (77.8)

Source: Table 14.1.3.1; Table 14.1.3.3; Appendix 16.2.4.3.2; Table 14.2.1.2; Appendix 16.2.6.2.2; Appendix 16.2.4.6

ULN = upper limit of normal; LLN = lower limit of normal

[a] Enrollment = date of informed consent

[b] Normal range = 350 to 2000 µmol/g/h.

[c] ULN is 73 U/l (males) or 50 U/l (females) for GGT, 50 U/l for AST and 67 U/l for ALT.

[d] ULN is 232 mg/dL for total cholesterol, 199 mg/dL for triglycerides, and 162 mg/dL for LDL, and LLN is 35 mg/dL for HDL.

7.4.3 Other Baseline Characteristics

Medical history and prior medications/therapies are presented below. Baseline patient health outcomes data are presented in Section 12.

7.4.3.1 Medical History

Medical history findings were consistent with those expected in this patient population, and none of these findings were thought to affect the validity or interpretation of study data. Seven subjects had a medical history of hepatomegaly and/or splenomegaly, and 2 subjects had findings indicative of more advanced liver disease, including cirrhosis and portal hypertension in one subject in Cohort 2 (416-05001) and periportal fibrosis in one subject in Cohort 3 (417-06001) (Appendix 16.2.4.2). All 9 (100%) subjects had a medical history of dyslipidemia, and 7 (77.8%) subjects also had a history of other cardiovascular conditions (Table 14.1.3.2). A listing of all medical history findings is provided in Appendix 16.2.4.2.

AUDIT questionnaires were also administered to screen for chronic overconsumption of alcohol, which can cause hepatic abnormalities similar to those associated with LAL Deficiency (e.g., steatosis, fibrosis, and cirrhosis) and could potentially confound the interpretation of response to treatment with SBC-102. AUDIT scores for the 9 treated subjects ranged from 0 to 7 (Table 14.1.3.4; Appendix 16.2.4.5.1), which is below the score of 8 recommended by the WHO as a cut-off for identification of hazardous or harmful alcohol use and alcohol dependence (Babor et al., 2001). These AUDIT scores are based on the version of the AUDIT questionnaire provided in the protocol. An inadvertent error in this version of the AUDIT questionnaire was found during data review: answers to questions 9 and 10 had the same format as the other questions (0 = never, 1 = monthly or less, 2 = 2 to 4 times a month, 3 = 2 to 3 times a week, 4 = 4 or more times a week) instead of the correct format (0 = no, 2 = yes, but not in the last year, 4 = yes, during the last year), as per WHO guidelines (Babor et al., 2001). As all but one subject had AUDIT scores of 4 or less, this error was unlikely to have missed excessive alcohol intake in these subjects. In one subject (414-03002) who had a total AUDIT score of 7, however, the error may have underestimated the true amount of alcohol intake.

7.4.3.2 Prior Medications and Treatments

Seven (77.8%) subjects were receiving one or more medications prior to enrollment in the study (Table 14.1.3.3), most of which were being administered chronically for the management of symptoms and complications of LAL Deficiency or co-morbidities (e.g., psychiatric illness) and were continued during the subject's participation in the study. All 7 subjects on medications were receiving treatment with lipid-modifying therapies, including ezetimibe, statins, and other medications. No subject received a prohibited prior medication.

Prior medications are listed for each subject in Appendix 16.2.9.1.

7.5 Concomitant Medications and Treatments

Eight (88.9%) subjects received one or more concomitant medications during treatment in this study, most commonly lipid-modifying agents (7 subjects), anti-inflammatory and anti-rheumatic products (5 subjects), and analgesics (4 subjects) (Table 14.3.6.4).

The 7 subjects who were receiving lipid-lowering medications prior to enrollment continued to receive these medications at the same dose and dosing regimen throughout their participation in the study, and no subject initiated treatment with a new lipid-modifying therapy during the study (Appendix 16.2.9.1).

Eight subjects received treatment with at least one new concomitant medication during the study. Medications administered for the treatment of TEAEs included non-steroidal anti-inflammatory drugs (4 subjects), paracetamol (3 subjects), pepto-bismol or peptac (2 subjects), amoxicillin and Biamotil-D/Ciprodex (1 subject), loperamide (1 subject), and triamcinolone and an unspecified herbal medication (1 subject). In addition, one subject (413-02001, Cohort 1) had an adjustment in medications to manage pre-existing post-traumatic stress disorder: this subject received a dose reduction in sertraline concurrent with initiation of therapy with venlafaxine hydrochloride.

While some of the concomitant medications administered during this study are known to be associated with a low incidence of laboratory abnormalities, including elevations in transaminases (e.g., sertraline) or total cholesterol (e.g., venlafaxine hydrochloride), these medications were not expected to interfere with the validity or interpretation of study data.

Concomitant medications are listed for each subject in Appendix 16.2.9.1.

7.6 Compliance with Study Treatment

The 9 treated subjects each received 4 complete infusions of SBC-102 at their allocated dose.

Minor deviations in the administration of IMP were reported for 3 subjects (Appendix 16.2.2.2):

- Subject 412-01001 (Cohort 2) received the first 2 study infusions with an in-line 15 micron filter. This deviation did not appear to have a meaningful effect on SBC-102 exposure, as the subject's PK profile was comparable to that of another subject in the dose cohort who did not receive infusions via an in-line filter (418-07001).
- Subject 416-05001 (Cohort 2) received each study infusion at a dose that was calculated based on the subject's weight at the infusion visit (range: 123.8 kg to 125.2 kg) rather than the subject's screening weight (124.8 kg). The actual dose administered (in mg) deviated by less than 1% of the planned dose.
- Subject 418-07001 (Cohort 2) received the first study infusion at a rate of 60 mL hr^{-1} instead of 50 mL hr^{-1}.

8 Efficacy Results

Several disease-related laboratory parameters were evaluated as markers of the biological activity of SBC-102 in LAL Deficiency. Results of these PD analyses are presented in Section 11.

9 Safety Results

9.1 Extent of Exposure

A total of 36 infusions of SBC-102 were administered to the 9 subjects treated in this study. Twelve infusions of SBC-102 were administered at each dose (0.35, 1, and 3 mg·kg^{-1}), with each of the 3 subjects in the dose cohort receiving 4 infusions.

All study infusions were completed, i.e., the entire infusion volume was administered. With the exception of one study infusion that was interrupted due to a loss of IV access (subject 416-05001), all infusions were administered without interruption or rate change.

Infusion details are listed in Appendix 16.2.5.1 and summarized in Table 14.3.6.5.

9.2 Adverse Events

A listing of all AEs reported in this study is provided Appendix 16.2.7.1.

9.2.1 Brief Summary of Adverse Events

Table 4 provides an overview of the incidence of AEs in study LAL-CL01.

Table 4: Overview of the Number (Percentage) of Subjects Reporting Adverse Events in Study LAL-CL01

	Cohort 1: 0.35 mg·kg^{-1} N=3	Cohort 2: 1 mg·kg^{-1} N=3	Cohort 3: 3 mg·kg^{-1} N=3	Total N=9
Death, n (%)	0	0	0	0
Treatment-Emergent SAE, n (%)	0	0	0	0
Treatment-Emergent AE (TEAE), n (%)				
Any TEAE	1 (33.3)	3 (100)	3 (100)	7 (77.8)
Grade 3 or 4 TEAE	0	0	1 (33.3)[b]	1 (11.1)[b]
Related TEAE[a]	1 (33.3)	0	1 (33.3)	2 (22.2)
Infusion-related reaction	0	0	0	0
Dose modification due to TEAE	0	0	0	0
Discontinuation due to TEAE	0	0	0	0

Source: Table 14.3.1.1; Table 14.3.1.3

[a] Includes events assessed by the Investigator as related or possibly related to IMP.

[b] Includes a TEAE of hypercholesterolemia that met the CTCAE cut-off for a Grade 4 laboratory toxicity (i.e., total cholesterol >500 mg/dL). The Investigator, Sponsor, and independent Safety Committee did not consider this event to be life-threatening.

9.2.2 Analysis of Adverse Events

A total of 44 treatment-emergent AEs (TEAEs) were reported by 7 (77.8%) of the 9 subjects treated in the study. TEAEs occurred most frequently within the SOCs of Gastrointestinal disorders (16 events in 5 [55.6%] subjects) and Nervous system disorders (9 events in 4 [44.4%] subjects). All reported TEAEs are tabulated in Table 14.3.1.2, and TEAEs reported by more than one subject in the study are summarized in Table 5.

The overall frequency of TEAEs was comparable for the 2 highest dose cohorts, with 23 events in 3 subjects in Cohort 2 (1 $mg \cdot kg^{-1}$) and 17 events in 3 subjects in Cohort 3 (3 $mg \cdot kg^{-1}$). Relative to these dose cohorts, TEAEs were less frequent in Cohort 1 (0.35 $mg \cdot kg^{-1}$), with 4 events reported by one subject. Given the small sample size, there were no clear dose-related trends in the occurrence of any specific TEAEs.

It was noted that a majority of the TEAEs reported in Cohorts 2 and 3 were reported by one subject in each cohort:

- In Cohort 2, 17 of the 23 events were reported by subject 416-05001. This subject, a 42-year old female and the only obese subject enrolled in the trial (BMI=42.4 $kg \cdot m^{-2}$), had an extensive medical history significant for liver cirrhosis with portal hypertension and a gastrointestinal (GI) bleed secondary to esophageal varices, edema, osteoarthritis and fractures, other GI abnormalities (hiatus hernia, functional bowel disturbance), and genitourinary problems (e.g., ovarian cysts, ectopic pregnancy, miscarriage, and endometriosis). During the study, the subject experienced recurrent TEAEs of peripheral edema, bone or musculoskeletal pain, various GI events (flatulence, diarrhea, lower abdominal pain, and rectal hemorrhage), vaginal hemorrhage, and headache, as well as single events of breast swelling and presyncope. All events were assessed by the Investigator as unrelated or unlikely related to IMP.
- In Cohort 3, 13 of the 17 events were reported by subject 412-01002. This subject was a 41-year old male with LAL Deficiency diagnosed at age 4 and a medical history significant for arterial hypertension, statin-resistant dyslipidemia, adrenal adenoma, depression and anxiety, as well as hepatic dysfunction evidenced by hepatomegaly and high ALT, AST, and GGT at Screening. During the course of the study, the subject reported recurrent headaches, abdominal discomfort or distension, abnormal urine odor, and nausea, as well as single events of night sweats and a viral URTI. All of these TEAEs were assessed as Grade 1 severity and unrelated to IMP. This subject also had worsening of baseline hypertriglyceridemia (Grade 2) and hypercholesterolemia (Grade 4), which were assessed as possibly related to IMP and are discussed further in Section 9.2.2.1.

Table 5: Summary of Treatment-Emergent Adverse Events, Regardless of Causality, for Preferred Terms Reported by More Than One Subject in Study LAL-CL01

System Organ Class Preferred Term[a]	Cohort 1: 0.35 mg·kg^{-1} N=3		Cohort 2: 1 mg·kg^{-1} N=3		Cohort 3: 3 mg·kg^{-1} N=3	
	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
Any TEAE	4	1 (33.3)	23	3 (100)	17	3 (100)
Gastrointestinal disorders						
Diarrhea	1	1 (33.3)	3	2 (66.7)	0	0
Nausea	3	1 (33.3)	0	0	1	1 (33.3)
Nervous system disorders						
Headache	0	0	3	1 (33.3)	4	2 (66.7)

Source: Table 14.3.1.2

9.2.2.1 Adverse Events by Severity

All but one of the 44 reported TEAEs were assessed by the Investigator as Grade 1 (38 [86.4%] events) or Grade 2 (5 [11.4%] events) in severity (Table 14.3.1.3).

One subject (412-01002, Cohort 3) had a TEAE of hypercholesterolemia. Although this subject was asymptomatic, this laboratory abnormality met CTCAE criteria for a Grade 4 event. This subject also had a concurrent Grade 2 TEAE of hypertriglyceridemia. The subject, a 41-year old male with a BMI of 27.4 kg·m^{-2}, had a medical history of hyperlipidemia and had been receiving treatment with simvastatin 40 mg QD since 2009. Table 6 presents the serum lipid levels for this subject during the study. At Screening (October 2011) and Day 0 (November 2011), triglycerides remained elevated despite ongoing treatment with simvastatin, whereas total cholesterol and LDL were within normal ranges. Marked elevations in total cholesterol, triglycerides, and LDL were observed at the next assessment at Day 28, which was one week after the subject's fourth infusion at a dose of 3 mg·kg^{-1}. The increases in total cholesterol and triglycerides were considered a clinically significant worsening from baseline and were reported as TEAEs of hypercholesterolemia and hypertriglyceridemia. No medical treatment was deemed necessary, and the subject's total cholesterol, LDL, and triglyceride levels decreased within a week and were within normal ranges (and below the subject's baseline levels for each parameter) by the last assessment at Day 52. The TEAEs of hypercholesterolemia and hypertriglyceridemia were assessed by the Investigator as possibly related to IMP, consistent with elevations in serum lipids being an expected pharmacological effect of SBC-102 therapy, and were assessed as Grade 4 and Grade 2 events, respectively, based on specific CTCAE cut-off values for each

laboratory parameter. Although elevations in total cholesterol were assessed as Grade 4 severity (>500 mg/dL), the Investigator, the Sponsor, and the independent Safety Committee did not consider the lipid changes in subject 412-01002 to be life threatening or to require urgent intervention. Thus, this TEAE was not considered to be an SAE.

Transient elevations in total cholesterol, LDL, and triglycerides observed in other subjects, which also returned to levels at or below baseline by Day 52 (see Section 9.4.2 and Section 11.2 for further details), were not assessed by the Investigator as clinically significant changes from baseline, and therefore were not reported as AEs.

Table 6: Serum Lipid Parameters for Subject 412-01002 in Cohort 3

	Total Cholesterol		Triglycerides		LDL		HDL	
	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L
LLN, ULN	69, 232	1.80, 6.00	NR, 199	NR, 2.25	NR, 162	NR, 4.20	35, NR	0.91, NR
Screening	213	5.52	253	2.86	149	3.86	27	0.70
Day 0 (baseline)[a]	220	5.70	277	3.13	143	3.70	26	0.67
Day 28	772	19.99	462	5.22	674	17.46	28	0.73
Day 35[b]	292	7.56	307	3.47	221	5.72	24	0.62
Day 52	166	4.30	140	1.58	102	2.64	39	1.01

Source: Appendix 16.2.6.2.2
NR= Not Reported
[a] The blood sample for serum lipids was collected prior to the first infusion on Day 0. Subsequent infusions of SBC-102 were administered on Days 0, 7, 14, and 21.
[b] This was an optional study visit.

9.2.2.2 Adverse Events by Relationship to Study Treatment

Of the 44 TEAEs reported in the study, 6 (13.6%) events in 2 subjects were related to IMP (Table 14.3.1.4b):

- Subject 414-03002 in Cohort 1 (0.35 $mg \cdot kg^{-1}$) experienced 3 TEAEs of Grade 1 nausea and 1 TEAE of Grade 1 diarrhea that were assessed by the Investigator as possibly related to IMP (Table 14.3.1.4; Appendix 16.2.7.1). These events had an onset between 5.5 hours and 4 days after the first or second infusion of SBC-102, and resolved the same day. The subject completed the third and fourth infusions of SBC-102 without incident.
- Subject 412-01002 in Cohort 3 (3.0 $mg \cdot kg^{-1}$) had TEAEs of Grade 4 hypercholesterolemia and Grade 2 hypertriglyceridemia that were assessed by the Investigator as possibly related to IMP (Table 14.3.1.4; Appendix 16.2.7.1). These events are discussed in further detail in Section 9.2.2.1.

No IRRs were reported during the study (Table 14.3.3.1; Table 14.3.3.2; Appendix 16.2.7.4). There were no TEAEs that were assessed by the Investigator as IRRs, nor were there any

TEAEs with an onset between initiation of an IMP infusion and 4 hours after completion of the infusion that were assessed by the investigator as at least possibly related to IMP.

9.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

9.3.1 Deaths

No subject died during participation in this study (Table 14.3.1.1).

9.3.2 Other Serious Adverse Events

No treatment-emergent SAEs were reported during this study (Table 14.3.2.1; Table 14.3.2.2; Appendix 16.2.7.3).

9.3.3 Other Significant Adverse Events

No subject discontinued treatment due to a TEAE (Table 14.3.1.5; Appendix 16.2.7.2).

No IRRs were reported during the study (Table 14.3.3.1; Table 14.3.3.2; Appendix 16.2.7.4). There were no TEAEs that were assessed by the Investigator as IRRs, nor were there any TEAEs with an onset between initiation of an IMP infusion and 4 hours after completion of the infusion that were assessed by the investigator as at least possibly related to IMP.

9.3.4 Case Narratives

There are no case narratives for this study.

9.4 Clinical Laboratory Evaluation

Meaningful decreases in hepatic transaminases (AST and ALT) and serum ferritin and increases in serum lipids (total cholesterol, triglycerides, and LDL) consistent with the mechanism of action of SBC-102 were observed during treatment at all doses of SBC-102 evaluated in this study, and are indicative of the biological activity of the IMP in this patient population. Results for these laboratory parameters and other PD markers (GGT, hsCRP, and HDL) are presented in Section 11. Implications of the increases in serum lipids for the safety profile of SBC-102 are discussed in Section 9.6.

No clinically relevant trends were apparent in any other hematology, serum chemistry, or urinalysis parameter, and no subject developed anti-SBC-102 antibodies. Further details of these other clinical laboratory evaluations are provided in Section 9.4.1 through Section 9.4.4.

All pregnancy tests for female subjects were negative (Appendix 16.2.8.4).

9.4.1 Hematology

There were no clinically meaningful mean changes over time in any standard hematology parameter based on examination of changes from baseline to each study time point (Table 14.3.5.1.1) and from Day 28 to the follow-up visit at Day 52 (Table 14.3.5.1.2). The majority of subjects had normal results at baseline and throughout the study (Table 14.3.5.3.1), and none of the reported abnormalities was considered clinically significant. No trends in

individual shifts between normal and abnormal values were apparent from baseline to each study time point (Table 14.3.5.3.1) or from Day 28 to Day 52 (Table 14.3.5.3.2). Standard hematology parameters are listed for each subject in Appendix 16.2.8.1.

Coagulation parameters were essentially unchanged from Screening to Day 52 in all subjects (Appendix 16.2.8.6). Two subjects had results for one or more coagulation parameters that were outside of the normal ranges provided by the local laboratory performing these tests. When coagulation parameters in these subjects were compared with ULN values typically used in clinical practice (prothrombin time [PT] = 13.8 msec, partial thromboplastin time [PTT] = 38 seconds, international normalized ratio [INR] = 1.2), only PT values were above normal: subject 414-03002 had a PT of 14.3 seconds at Screening and 14.6 seconds at Day 52, and subject 416-05001 had a PT of 14.6 seconds at Screening (the PT of 13.6 seconds at Day 52 was considered normal). One other subject also had PT values that were above the ULN typically used in clinical practice despite being within the normal range of the testing laboratory (14.8 seconds at Screening and 14.6 seconds at Day 52). None of these abnormalities were considered clinically significant.

There were no clinically relevant trends in ESR over time. Four subjects had abnormal ESR results at one or more time points, none of which were considered clinically significant (Appendix 16.2.8.7).

No hematological AEs were reported during this study.

9.4.2 Serum Chemistry

As described in Section 11, increases from baseline (Day 0) in total cholesterol, triglycerides, and LDL were observed at the assessment performed 1 week after the fourth infusion (Day 28) at all doses of SBC-102 evaluated in this study, and in nearly all subjects in each dose cohort. These serum lipid changes are consistent with the mechanism of action of SBC-102. On average, the magnitude of this effect on serum lipids was greatest in Cohort 3, and was lower and broadly comparable in Cohorts 1 and 2 (see Table 8 in Section 11). Reversibility was observed within approximately 30 days of discontinuation of SBC-102 therapy (Day 52), with normal or near-normal lipid levels reported by at this time point in all subjects with available data. One subject had abnormal lipid levels that were assessed by the investigator as a clinically significant worsening from baseline and were reported as AEs. As previously discussed in Section 9.2.2.1, this subject, 412-01002, had peak levels of total cholesterol (772 mg/dL [19.99 mmol/L]) and triglycerides (462 mg/dL [5.22 mmol/L]) at Day 28 of treatment that were reported as AEs of Grade 4 hypercholesterolemia and Grade 2 hypertriglyceridemia based on the CTCAE grading scale used in this study. Of note, the hypercholesterolemia was not considered to be life threatening, but was classified as a Grade 4 event based on specific CTCAE cut-off values for total cholesterol. See Section 9.2.2.1 for further details of these lipid-related TEAEs.

Meaningful decreases in hepatic transaminases (AST and ALT) and serum ferritin were observed during treatment at all doses of SBC-102 evaluated in this study. A clinically relevant increase in HDL was observed during the post-treatment follow-up period for subjects in Cohort 3 (3 $mg \cdot kg^{-1}$) only. These laboratory changes are indicative of biological activity, and are discussed in Section 11.

Evaluation of other standard serum chemistry parameters (Appendix 16.2.7.2) did not reveal any clinically meaningful mean changes over time, either from baseline to each study time point (Table 14.3.5.2.1) or from Day 28 to the follow-up visit at Day 52 (Table 14.3.5.2.2). For one subject in Cohort 1 (413-02001), total bilirubin increased from 23.9 µmol/L at baseline to a peak level of 39.3 µmol/L at Day 21 (prior to the last infusion of IMP), without a significant corresponding change in direct bilirubin (6.8 µmol/L to 8.5 µmol/L). The significance of the increase in total bilirubin is unclear, given that the subject's bilirubin levels were already elevated at Screening (total bilirubin = 47.9 µmol/L, direct bilirubin = 15.4 µmol/L). Another subject (418-07001, Cohort 2) also had small elevations in total and direct bilirubin, of unclear significance, between baseline (23.9 µmol/L and 4.3 µmol/L, respectively) and Day 28 (32.3 µmol/L and 7.9 µmol/L, respectively). Both of these subjects had decreases in liver enzymes during treatment in the study.

Results for the other serum chemistry parameters were normal in the majority of subjects at baseline and throughout the study (Appendix 16.2.8.2), and there were no trends in individual shifts between normal and abnormal values from baseline to each study time point (Table 14.3.5.4.1) or from Day 28 to Day 52 (Table 14.3.5.4.2). There were no clinically significant abnormalities in any of these parameters. A listing of these serum chemistry parameters is provided in Appendix 16.2.8.2.

One subject had AEs related to increases in serum total cholesterol and triglycerides, as described above. No other TEAEs related to changes in serum chemistries were reported during this study.

9.4.3 Urinalysis

Abnormal (positive) urinalysis findings were infrequent, and were assessed by the Investigator as not clinically significant (Appendix 16.2.8.3). No AEs related to urinalysis test results were reported in the study.

9.4.4 Immunogenicity

All 9 subjects tested negative for anti-SBC-102 antibodies at each of the 4 scheduled time points when this testing was performed (Appendix 16.2.8.5).

9.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

9.5.1 Vital Signs

There were no clinically relevant trends in systolic or diastolic blood pressure, heart rate, respiratory rate, or body temperature, either in association with SBC-102 infusions or over the course of the study. Two subjects (414-03001 and 417-06001), both young males, had a low resting heart rate at baseline (48 bpm and 49 bpm, respectively) without significant change during the study. No vital sign-related AEs were reported for any subject. Vital sign data are listed for each subject in Appendix 16.2.9.2.

9.5.2 Physical Examinations

Physical examination findings reported at screening are listed in Appendix 16.2.4.3.1, and were consistent with those expected in this patient population. Eight of the 9 subjects had a palpable liver with a smooth edge that extended between 2 and 8 cm below the costal margin (Appendix 16.2.4.3.2). One subject had lymphadenopathy, which was present in the cervical and inguinal regions (Appendix 16.2.4.3.3). Ankle brachial indices were determined for 7 subjects, and were essentially normal, ranging from 0.9 to 1.3 (Appendix 16.2.4.3.3).

During treatment in the study, one subject (417-06001) had new physical examination findings that were assessed by the Investigator as clinically significant changes from screening (Appendix 16.2.9.3), including a reported TEAE of contact dermatitis that was assessed as unrelated to treatment (Appendix 16.2.7.1).

9.5.3 Electrocardiograms

No clinically meaningful trends were apparent in PR, QRS, QT, or QTc between Screening and the Day 52 follow-up visit. No individual ECG abnormalities of clinical significance were identified in any subject upon review of these data, and no ECG-related AEs were reported by the Investigator. QTc intervals >450 msec were observed in 2 subjects: Subject 413-02001, a young male, had a QTc interval of 453 msec at Screening and Day 52, and subject 414-03002, a young female, had a QTc interval of 421 msec at Screening and 452 msec at Day 52. Electrocardiogram data are listed for each subject in Appendix 16.2.9.4.

9.5.4 Pregnancies

No pregnancies were reported during this study for female subjects participating in the study or for female partners of male subjects participating in the study.

9.6 Summary of Safety

There were no deaths or treatment-emergent SAEs in this study. Most (86.4%) TEAEs were unrelated to IMP, and all but one TEAE was Grade 1 (86.4% events) or Grade 2 (11.4% events) in severity. No subject experienced an IRR or developed anti-SBC-102 antibodies. Treatment was not modified or discontinued in any subject due to a TEAE.

There were no clinically important changes in any vital sign or ECG parameters, and no clinically relevant trends in physical examination findings. With the exception of increases in total cholesterol, triglycerides, and LDL (see further discussion below), there were no trends in any laboratory parameters that presented a potential safety concern for SBC-102 treatment.

Increases in total cholesterol, LDL and triglycerides were observed between baseline and Day 28 at all doses of SBC-102 evaluated in this study (Appendix 16.2.6.2.2). These lipid elevations occurred irrespective of whether a subject was receiving statin therapy and were most pronounced in Cohort 3 (3 $mg \cdot kg^{-1}$), with increases of lesser and comparable magnitude in the 2 lower dose cohorts (0.35 and 1 $mg \cdot kg^{-1}$). The maximum increases from baseline in serum lipids were observed for 2 subjects in Cohort 3, one having the greatest increase in total cholesterol (from 220 mg/dL to 772 mg/dL [5.70 to 19.99 mmol/L]) and LDL (from 143 mg/dL to 674 mg/dL [3.70 to 17.46 mmol/L]), and the other the greatest increase in triglycerides (from 80 mg/dL to 351 mg/dL [0.90 to 3.97 mmol/L]). While the more marked elevations in serum lipids observed in these 2 subjects may be dose-related, the possibility of genetic differences in the regulation of serum lipid metabolism in these subjects cannot be excluded. In one of the 2 subjects, the observed increases in total cholesterol and triglycerides were considered by the Investigator to be a clinically significant worsening from baseline, and were reported as TEAEs of Grade 4 hypercholesterolemia and Grade 2 hypertriglyceridemia that were possibly related to IMP. The severity of these TEAEs was defined based on the CTCAE criteria used in this study. While the elevation in total cholesterol was assessed as a Grade 4 event based on the specific CTCAE cut-off for Grade 4 laboratory toxicity (total cholesterol >500 mg/dL), the Investigator, the Sponsor, and the independent Safety Committee did not consider this event to be life threatening or to require urgent intervention. Lipid levels in this subject decreased within a week and returned to normal range (and below baseline levels) by Day 52, without additional medical treatment. A similar reversibility of total cholesterol, triglycerides, and LDL after discontinuation of SBC-102 therapy was observed for the other 5 subjects in Cohorts 2 and 3 (data were not available for Cohort 1 due to an oversight in protocol schedule of assessments). By Day 52, 5 of the 6 subjects in these 2 cohorts had total cholesterol, triglyceride, and LDL levels that were below those at baseline.

As discussed in Section 13.1.1, the increases in total cholesterol, triglycerides, and LDL observed in this study are consistent with the mechanism of action of SBC-102, and are anticipated to be transient. However, it is recognized that marked hypercholesterolemia and hypertriglyceridemia warrant attention as a potential safety concern, particularly if the levels of these lipids are sustained for extended periods of time. Therefore, review of serum lipid levels for evidence of marked or sustained hyperlipidemias will continue to be an important component of safety monitoring and the ongoing benefit-risk assessment in longer-term clinical studies with SBC-102.

10 Pharmacokinetic Results

The descriptive statistics of the derived PK serum parameters of SBC-102 are presented in Table 14.4.2. Individual subject serum SBC-102 concentrations and SBC-102 PK parameters are listed in Appendix 16.2.5.2 and Appendix 16.2.5.3, respectively. Individual SBC-102 concentration-time plots are displayed on the linear scale and semi-logarithmic scale in Figure 14.4.1.1, Figure 14.4.1.2, and Figure 14.4.1.3, and mean SBC-102 concentration-time plots are displayed on the linear and semi-logarithmic scale in Figure 14.4.2.1, Figure 14.4.2.2, and Figure 14.4.2.3.

10.1 Serum Concentrations of SBC-102

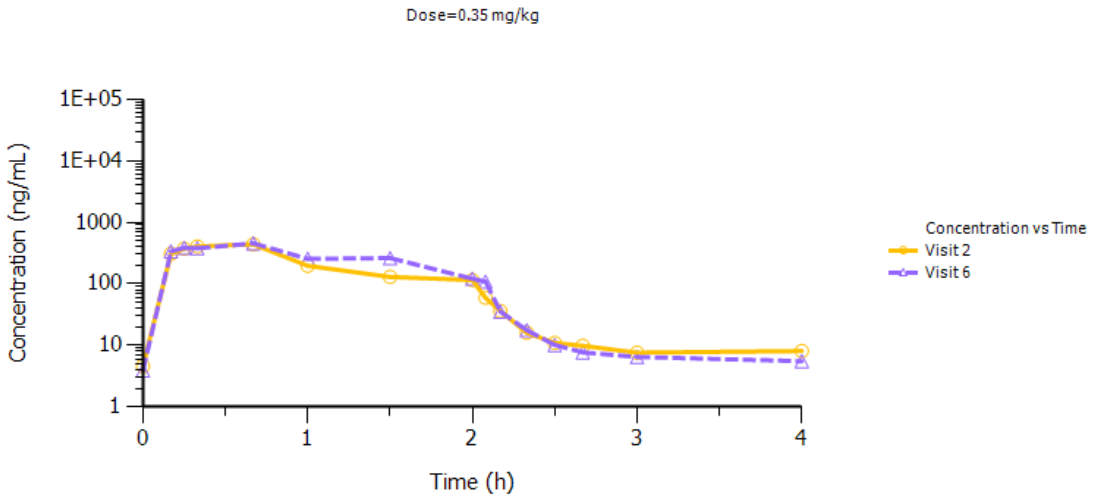
SBC-102 concentration-time plots for doses of 0.35, 1, and 3 $mg \cdot kg^{-1}$ are displayed on the semi-logarithmic scale in Figure 1, Figure 2, and Figure 3, respectively. At each dose level, the respective Visit 2 (Day 0) and Visit 6 (Day 21) post-infusion serum concentrations of SBC-102 declined in a parallel fashion. An exception was noted in individual concentration-time profile for subject 417-06001 in Cohort 3 (3 $mg \cdot kg^{-1}$): at Visit 2, this subject had a concentration below the lower limit of quantification (<LLOQ) at 10 minutes after completion of the infusion (elapsed time 2.17 hours), which was followed by measurable concentrations of 227 ng/mL at 20 minutes post-infusion (elapsed time 2.33 hours) and 910 ng/mL at 30 minutes post-infusion (elapsed time 2.50 hours) (Figure 14.4.1.1; Appendix 16.2.5.2). While one possible explanation would be that the 10-minute and 30-minute post-infusion samples were mislabelled at the site, this could not be verified.

Two other subjects were noted to have some minor inconsistencies in their SBC-102 serum concentration-time profiles:

- For subject 414-03002 in Cohort 1 (0.35 $mg \cdot kg^{-1}$), SBC-102 serum concentrations during the Visit 2 infusion declined to 84.46 ng/mL at 60 minutes, and then increased to 171.41 ng/mL at the end of the 2-hour infusion.
- For subject 418-07001 in Cohort 2 (1 $mg \cdot kg^{-1}$), the first measurable SBC-102 serum concentration occurred at 40 minutes during the Visit 6 infusion, whereas drug concentration was measurable by 10 minutes during the Visit 2 infusion.

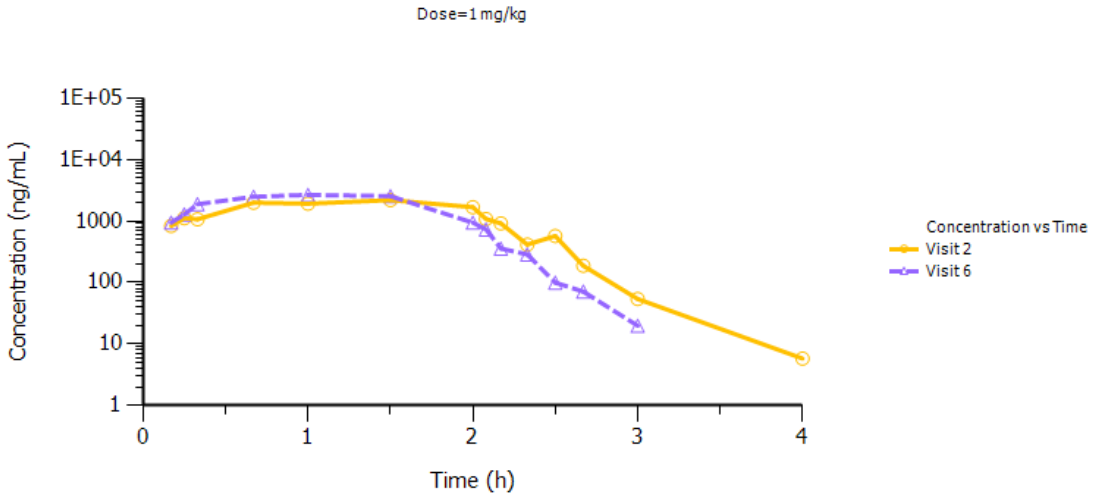
For subject 416-05001 in Cohort 2 (1 $mg \cdot kg^{-1}$), SBC-102 serum concentrations were up to 6-fold greater than those of the other 2 subjects in this dose cohort. This difference in exposure was apparent at both Day 0 and Day 21. The basis for the higher drug concentrations in subject 416-05001 is not understood. It is noted that this subject was obese and received a substantially higher dose (mg) of SBC-102 than other subjects in this cohort.

Figure 1: Mean SBC-102 Serum Concentration-Time Profile Following a Dose of 0.35 mg·kg^{-1} via a 2-Hour Infusion



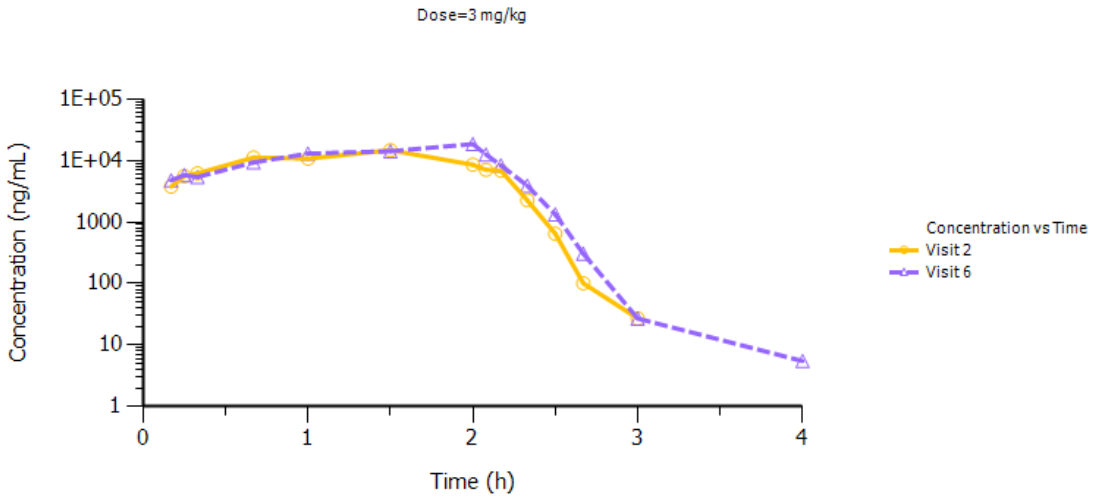
Source: Table 14.4.1

Figure 2: Mean SBC-102 Serum Concentration-Time Profile Following a Dose of 1 mg·kg^{-1} via a 2-Hour Infusion



Source: Table 14.4.1

Figure 3: Mean SBC-102 Serum Concentration-Time Profile Following a Dose of 3 mg·kg^{-1} via a 2-Hour Infusion



Source: Table 14.4.1

10.2 SBC-102 Pharmacokinetic Parameters

Table 7 summarizes the derived PK parameters for SBC-102, by dose cohort, after the first infusion (Day 0) and the fourth and final infusion (Day 21). Following IV infusion over 2 hours, SBC-102 was rapidly eliminated from the systemic circulation. Within each dose cohort, $t_{1/2}$ was reasonably consistent after the first and fourth infusions of SBC-102. Across dose cohorts, $t_{1/2}$ was longer for the 0.35 mg·kg^{-1} dose compared with the other 2 doses. At Day 21, the respective median $t_{1/2}$ values at 0.35 mg·kg^{-1}, 1 mg·kg^{-1}, and 3 mg·kg^{-1} were 0.78 hours, 0.11 hours, and 0.13 hours, respectively.

There was a reasonably dose-proportional increase in exposure from 0.35 mg·kg^{-1} to 1 mg·kg^{-1} based on median values for $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}\infty)}$, and C_{max} after both the first and fourth infusions of SBC-102 (Table 14.4.2).

A greater than dose-proportional increase in exposure was observed from 1 mg·kg^{-1} to 3 mg·kg^{-1}. This 3-fold increase in dose resulted in an approximate 10-fold increase in exposure based on the median for AUC and C_{max}. This observation was consistent after both the first and fourth infusions of SBC-102.

There was a small, though pharmacokinetically unimportant and dose-independent, increase in AUC from Day 0 to Day 21, with no evidence of accumulation in the pre-infusion sample at Day 21. The mean increase in $AUC_{(0\text{-last})}$ was 13.4%, 16.9% and 13.6%, respectively, at SBC-102 doses of 0.35 mg·kg^{-1}, 1 mg·kg^{-1}, and 3 mg·kg^{-1}.

Serum clearance of SBC-102 was similar at doses of 0.35 $mg \cdot kg^{-1}$ and 1 $mg \cdot kg^{-1}$, with median values ranging from 541.22 to 916.17 mL/h/kg, and was around 4- to 5-fold lower at the 3 $mg \cdot kg^{-1}$ dose.

The apparent volume of distribution (V_z) decreased with increasing dose. The estimated median V_z was higher at 0.35 $mg \cdot kg^{-1}$ compared with the other dose cohorts. A marked decrease in V_z was also apparent between Day 0 and Day 21 for the 0.35 $mg \cdot kg^{-1}$ and 1 $mg \cdot kg^{-1}$ dose cohorts, with respective decreases of 47% and 54%.

Table 7: Summary of SBC-102 PK Parameters After the First (Day 0) and Fourth (Day 21) 2-Hour Intravenous Infusions of SBC-102

Infusion (Study Day)	Dose ($mg \cdot kg^{-1}$)	Statistic	C_{max} (ng/mL)	$AUC_{(0\text{-last})}$ (ng·h/mL)	T_{max} (h)	$t_{1/2}$ (h)	V_z (mL/kg)	CL (mL/h/kg)
Infusion 1 (Day 0)	0.35	N	3	3	3	3	3	3
		Min	262.41	440.61	0.33	0.60	454.69	523.57
		Median	369.93	448.92	0.67	1.37	1489.02	722.06
		Max	717.75	663.03	1.58	3.51	3652.86	754.74
	1.00	N	3	3	3	3	3	3
		Min	561.09	846.10	1.00	0.11	48.10	121.13
		Median	835.85	1090.70	1.00	0.11	151.87	916.17
		Max	5483.84	8253.56	1.50	0.28	182.67	1180.28
	3.00	N	3	3	3	3	3	3
		Min	9080.49	12796.33	1.50	0.10	16.07	110.97
		Median	15026.64	22029.84	1.50	0.13	25.83	136.15
		Max	19903.53	27029.03	1.50	0.24	78.07	228.89
Infusion 4 (Day 21)	0.35	N	3	3	3	3	3	3
		Min	330.04	493.67	0.67	0.07	47.98	461.70
		Median	378.68	509.85	0.67	0.78	788.18	665.07
		Max	655.22	756.50	0.67	2.05	1963.62	699.68
	1.00	N	3	3	3	2 [a]	2 [a]	2 [a]
		Min	814.31	1026.34	1.00	0.08	21.66	108.67
		Median	1212.27	1686.73	1.25	0.11	70.01	541.22
		Max	5991.09	9197.91	1.50	0.14	118.36	973.77
	3.00	N	3	3	3	3	3	3
		Min	9615.91	16661.24	1.75	0.09	18.27	95.43
		Median	16080.29	22136.84	1.80	0.13	22.05	135.50
		Max	29612.82	31436.59	2.08	0.16	34.97	180.04

Source: Table 14.4.2
Min= minimum; Max = maximum
[a] Terminal elimination rate ($t_{1/2}$) could not be determined for subject 412-01001 at Day 21, and thus $t_{1/2}$ and other PK parameters dependent upon $t_{1/2}$ are not reported for this subject at Day 21

11 Pharmacodynamic Biomarker Results

11.1 Liver Enzymes

11.1.1 Transaminases

At baseline, ALT and/or AST were elevated (>ULN) in 6 (66.7%) subjects based on the normal ranges from the central laboratory (Appendix 16.2.6.1), including 4 subjects with elevations in both transaminases. In subjects with elevated baseline transaminases, ALT ranged from 70 to 119 (ULN = 67 U/l) and AST ranged from 52 to 69 (ULN = 50 U/l).

Following initiation of treatment with SBC-102, levels of ALT (Figure 4) and AST (Figure 5) decreased rapidly in 7 of the 9 subjects, regardless of whether their baseline levels were within or above the normal range. This reduction in ALT and AST was apparent within 2 weeks of the first infusion (i.e., by Day 14). Levels continued to decrease in most subjects through Day 28, approximately 1 week after the fourth infusion, at which time transaminases had normalized in 4 (66.7%) of 6 subjects with abnormal baseline AST levels and all 6 (100%) subjects with abnormal baseline ALT levels (Table 14.2.5.1). In the two other subjects, ALT and AST either fluctuated around baseline levels (413-02001, Cohort 1) or increased transiently and then returned to near baseline levels (416-05001, Cohort 2). Of note, subject 416-05001 had a medical history of cirrhosis, low baseline ALT and pre-treatment ALT and AST values that were notable for the variability between Screening (50 U/l and 124 U/l, respectively) and baseline (22 U/l and 67 U/l, respectively). In this subject, ALT and AST increased at Day 7 (50 U/l and 175 U/l, respectively) and then declined and were near baseline levels from Day 21 through Day 52. Although serum transaminases were not reduced in either subject 413-02001 or 416-05001, both subjects had increases in total cholesterol and triglycerides suggestive of biological activity of SBC-102 (see Section 11.2).

For all 9 subjects, the mean decreases from baseline to Day 28 were 18.2 ± 15.0 U/l (31.8% decrease) for AST and 38.7 ± 25.6 U/l (43.1% decrease) for ALT (Table 14.2.2.1).

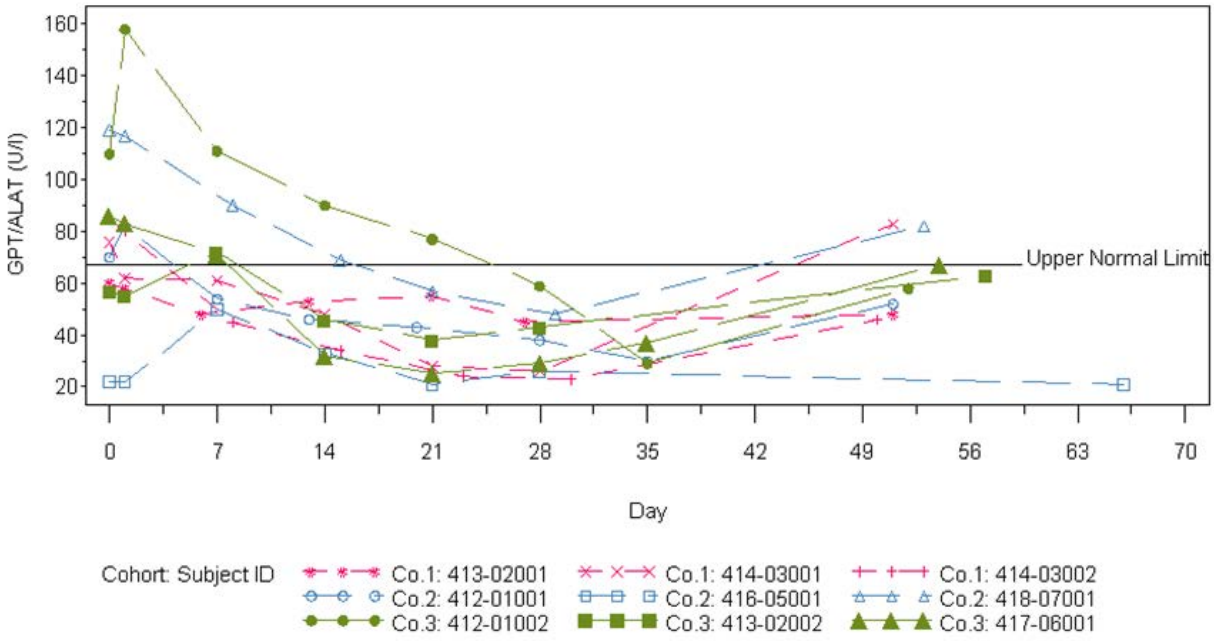
During the post-treatment follow-up period, a reversal (increase) in AST and ALT levels was observed in all 8 subjects who demonstrated an improvement (decrease) in transaminases during treatment with SBC-102 (Table 14.2.5.2; Table 14.2.2.2). By Day 52, AST and ALT were at or approaching baseline levels in all subjects (Figure 4; Figure 5).

There was no evidence of a dose-related effect in the time to onset or magnitude of the reduction in AST and ALT, or in the reversal of that effect after discontinuation of treatment (Table 14.2.5.1; Figure 4; Figure 5).

AST and ALT are listed for all subjects in Appendix 16.2.6.1. Changes and percent changes from baseline to each study time point and from Day 28 to Day 52 are summarized in Table 14.2.5.1 and Table 14.2.5.2, respectively. Shifts from baseline to each study time point and from Day 28 to Day 52 are presented in Table 14.2.2.1 and Table 14.2.2.2, respectively.

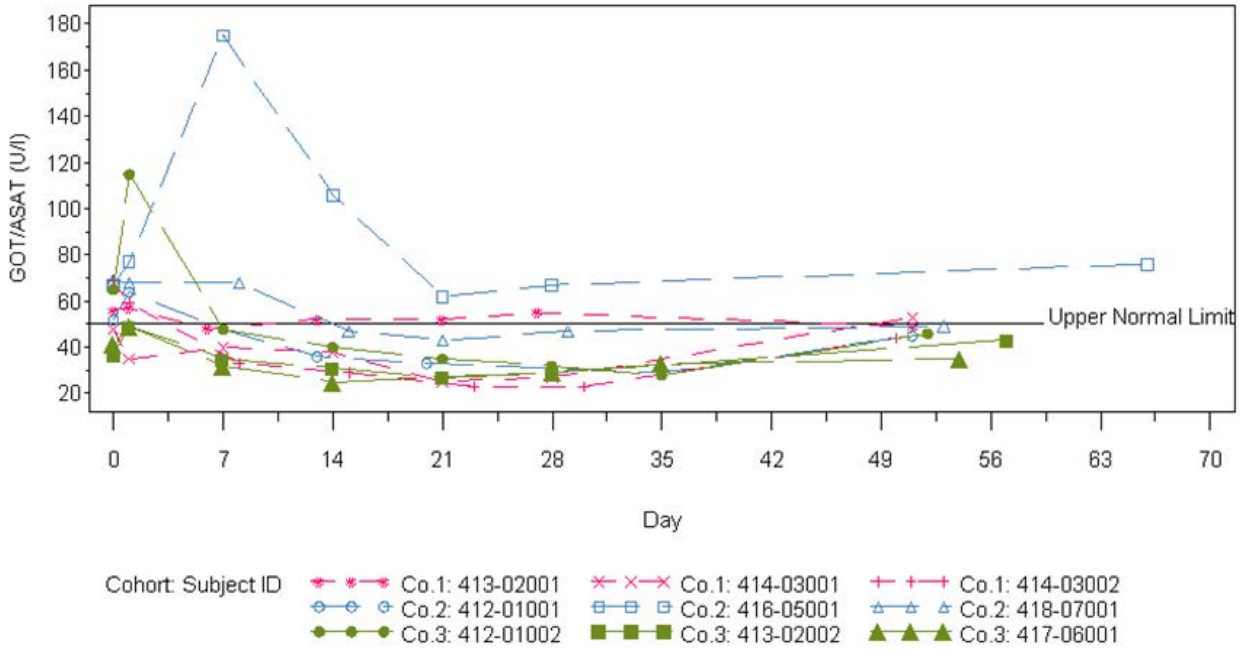
The number and percentage of subjects with abnormal transaminases is summarized by study visit in Table 14.2.1.1.

Figure 4: Individual ALT Profiles By Study Visit



Source: Figure 14.3.7.2
Note: Visit 8 was delayed for subject 416-05001 as she was unable to travel to the site.

Figure 5: Individual AST Profiles By Study Visit



Source: Figure 14.3.7.1
Note: Visit 8 was delayed for subject 416-05001 as she was unable to travel to the site.

11.1.2 GGT

At baseline, GGT was elevated in 2 subjects, who had respective levels of 203 U/l (subject 412-01002, ULN = 73 U/l [males]) and 84 U/l (subject 416-05001; ULN = 50 U/l [females]).

GGT levels declined with treatment in the one male subject who had a marked elevation at baseline (412-01002, Cohort 3), decreasing from 203 U/l at Day 0 to 96 U/l at Day 28, but remained above the normal range of 73 U/l. Subject 416-05001 (Cohort 3), who had a medical history of cirrhosis, had a transient increase in GGT from 84 U/l at baseline to 112 U/l at Day 7, after which levels trended back toward baseline. This subject also had transient increases in ALT and AST (see Section 11.1.1). For all other subjects, GGT levels were normal at baseline and were essentially unchanged during treatment, with levels at Day 28 similar to or slightly lower than those at baseline. The mean decrease in GGT from baseline to Day 28 was 16.3 ± 34.8 U/l (18.1% decrease).

GGT is listed for all subjects in Appendix 16.2.6.1. Changes and percent changes from baseline to each study time point and from Day 28 to Day 52 are summarized in Table 14.2.5.1 and Table 14.2.5.2, respectively. Shifts from baseline to each study time point and from Day 28 to Day 52 are presented in Table 14.2.2.1 and Table 14.2.2.2, respectively. The number and percentage of subjects with abnormal GGT is summarized by study visit in Table 14.2.1.1.

11.2 Serum Lipids

11.2.1 Total Cholesterol, Triglycerides and LDL

At baseline (Day 0), 7 of the 9 subjects had abnormal levels of one or more serum lipids based on the normal ranges from the central laboratory (Appendix 16.2.6.2.2). Two subjects had elevated levels of both total cholesterol (391 and 256 mg/dL [10.13 and 6.63 mmol/L]; ULN = 232 mg/dL [6.0 mmol/L]) and LDL (300 and 208 mg/dL [6.76 and 5.39 mmol/L]; ULN=162 mg/dL [4.2 mmol/L]). The other 5 subjects had high triglycerides (range: 218 to 277 mg/dL [2.46 to 3.13 mmol/L]; ULN = 199 mg/dL [2.25 mmol/L]) and/or low HDL (range: 22 to 28 mg/dL [0.57 to 0.73 mmol/L]; lower limit of normal [LLN] = 35 mg/dL [0.91 mmol/L]).

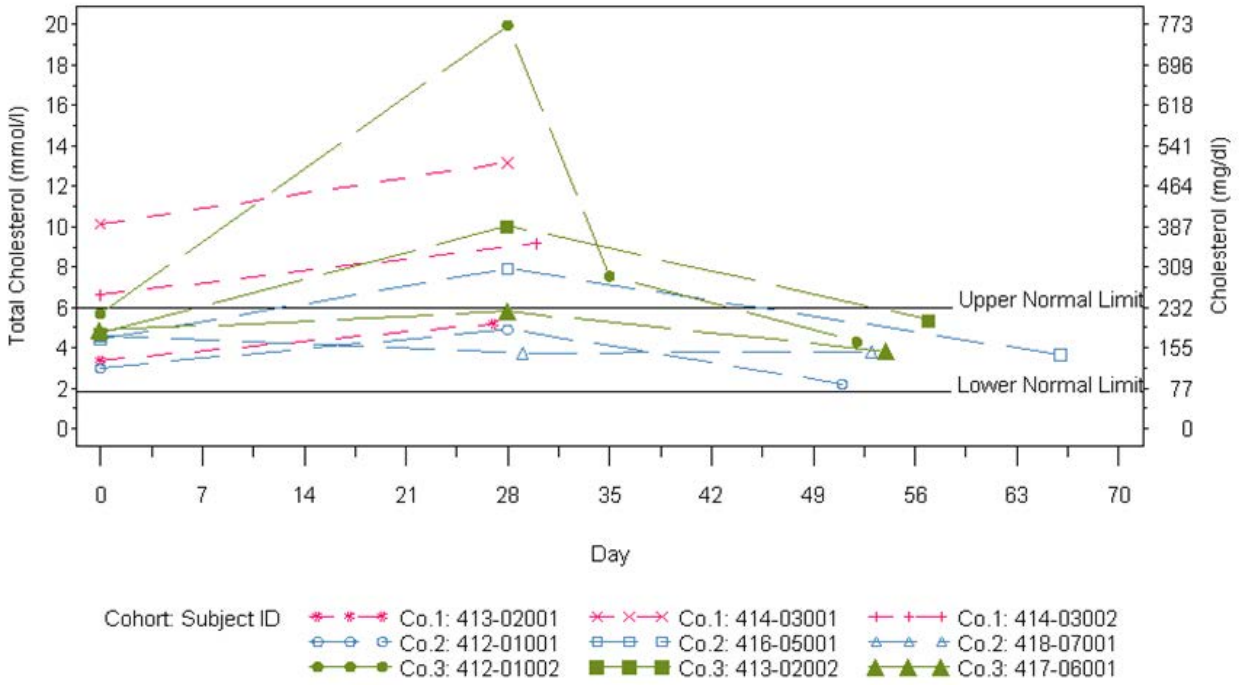
Total cholesterol, triglycerides, and LDL increased for the majority of subjects across all dose cohorts by the next assessment at Day 28, which was approximately 1 week after the fourth infusion of SBC-102. Increases in total cholesterol (Figure 6) and triglycerides (Figure 7) were observed for 8 subjects, with 7 of these subjects also having increases in LDL and 1 subject (414-03001) having no change in LDL (Figure 8) at Day 28. Shifts from normal to abnormal lipid levels were reported for 3 of 7 subjects with normal baseline total cholesterol, 1 of 6 subjects with normal baseline triglycerides, and 3 of 7 subjects with normal baseline LDL (Table 14.2.6). In one other subject (418-07001, Cohort 2) no increases were observed in total cholesterol, triglycerides, or LDL from baseline to Day 28, and all results for this subject were within normal range at each time point (Figure 6; Figure 7; Figure 8). Of note, this subject (418-07001) was the only subject in the study receiving cholestyramine.

On average, the magnitude of the increases in total cholesterol, triglycerides, and LDL was comparable in the 2 lowest dose cohorts (0.35 and 1 $mg \cdot kg^{-1}$), and more pronounced in Cohort 3 (3 $mg \cdot kg^{-1}$), as shown in Table 8. The more marked mean increases in serum lipids in Cohort 3 were due to pronounced lipid elevations in 2 of the 3 subjects in this cohort, one of whom (412-01002) had levels of total cholesterol and triglycerides at Day 28 that were reported as AEs of Grade 4 hypercholesterolemia and Grade 2 hypertriglyceridemia (see Section 9.2.2.1 for further details).

Of note, total cholesterol, triglycerides, and LDL increased during treatment with SBC-102, irrespective of whether a subject was receiving ongoing statin therapy. All 6 subjects on statin therapy (2 of whom were also receiving ezetimibe) had increases in all 3 serum lipid parameters, including the 2 subjects in Cohort 3 who had the maximum observed increases in total cholesterol and LDL (412-01002) and triglycerides (413-02002, from 80 mg/dL to 351 mg/dL [0.90 to 3.97 mmol/L]). Interestingly, one subject receiving cholestyramine and ezetimibe (418-07001) did not demonstrate increases in total cholesterol, triglycerides, or LDL during treatment with SBC-102. The other 2 subjects in the study, who were not receiving any lipid-lowering medications, had elevations in total cholesterol, triglycerides and, in one subject, LDL.

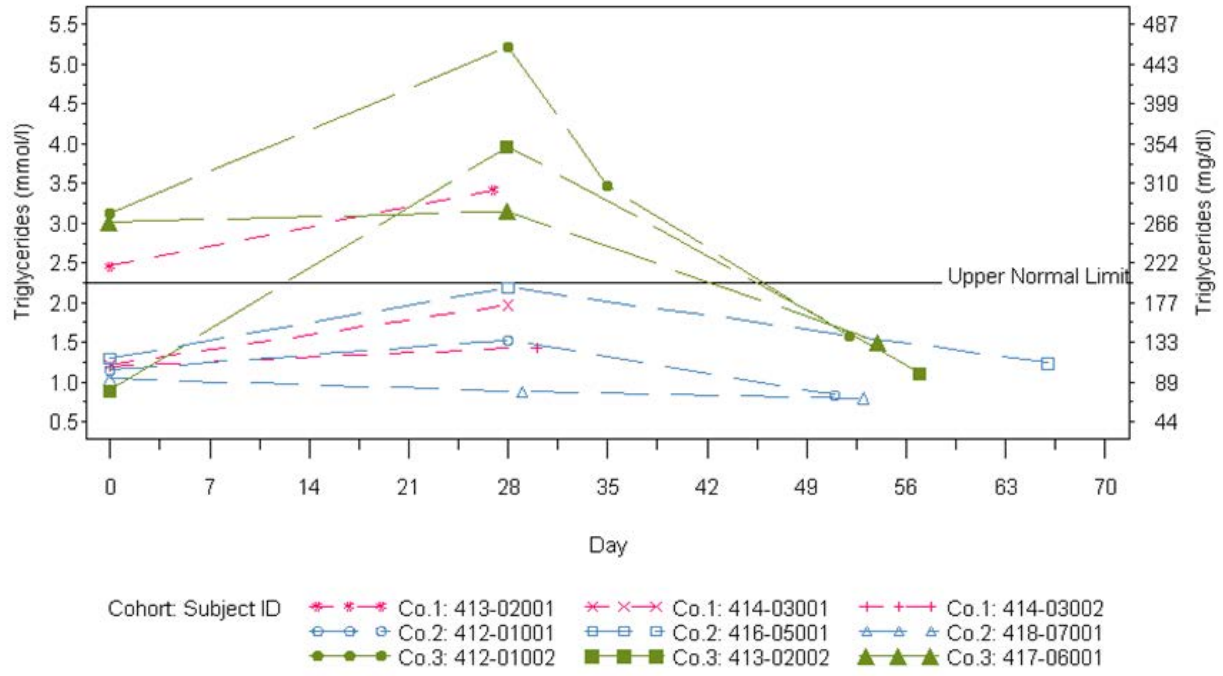
During the post-treatment follow-up period, a reversal (decrease) in total cholesterol, triglycerides, and LDL levels was observed for the 5 subjects in Cohorts 2 and 3 who had increases in these lipid parameters during treatment with SBC-102 (Figure 6; Figure 7; Figure 8; Table 14.2.6.1). By Day 52, 5 of the 6 subjects in these two dose cohorts had levels for each lipid parameter within the normal range and below their baseline values (including the one subject who had no increase in serum lipids). The one other subject (413-02002) had serum lipid levels that were approaching baseline levels and were normal for total cholesterol and triglycerides and borderline abnormal for LDL. Reversibility of the effects on serum lipids was not evaluated for subjects in Cohort 1 due to an oversight in protocol schedule of assessments, as described in Section 6.8.1.3.

Figure 6: Individual Total Cholesterol Profiles By Study Visit



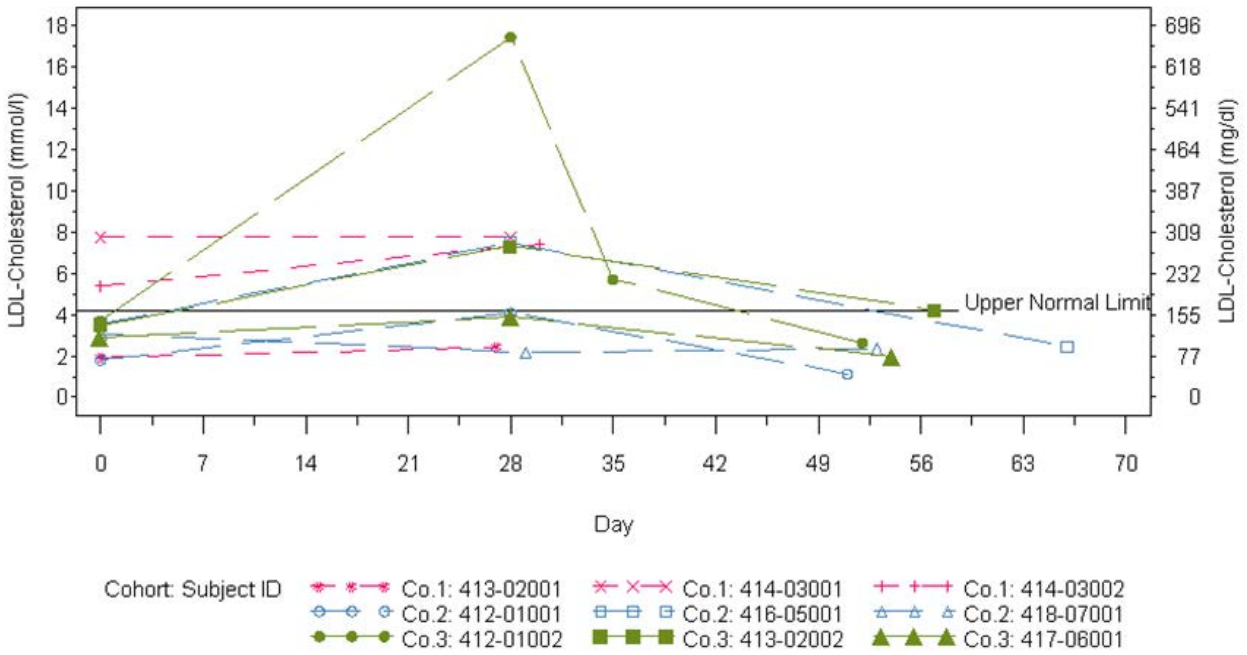
Source: Figure 14.3.7.3
Note: Visit 8 was delayed for subject 416-05001 as she was unable to travel to the site.

Figure 7: Individual Triglyceride Profiles By Study Visit



Source: Figure 14.3.7.6
Note: Visit 8 was delayed for subject 416-05001 as she was unable to travel to the site.

Figure 8: Individual LDL Profiles By Study Visit



Source: Figure 14.3.7.5
Note: Visit 8 was delayed for subject 416-05001 as she was unable to travel to the site.

Table 8: Mean (SD) Changes from Baseline in Serum Lipid Parameters, by Dose Cohort, in Study LAL-CL01

	Cohort 1: 0.35 mg·kg^{-1} N=3		Cohort 2: 1 mg·kg^{-1} N=3		Cohort 3: 3 mg·kg^{-1} N=3	
	Day 28	**Day 52**	**Day 28**	**Day 52**	**Day 28**	**Day 52**
Total Cholesterol, mg/dL	95.7 (23.6)	ND[a]	58.3 (85.6)	-30.0 (0)	264.7 (263.0)	-22.3 (43.3)
Triglycerides, mg/dL	57.3 (32.9)	ND[a]	32.7 (46.5)	-18.0 (11.8)	156.3 (131.4)	-83.3 (88.7)
LDL, mg/dL	32.7 (41.2)	ND[a]	68.7 (94.5)	-32.0 (8.72)	239.0 (258.8)	-16.0 (38.2)
HDL, mg/dL	2.3 (6.11)	ND[a]	-1.7 (4.62)	0.3 (1.53)	-3.3 (5.03)	13.0 (0)

Source: Table 14.2.3.2
ND = not determined
Note: Mean (SD) changes from baseline, in SI units, are presented in Table 14.2.3.1.
[a] Serum lipids were not measured at Day 52 due to an oversight in the protocol schedule of assessments.

Total cholesterol, triglycerides, and LDL are listed for all subjects in SI units and conventional units in Appendix 16.2.6.2.1 and Appendix 16.2.6.2.2, respectively. Changes and percent

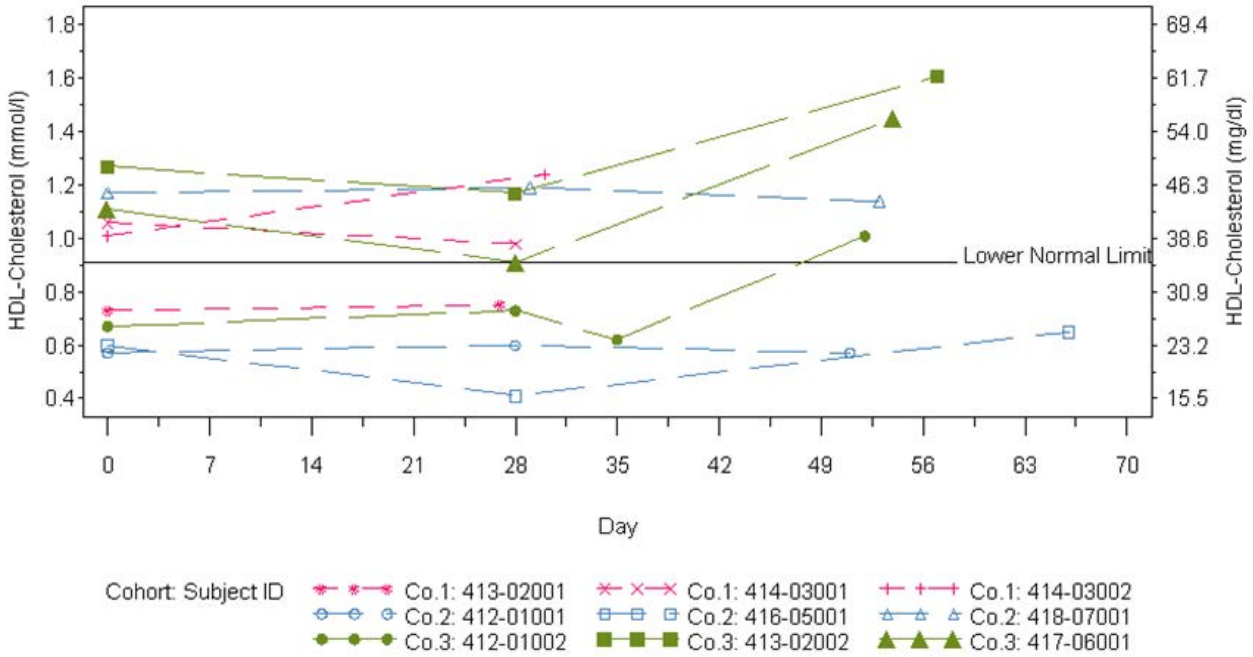
changes from baseline to each study time point are summarized in SI units and conventional units in Table 14.2.3.1 and Table 14.2.3.2, respectively. Changes and percent changes from Day 28 to Day 52 are summarized in SI units and conventional units in Table 14.2.3.1.1 and Table 14.2.3.2.1, respectively. Shifts from baseline to each study time point and from Day 28 to Day 52 are presented in Table 14.2.6 and Table 14.2.6.1, respectively. The number and percentage of subjects with abnormal serum lipids is summarized by study visit in Table 14.2.1.1.

11.2.2 HDL

HDL levels were generally stable during treatment with SBC-102, with only slight increases or decreases in individual subjects between baseline and Day 28 (range: -8 to +9 mg/dL [-0.20 to +0.23 mmol/L) (Table 14.2.3.2; Table 14.2.3.1), and no apparent dose-related trends in the direction or magnitude of changes in HDL (Figure 9).

During the post-treatment follow-up period, HDL levels increased by >25% from baseline for all subjects in Cohort 3 (3 mg·kg^{-1}), a trend that was not apparent for any subject in Cohort 2 (1 mg·kg^{-1}), including the subject who had substantially higher SBC-102 C_{max} and AUC. At Day 52, the 3 subjects in Cohort 3 had percent increases from baseline in HDL of 26.5%, 30.2%, and 50.0%, while changes in HDL ranged from -2.2% (decrease) to 8.7% for the 3 subjects in Cohort 2 (Table 14.2.3.2). Post-treatment HDL levels were not available for subjects in Cohort 1.

Figure 9: Individual HDL Profiles By Study Visit



Source: Figure 14.3.7.4
Note: Visit 8 was delayed for subject 416-05001 as she was unable to travel to the site.

HDL is listed for all subjects in SI units and conventional units in Appendix 16.2.6.2.1 and Appendix 16.2.6.2.2, respectively. Changes and percent changes from baseline to each study

time point are summarized in SI units and conventional units in Table 14.2.3.1 and Table 14.2.3.2, respectively. Changes and percent changes from Day 28 to Day 52 are summarized in SI units and conventional units in Table 14.2.3.1.1 and Table 14.2.3.2.1, respectively. Shifts from baseline to each study time point and from Day 28 to Day 52 are presented in Table 14.2.6 and Table 14.2.6.1, respectively. The number and percentage of subjects with abnormal serum lipids is summarized by study visit in Table 14.2.1.1.

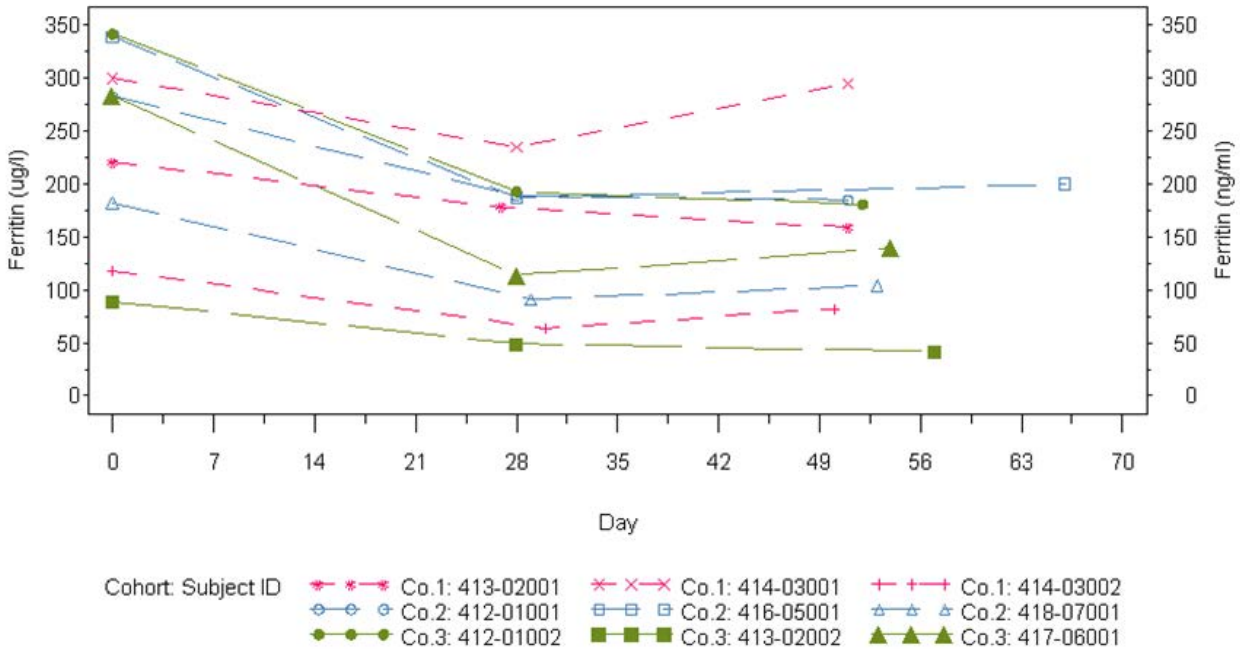
11.3 Serum Ferritin and High Sensitivity C-Reactive Protein

Baseline serum ferritin levels were normal in 8 of 9 study subjects based on the normal ranges for males (30 to 400 ng/mL) and females (13 to 150 ng/mL) provided by the central laboratory (Table 14.2.7.1; Figure 10). An abnormal (high) baseline serum ferritin of 339 ng/mL was reported for one female subject who had a complicated medical history including significant liver dysfunction (Appendix 16.2.6.3.2).

Serum ferritin decreased in all 9 subjects by the next assessment at Day 28 (Figure 10). In subject 416-05001, serum ferritin was still borderline abnormal despite a marked decrease to 187 ng/mL at Day 28. Serum ferritin levels in the other 8 subjects remained within the normal range at Day 28. Mean percent decreases in serum ferritin from baseline to Day 28 were comparable for Cohort 2 (42.7 ± 8.6%) and Cohort 3 (49.4 ± 9.0%), and appeared to be slightly greater than those for Cohort 1 (29.0 ± 14.6%) (Table 14.2.4.1.2).

No consistent trends in serum ferritin were observed during the post-treatment follow-up period (Figure 10).

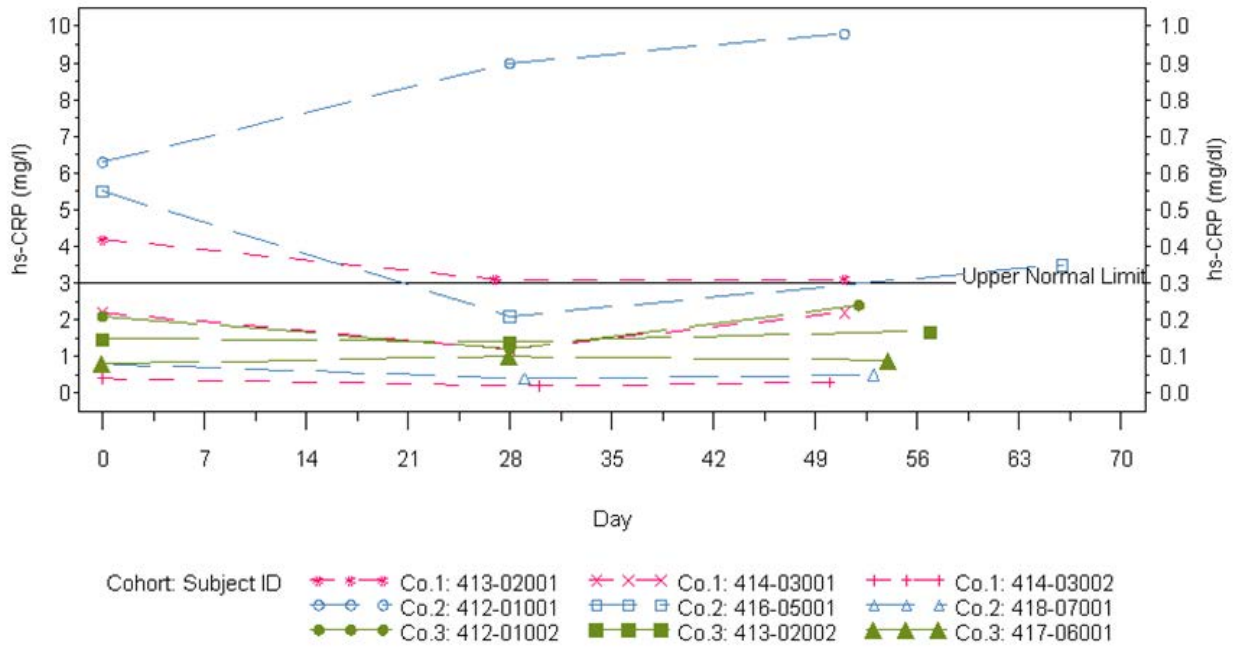
Figure 10: Individual Serum Ferritin Profiles By Study Visit



Source: Figure 14.3.7.7
Note: For female subjects 414-03002 (Cohort 1), 416-05001 (Cohort 2), and 413-02002 (Cohort 3), the normal range for serum ferritin was 13 to 150 ng/mL. Based on this normal range, serum ferritin results for subject 416-05001 remained >ULN throughout the study despite a decrease in ferritin from Day 0 to Day 28.
Note: Visit 8 was delayed for subject 416-05001 as she was unable to travel to the site.

There were no consistent trends in hsCRP in any dose cohort, either during treatment or the post-treatment follow-up period (Figure 11). Of the 3 subjects who had abnormal (high) hsCRP at baseline, decreases in hsCRP were observed in 2 subjects and an increase in hsCRP was noted in the third subject.

Figure 11: Individual hsCRP Profiles By Study Visit



Source: Figure 14.3.7.8
Note: Visit 8 was delayed for subject 416-05001 as she was unable to travel to the site.

Serum ferritin and hsCRP are listed for all subjects in SI units and conventional units in Appendix 16.2.6.3.1 and Appendix 16.2.6.3.2, respectively. Changes and percent changes from baseline to each study time point are summarized in SI units and conventional units in Table 14.2.4.1.1 and Table 14.2.4.1.2, respectively. Changes and percent changes from Day 28 to Day 52 are summarized in SI units and conventional units in Table 14.2.4.2.1 and Table 14.2.4.2.2, respectively. Shifts from baseline to each study time point and from Day 28 to Day 52 are presented in Table 14.2.7.1 and Table 14.2.7.2, respectively. The number and percentage of subjects with abnormal ferritin or hsCRP is summarized by study visit in Table 14.2.1.3.

12 Other Study Results: Patient Health Outcomes

12.1 SF-36v2

The SF-36v2 was used to provide insights on the general health status of subjects with LAL Deficiency, prior to treatment with SBC-102.

For all 9 subjects, the mean norm-based PCS score was 52.5 ± 10.0 and the mean norm-based MCS score was 43.0 ± 15.0 (Table 14.1.3.5b). The subscale scores composing each summary component were generally of similar magnitude, assuming a minimally important difference of 5 units. For MCS, mean norm-based subscale scores for vitality (46.9 ± 13.4), social functioning (44.7 ± 11.2), role-emotional (47.7 ± 12.1) and mental health (43.8 ± 11.4) were all similar to the mean norm-based MCS score 43.0 ± 15.0. For PCS, mean norm-based subscale scores for physical functioning (52.8 ± 7.9), role-physical (50.9 ± 7.9), and bodily pain (51.3 ± 9.4) were similar to the mean norm-based PCS score (52.5 ± 10.0), whereas the mean norm-based subscale score for general health (45.3 ± 7.0) was slightly lower.

As expected, there was considerable between-subject variability in pre-treatment SF-36v2 scores in this study, both for the summary scores, PCS (range: 31.3 to 61.7) and MCS (range: 13.7 to 59.0), and for each of the subscale scores (Appendix 16.2.4.5.2b).

SF-36v2 norm-based scores for summary components and subscales are listed in Appendix 16.2.4.5.2b and summarized in Table 14.1.3.5b. SF-36v2 norm-based summary scores and original 0-100 subscale scores are listed in Appendix 16.2.4.5.2 and summarized in Table 14.1.3.5.

See Section 13.1.4 for a comparison of SF-36v2 scores in subjects with LAL Deficiency with those reported for other reference populations.

12.2 CLDQ and FACIT-Fatigue

The CLDQ and FACIT-Fatigue were used to assess the impact of LAL Deficiency on a subject's overall quality of life and level of fatigue, respectively, prior to treatment with SBC-102.

For all 9 subjects, the mean total CLDQ score was 152.4 ± 26.8 (Table 14.1.3.4), and the mean total FACIT-Fatigue score was 37.4 ± 12.3 (Table 14.1.3.4). To facilitate comparison other patient populations (see Section 13.1.4), per-item CLDQ scores were computed as the average of the 29 item scores, i.e., the total score divided by 29. The mean per-item CLDQ score in subjects with LAL Deficiency was 5.26.

As expected, there was considerable between-subject variability in the pre-treatment values for the CLDQ per-item score (range: 3.7 to 6.7) and FACIT-Fatigue total score (range: 12 to 52). Despite this, there appeared to be good correlation between scores on these 2 questionnaires, as the 4 subjects with CLDQ per-item scores <5 also had the lowest total scores for FACIT-Fatigue.

FACIT-Fatigue and CLDQ scores are listed for each subject in Appendix 16.2.4.5.1, and are summarized in Table 14.1.3.4.

See Section 13.1.4 for a comparison of CLDQ and FACIT-Fatigue scores in subjects with LAL Deficiency with those reported for other reference populations.

13 Discussion and Overall Conclusions

13.1 Discussion

In this first clinical study with SBC-102 (rhLAL), 9 subjects with late onset LAL Deficiency each received 4 qw infusions of SBC-102 in sequential dose cohorts of 0.35 $mg \cdot kg^{-1}$, 1 $mg \cdot kg^{-1}$, and 3 $mg \cdot kg^{-1}$ (3 subjects per cohort).

The patient population enrolled in this study was selected for baseline liver involvement, which is a predominant clinical feature of late onset LAL Deficiency (Assmann & Seedorf, 2001). Accordingly, all subjects had baseline hepatomegaly (8 subjects) and/or ALT or AST ≥ 1.5x ULN (but <3x ULN) (2 subjects). Dyslipidemias, particularly type II hyperlipidemia and decreased HDL levels, are another common clinical manifestation of late onset LAL Deficiency and are associated with accelerated atherosclerosis (Beaudet, et al., 1977; Anderson et al., 1999; Elleder, et al., 2000). In this study, 8 of the 9 subjects had abnormal total cholesterol, triglycerides, LDL, and/or HDL at baseline. The degree and type of dyslipidemia patterns in subjects enrolled in this study were somewhat different from the classic type IIb dyslipidemia previously described in patients with late onset LAL Deficiency. Although this discrepancy may reflect confounding effects of the subjects' background lipid-lowering therapy (7 of 9 subjects were receiving at least one lipid-lowering medication) it is also possible that the lipid phenotype in this disease may be broader than that described in the medical literature.

All subjects completed treatment in this study, receiving 4 infusions of SBC-102 in their entirety at the allocated dose, and were included in the primary analysis of safety as well as all secondary and exploratory study analyses. There were no major deviations in study conduct or data analysis that would affect the validity or interpretation of the study data.

13.1.1 Safety

SBC-102 was well tolerated at all 3 doses evaluated in this study. There were no deaths or treatment-emergent SAEs, and no subject experienced an IRR or discontinued treatment due to a TEAE. Most (86.4%) TEAEs were considered unrelated to IMP, and all but one TEAE was Grade 1 (mild) or Grade 2 (moderate) in severity.

There were no clinically relevant trends in vital signs, ECG parameters, or physical examination findings. No subject developed anti-SBC-102 antibodies.

As previously noted, dyslipidemias are common in patients with LAL Deficiency, as a consequence of the body's inability to metabolize cholesteryl esters and triglycerides and disturbed lipid homeostasis. It was anticipated that initiation of SBC-102 treatment and restoration of normal lipid metabolism would cause the breakdown products of accumulated lysosomal lipids (free cholesterol and free fatty acids) to be mobilized from the tissues, leading to an increase in total cholesterol, triglycerides, and LDL. Thus, serum lipids were measured in this study, both as a safety endpoint and as a marker of biological activity.

Elevations in total cholesterol, LDL and triglycerides were observed in all 3 dose cohorts in this study, irrespective of whether subjects were receiving ongoing statin therapy, and were more pronounced at the highest dose (3 mg·kg^{-1}). The maximum observed increases from baseline occurred in 2 subjects in Cohort 3, one having the greatest increase in total cholesterol (from 220 mg/dL to 772 mg/dL [5.70 to 19.99 mmol/L]) and LDL (from 143 mg/dL to 674 mg/dL [3.70 to 17.46 mmol/L]), and the other the greatest increase in triglycerides (from 80 mg/dL to 351 mg/dL [0.90 to 3.97 mmol/L]). While the more marked elevations in serum lipids observed in these 2 subjects may be dose-related, the possibility of genetic differences in the regulation of serum lipid metabolism in these subjects cannot be excluded. In one of the 2 subjects, the observed increases in total cholesterol and triglycerides were considered by the Investigator to be a clinically significant worsening from baseline, and were reported as TEAEs of Grade 4 hypercholesterolemia and Grade 2 hypertriglyceridemia that were possibly related to IMP. Of note, while the elevation in total cholesterol was assessed as a Grade 4 event based on the specific CTCAE cut-off for Grade 4 toxicity (total cholesterol >500 mg/dL), the Investigator, the Sponsor, and the independent Safety Committee did not consider this event to be life threatening or to require urgent intervention. Lipid levels in this subject decreased within one week and had returned to normal ranges (and below baseline levels) by Day 52, without additional medical treatment. A similar reversibility of total cholesterol, triglycerides, and LDL levels after discontinuation of SBC-102 therapy was observed for the other 4 subjects in Cohorts 2 and 3 who had increases in serum lipids during treatment (data were not available for Cohort 1). By Day 52, 5 of the 6 subjects in these 2 dose cohorts had total cholesterol, triglyceride, and LDL levels that were below those at baseline.

The elevations in total cholesterol, triglycerides, and LDL observed upon initiation of SBC-102 treatment are expected to be transient, as abnormal accumulated lipid substrate becomes depleted and normal lipid homeostasis is restored. Krivit et al reported similar transient lipid elevations in a patient with early onset LAL Deficiency following a bone marrow transplant (BMT). In this patient, total cholesterol and triglycerides peaked at 1 to 2 months post-BMT (1099 mg/dL and 1161 mg/dL, respectively) and returned to normal within 18 months (Krivit et al., 2000).

A number of medicines approved for other indications have been shown to cause hypercholesterolemia and/or hypertriglyceridemia (Henkin et al., 1992; Tziomalos, et al., 2011). In contrast to these indications however, dyslipidemia and accelerated atherosclerosis is a recognized complication of LAL Deficiency. Moreover, long-term treatment with SBC-102 is anticipated to lead to an improvement in the patients' baseline dyslipidemias. Early evidence of this was apparent at the End of Study Visit (Day 52) when increases in HDL were observed for all subjects in the 3 mg·kg^{-1} dose cohort and reductions in total cholesterol, LDL, and triglycerides to below-baseline levels were noted for 5 of the 6 subjects in Cohorts 2 and 3. Despite this potential for therapeutic benefit, sustained increase in LDL over an extended period of time remains a potential safety concern, given the association between elevated LDL and cardiovascular disease risk. Some of the impact of elevations in LDL may offset, however, by improvements in reverse cholesterol transport due to increased substrate clearance in

atherosclerotic plaque (Du et al., 2004). Acute increases in serum triglycerides would be of more immediate concern, given the association between severe hypertriglyceridemia and acute pancreatitis, particularly if triglyceride levels exceed 1,000 mg/dL (11.4 mmol/L) (Tsuang, et al., 2009). Given the findings in this study, a review of serum lipids for evidence of marked or sustained hyperlipidemias will continue to be an important component of safety monitoring and the ongoing benefit-risk assessment in longer-term clinical studies with SBC-102. With the exception of increases in total cholesterol, triglycerides, and LDL discussed above, there were no trends in any clinical laboratory parameters that presented a potential safety concern for SBC-102 treatment.

13.1.2 Pharmacokinetics

SBC-102 serum concentrations increased rapidly during the first 10 to 15 minutes of the 2-hour infusion, with a further slower increase thereafter. Median T_{max} ranged from 0.67 to 1.80 hours, and appeared to increase with increasing dose. At the end of infusion, serum concentrations fell rapidly for the 1 and 3 $mg \cdot kg^{-1}$ dose (mean $t_{1/2}$ = 0.111 to 0.166 hours). This fall was less rapid for the 0.35 $mg \cdot kg^{-1}$ dose (mean $t_{1/2}$ = 1.825 at Day 0 and 0.966 at Day 21). Decreases in the mean clearance were noted in the 3 $mg \cdot kg^{-1}$ dose cohort relative to the other dose cohorts at both Day 0 and Day 21.

SBC-102 serum concentrations were reasonably dose proportional over the 3-fold increase in dose from 0.35 $mg \cdot kg^{-1}$ to 1 $mg \cdot kg^{-1}$ based on median values for AUC and C_{max} in this limited study population. Concentrations increased in a greater than dose proportional manner (approximately 10-fold) over the 3-fold increase in dose from 1 $mg \cdot kg^{-1}$ to 3 $mg \cdot kg^{-1}$, which suggests that either binding or serum clearance mechanisms for SBC-102 may become saturated between 1 $mg \cdot kg^{-1}$ to 3 $mg \cdot kg^{-1}$.

Decreases in V_z of SBC-102 were noted with increasing dose and after multiple dosing within the 0.35 $mg \cdot kg^{-1}$ and 1 $mg \cdot kg^{-1}$ dose cohort. In both these cohorts, the reduction in V_z between Day 0 and Day 21 did not alter the subject's rank order with respect to the parameter value. This suggests that the variability in V_z may reflect inter-individual differences in a saturable distribution process (binding or uptake) of SBC-102. The appearance of saturation is more likely with increasing magnitude of dose and dosing duration.

It would be expected that changes in V_z would lead to differences in half-life between Day 0 and Day 21. With the exception of the 0.35 $mg \cdot kg^{-1}$ dose group, half-life was time- and dose-independent. The longer half-life noted following the 0.35 $mg \cdot kg^{-1}$ dose is consistent with the higher volume of distribution relative to clearance for this dose in comparison with other doses (1 $mg \cdot kg^{-1}$ and 3 $mg \cdot kg^{-1}$).

In summary, SBC-102 demonstrates pharmacokinetic characteristics consistent with a mannose receptor-mediated uptake mechanism. The absence of anti-SBC-102 antibodies means that the effect of antibody formation on the PK profile of SBC-102 could not be assessed in this study.

13.1.3 Pharmacodynamics

Observed changes in hepatic transaminases and serum lipids provide evidence of SBC-102 biological activity at all doses evaluated in this study.

ALT and AST decreased rapidly following initiation of SBC-102 treatment in all 3 dose cohorts. Eight of the 9 subjects had reduced transaminase levels within 1 to 2 weeks of treatment initiation. After 4 qw infusions, the mean decreases from baseline in ALT and AST in the overall study population were 38.7 U/l (41.1%) and 18.2 U/l (31.8%), respectively. There was no evidence of dose-dependence in the time to onset or magnitude of effect. Importantly, transaminases had normalized in all 6 subjects with baseline ALT levels >ULN and in 4 of 6 subjects with baseline AST levels >ULN. In addition to providing evidence of SBC-102 biological activity, the reductions in hepatic transaminases observed in this study provide supportive evidence that substrate reduction alleviates the hepatic abnormalities associated with LAL Deficiency. This is premised on the observed concordance between reductions in serum transaminases and improvements in hepatic steatosis and hepatosplenomegaly in a homozygous rat model of LAL Deficiency (Leavitt, et al., 2011).

Elevations in total cholesterol, triglycerides, and LDL were also observed in all 3 dose cohorts during the study treatment period (Day 1 to Day 28). As previously discussed in Section 13.1.1, increases in these serum lipids are consistent with the mechanism of action of SBC-102, as abnormal lipids are mobilized from the lysosomes in affected tissues. The increases in total cholesterol, LDL and triglycerides were more pronounced at a dose of 3 $mg \cdot kg^{-1}$, with 2 of the 3 subjects in this dose cohort having the greatest observed increases in these serum lipids. Although no meaningful changes were noted in HDL levels during treatment with SBC-102, all 3 subjects in Cohort 3 showed >25% increases in HDL during the post-treatment follow-up period between Day 28 and Day 52, a trend that was not apparent at a dose of 1 $mg \cdot kg^{-1}$ (data were not available for the 0.35 $mg \cdot kg^{-1}$ dose cohort). The increases in HDL are not unexpected given the previously described relationship between decreased LAL activity and impaired expression of ATP-binding cassette transporter A1 (ABCA-1), a critical mediator in the regulation of reverse cholesterol transport and serum HDL levels (Bowden et al., 2011). The distinct lipid profile observed in Cohort 3, with the greater increases in total cholesterol, triglycerides, and LDL during the study treatment period and the >25% increases in HDL at Day 52, suggests a dose-dependent effect of SBC-102 on serum lipids.

Reversal of the SBC-102 treatment effect on ALT, AST, total cholesterol, triglycerides, and LDL was observed during the post-treatment follow-up period of this study. Reversibility was consistently observed in all subjects who had demonstrated a response to treatment and had post-treatment data, supporting the utility of these laboratory parameters as markers of SBC-102 biological activity.

This study also provides evidence to support the hypothesis that SBC-102 therapy will improve LAL Deficiency-related dyslipidemia. With time, ERT with SBC-102 is expected to restore normal lipid metabolism as the abnormal lipid accumulations are cleared. For 5 of the 6 subjects with post-treatment follow-up data, total cholesterol, triglycerides, and LDL at Day 52 were

actually lower than those at baseline, suggestive of an early improvement in dyslipidemia as a result of the clearance of some accumulated intracellular lipid during the 4-week treatment period. The increases in HDL at Day 52 in the 3 $mg \cdot kg^{-1}$ dose cohort also support an early improvement in dyslipidemia with SBC-102 therapy.

Longer term studies of SBC-102 with a larger number of subjects will be required to further characterize the time course and magnitude of the effect of SBC-102 on hepatic transaminases and serum lipids, including the potential for long-term beneficial effects on dyslipidemia, and the correlation of these changes with improvement in other clinical manifestations of LAL Deficiency.

13.1.4 Patient Health Outcomes

As is the case for many rare diseases, little is known about the effect of LAL Deficiency on the overall health and quality of life of these patients, and no systematic research has been done to date. To gain a better understanding of the patient impact of this disease, pre-treatment patient health outcomes data were collected in this study using 3 tools that have been developed to assess general health (SF-36v2), the quality of life in patients with chronic liver disease (CLDQ), and levels of fatigue due to chronic illness (FACIT-Fatigue). These data demonstrate, for the first time, the impact of LAL Deficiency on the overall health of patients.

For SF-36v2, mean norm-based MCS and PCS scores for the subjects in this study (43.0 and 52.5, respectively) suggest that, on average, the mental health of the study subjects is slightly worse than that of the general US population, while physical health is comparable to that of the general US population, assuming a minimally clinically important difference of 5 units from the US population norm (represented by a mean of 50.0) (David et al., 2009; Sloan et al., 2005). The same trend is apparent in mean norm-based subscale scores, with the exception of a lower general health subscale score (a component of the PCS) in subjects with LAL Deficiency compared to the general US population (see Table 9).

SF-36v2 mean norm-based MCS and PCS scores in subjects with late onset LAL Deficiency were also compared with those for 2 other patient populations with liver dysfunction: non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) (David et al., 2009). On average, subjects with LAL Deficiency had higher PCS scores and lower MCS scores than patients with NAFLD and NASH, as shown in Table 9.

Table 9: Comparison of Baseline SF-36v2 Mean (SD) Norm-Based Scores for Patients with LAL Deficiency (Study LAL-CL01), NAFLD, and NASH

	LAL Deficiency Study LAL-CL01 [a] (N=9)	NAFLD (N=713)	NASH (N=436)
Physical Component Summary (PCS)	52.5 (10.0)	45.2 (10.9)	44.5 (11.0)
Physical Functioning	52.8 (7.9)	45.6 (11.3)	44.9 (11.7)
Role-Physical	50.9 (7.9)	46.5 (11.6)	45.8 (11.6)
Bodily Pain	51.3 (9.4)	48.0 (11.2)	47.7 (11.2)
General Health	45.3 (7.0)	42.4 (10.8)	41.8 (10.9)
Mental Component Summary (MCS)	43.0 (15.0)	47.6 (11.0)	47.5 (10.9)
Vitality	46.9 (13.4)	44.8 (11.2)	44.4 (11.1)
Social Functioning	44.7 (11.2)	46.9 (11.6)	46.9 (11.3)
Role-Emotional	47.7 (12.1)	47.1 (12.2)	46.9 (12.1)
Mental Health	43.8 (11.4)	48.3 (10.8)	48.0 (10.7)

Source: Table 14.1.3.5b; David et al., 2009
NR = not reported
[a] Compared to the US general population, norm-based scores <50 represent worse health and norm-based scores >50 represent better health.

It should be noted that while SF-36v2 scores did not suggest a marked effect of late onset LAL Deficiency on physical health in the overall study population, 2 subjects (412-01001 and 416-05001) had scores for PCS and the 4 physical health subscales that were consistently lower (worse) than mean scores for the general US population and for patients with NAFLD and NASH. Interestingly, both of these subjects had been more recently diagnosed with LAL Deficiency (<3 years for subject 412-01001 and <1 year for subject 416-05001) and both had significant medical histories with multiple comorbidities. Conversely, although mental health was worse, on average, in subjects with LAL Deficiency compared with the general US population and patients with NAFLD or NASH, 3 subjects (414-03001, 412-01001, and 413-02002) had scores for MCS and the 4 mental health subscales that were consistently higher (better) than those of each reference population. Of note, the 2 subjects with the lowest mental health scores had medical histories significant for chronic fatigue, insomnia, and post-traumatic stress disorder (subject 413-02001) and depression, anxiety and insomnia (subject 412-01002).

For CLDQ, the mean per-item score in subjects with LAL Deficiency (5.26) was similar to that in patients with Hepatitis C (5.1 ± 1.2 for females, 5.3 ± 1.0 for males, and 5.3 ± 1.2 for patients of both genders <70 years of age) (Mahmood et al., 2008). The CLDQ mean per-item score in the subjects in this study appeared to be slightly worse (lower) than that reported for patients with NAFLD or Hepatitis B (~5.5) and noticeably worse than the mean per-item score in a healthy population (~6) based on estimation of mean per-item scores from a graphical presentation of data for these reference populations (Mahmood et al., 2008).

For FACIT-Fatigue, the mean total score in subjects with LAL Deficiency (37.4 ± 12.3) suggests that, on average, these subjects experienced more fatigue than both a general US population (mean score = 43.6 ± 9.4, n=1010) and non-anemic cancer patients (mean score = 40.0 ± 9.8, n=113), but less fatigue than anemic cancer patients (mean score = 23.9 ± 12.6, n=2292) (Cella et al., 2002).

Overall, the patient health outcomes data collected in this study suggest that late onset LAL Deficiency has an effect on general health, quality of life, and fatigue that is generally comparable to that observed in other patient populations with recognized impairment of health. While these findings are deemed exploratory, given the limited dataset (i.e., 9 subjects at a single time point) and lack of concurrent control subjects in this study, these data support the further evaluation of patient health outcomes in patients with LAL Deficiency.

13.2 Overall Conclusions

All 3 doses of SBC-102 (0.35, 1 and 3 $mg \cdot kg^{-1}$ qw) were well tolerated by the adult patients with late onset LAL Deficiency treated in this study. No safety concerns were identified that would preclude further development of SBC-102.

SBC-102 AUC and C_{max} increased proportional to dose from 0.35 to 1 $mg \cdot kg^{-1}$ and more than proportional to dose from 1 to 3 $mg \cdot kg^{-1}$.

All 3 doses of SBC-102 were biologically active, as evidenced by decreases in ALT and AST and increases in serum lipids (total cholesterol, triglycerides, and LDL), which were observed within 2 and 4 weeks, respectively, and were reversible following discontinuation of SBC-102 therapy.

Effects on serum lipids appeared more pronounced in the 3 $mg \cdot kg^{-1}$ dose cohort, whereas effects on ALT and AST appeared to be independent of dose.

The general health, quality of life, and level of fatigue in patients with late onset LAL Deficiency, prior to treatment in this study, appeared to be impaired. Patient health outcomes scores in these patients were similar to those described in other patient populations with recognized impairment of health.

14 Tables, Figures, and Graphs Referred to but Not Included in the Text

14.1 Demographic and Background Data

14.2 Efficacy Data

14.2.1 Pharmacodynamic and Questionnaire Tables

14.2.2 Pharmacodynamic Figures

14.2.3 Pharmacokinetic Tables

14.2.4 Pharmacokinetic Figures

14.3 Safety Data

14.3.1 Displays of Adverse Events

14.3.2 Laboratory and Other Safety Data

14.3.3 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

None

15 List of References

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