A PHASE I/II OPEN LABEL STUDY IN PREVIOUSLY STUDIED, SBC-103 TREATMENT NAÏVE MPS IIIB SUBJECTS TO INVESTIGATE THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS/EFFICACY OF SBC-103 ADMINISTERED INTRAVENOUSLY

Protocol Number: NGLU-CL01-T

Amendment Number: 2.0

Date of Protocol: 24 February 2016

EudraCT Number: 2015-001983-20

IND Number: IND 118402

Product: SBC-103

Sponsor: Alexion Pharmaceuticals, Inc.

[redacted]

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

APPROVAL SIGNATURE PAGE

Protocol Title:	A Phase I/II Open Label Study in Previously Studied, SBC-103 Treatment Naïve MPS IIIB Subjects to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics/Efficacy of SBC-103 Administered Intravenously
Protocol Number:	NGLU-CL01-T
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Date of Protocol:	24 February 2016

REVIEWED/APPROVED BY:

[redacted]

INVESTIGATOR STATEMENT

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects. This study may be terminated at any time by the Sponsor, with or without cause.

I agree to personally conduct and supervise this investigation at my institution and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical, and scientific principles that justify medical research. The study will be conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of subjects.

I will ensure that the requirements relating to Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval are met. I will provide the Sponsor with any material that is provided to the IRB/IEC for ethical approval.

I agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements.

I agree to promptly report to the IRB/IEC any changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB/IEC and Sponsor approval, except where necessary to ensure the safety of study subjects.

Investigator Name	Investigator Signature	Date

Investigational Site or Name of Institution

CLINICAL STUDY SYNOPSIS

Protocol Title	A Phase I/II Open Label Study in Previously Studied, SBC-103 Treatment Naïve MPS IIIB Subjects to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics/Efficacy of SBC-103 Administered Intravenously
Protocol Number	NGLU-CL01-T
EudraCT Number	2015-001983-20
IND Number	IND 118402
Objectives	**Primary Objective** To evaluate the safety and tolerability of intravenous (IV) administration of SBC-103 in previously studied, SBC-103 treatment naïve subjects with mucopolysaccharidosis III, type B (MPS IIIB, Sanfilippo B) who participated in the NGLU-CL01 study. The NGLU-CL01 study was a non-interventional study that evaluated structural brain abnormalities and blood brain barrier (BBB) integrity by magnetic resonance imaging (MRI) and cerebrospinal fluid/serum albumin index (CSF-AI). **Secondary Objectives** • To characterise the pharmacokinetic (PK) profile of SBC-103 administered IV. • To determine the effects of dosing with SBC-103 administered IV on the levels, onset, and magnitude of changes in levels of total heparan sulphate (HS) in cerebrospinal fluid (CSF), serum, and urine. • To evaluate the pharmacodynamics (PD)/efficacy of treatment with SBC-103 administered IV as measured by neurocognitive and developmental function, changes in brain structure, and BBB integrity. • To evaluate change from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period) in the following where available: clinical laboratory tests including HS in CSF, in serum, and in urine, electrocardiograms (ECGs), physical examination, vital signs, concomitant medications, neurocognitive and developmental function, brain structure, microstructural integrity, and BBB integrity. **Exploratory Objectives** • To examine the onset and magnitude of changes in biomarkers, SBC-103 concentration in CSF, MPS IIIB disease characteristics and symptoms, and quality of life (QOL) after IV administration of SBC-103. • To evaluate change in biomarkers and MPS IIIB disease characteristics and symptoms from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period).

Methodology	This study (NGLU-CL01-T) will be conducted in MPS IIIB patients who participated in the NGLU-CL01 study, a non-interventional study that evaluated structural brain abnormalities and BBB integrity by MRI and CSF-AI. All subjects enrolled in the NGLU-CL01 study were ≥ 5 years of age and had a definitive diagnosis of MPS IIIB, as determined by documented deficiency in alpha-N-acetylglucosaminidase (NAGLU) enzyme activity of < 10% of the lower limit of normal based on a historical test result from a local laboratory, or from a qualified laboratory at screening, or documented functionally-relevant mutations in both alleles of the NAGLU gene. This study is designed to evaluate the safety and tolerability of IV administration of recombinant human alpha-N-acetylglucosaminidase (rhNAGLU), referred to here as SBC-103, for the treatment of MPS IIIB. Following completion of screening assessments to confirm study eligibility, up to 5 subjects will be treated with 1 mg/kg IV for a minimum of 12 weeks. After 12 weeks of treatment, review of safety and PD data will be conducted to determine whether it is appropriate to escalate the dose to 3 mg/kg. The dose escalation decision will be made individually for each subject based on data from that subject and with consideration of any other available data on SBC-103. Each subject will be administered SBC-103 by IV infusion once every other week (qow) for a total duration of up to 3 years (156 weeks). Safety, PK and PD/efficacy assessments will be performed in all subjects. All subjects will be monitored in an in-patient setting for safety and tolerability for 24 hours following the first dose of SBC-103. **Criteria for continued dosing after the first dose and for dose escalation after 12 weeks of treatment** The decision to **continue dosing in each subject** will be made by the Sponsor in consultation with the Principal Investigator (PI) after review of 24-hour safety data from that subject and available safety data from all other treated subjects in the SBC-103 program. The decision to **escalate to the 3 mg/kg dose in each subject** will be made by the Sponsor in consultation with the PI based on safety, tolerability and PD data after 12 weeks of treatment on 1 mg/kg and with consideration of any other available data on SBC-103. Additional dose modifications (including reductions in dose) may be considered by the Sponsor after consultation with the PI, based on review of safety, tolerability, and response to treatment data. Dose frequency (e.g., weekly) modifications may be considered by the Sponsor after consultation with the Safety Review Committee (SRC) and PI, based on a review of safety, tolerability, and response to treatment data.

	With the intent of treating subjects with the lowest dose that is safe and tolerable and which has potential for efficacy, dose modification (either an increase to 3 mg/kg or a decrease to 0.3 or 1 mg/kg) may be proposed for individual subject(s) during the study following ongoing evaluation of safety and tolerability data as well as biomarker and response to treatment data. Safety and efficacy assessments will be conducted at regular intervals throughout the study and will include, but not be limited to, blood samples for PK analysis and blood and CSF samples for biomarkers. At least 4 weeks after a subject's last dose of SBC-103 is administered in this protocol, the subject (or the subject's parent or caregiver) will receive a follow-up phone call to assess adverse events (AEs) and concomitant medications unless the subject has a scheduled follow-up study visit. During the study the SRC or Sponsor may request a pause in dosing in individual, multiple, or all subjects based on review of reported events and available data. Dosing will resume only after the review of data and agreement to do so by the PI, Sponsor, and SRC.
Study Duration	The total duration of the study is approximately 164 weeks. This will include a Screening period that may last up to 4 weeks, treatment period that will last up to 156 weeks, and a 4-week follow-up period after the last dose is administered.
Study Centres	One centre is expected to participate in this study.
Number of Subjects Planned	Up to 5 subjects are expected to participate in this study.
Inclusion and Exclusion Criteria	**Inclusion Criteria** A subject who meets <u>all</u> of the following inclusion criteria will be eligible to participate in this study: 1. Previous participation in the NGLU-CL01 study. 2. Subject consents or subject's parent or legal guardian (if applicable) grants consent for the subject to participate in the study and provides informed consent prior to any study procedures being performed. If the subject is of minor age; he/she is willing to provide assent where required per local regulations, and if deemed able to do so. 3. Female subjects who are of childbearing potential at the time of consent or who become of childbearing potential during participation on study (a) must have a negative urine pregnancy test at Screening, (b) cannot be breast feeding, and (c) must use a highly reliable method of birth control (expected failure rate less than 5% per year) for the duration of the study and for 30 days after last dose of SBC-103. Women may be considered of non-childbearing potential if they have not started their menses or are surgically sterile (i.e. hysterectomy, bilateral salpingectomy or bilateral oophorectomy).

	4. Male subjects must use a highly reliable method of birth control (expected failure rate less than 5% per year) during any sexual contact with females of childbearing potential while participating in the study and for 30 days following discontinuation from this study even if he has undergone a successful vasectomy. 5. Willingness and ability to comply with protocol requirements to the extent that may be expected of a subject with cognitive impairment. **Exclusion Criteria:** A subject who meets <u>any</u> of the following exclusion criteria will be ineligible to participate in this study: 1. Received treatment with gene therapy at any time, or any investigational drug (including high dose genistein > 150 mg/kg/day) or device intended as a treatment for MPS IIIB within 30 days prior to Screening, or is currently being treated in another study that involves an investigational drug or device. 2. Has any internal or non-removable external metal items that may present a safety risk for study assessments that utilise magnetic fields, or any other medical condition or circumstance in which an MRI is contraindicated according to local institutional policy. 3. Previous hematopoietic stem cell or bone marrow transplant. 4. Known or suspected hypersensitivity to anaesthesia or the use of a sedative is contraindicated for any other reason. 5. History of poorly controlled seizure disorder. 6. A bleeding disorder, or any other medical condition or circumstance in which a lumbar puncture (for collection of CSF) is contraindicated according to local institutional policy. 7. Known hypersensitivity to eggs. Subjects at high risk for food allergy that may include eggs should be tested according to local guidelines. 8. Other medical conditions or comorbidities (e.g., alanine aminotransferase or aspartate aminotransferase > 3x the upper limit of normal, confirmed by repeat testing, analysed locally and based on the standardised reference range provided in the laboratory manual), or other markers of clinically significant liver dysfunction (e.g. elevated bilirubin, [with the exception of subjects with confirmed Gilberts Disease] confirmed by repeat testing, or elevated prothrombin time/international normalised ratio confirmed by repeat testing analysed locally and based on the standardised reference range provided in the laboratory manual) which in the opinion of the Investigator, in consultation with the Sponsor, would interfere with study compliance, or confound data interpretation.

Investigational Product, Dose, Route, Regimen	SBC-103 is rhNAGLU manufactured using transgenic *Gallus,* which produce rhNAGLU in egg white. **Dosing Schedule** The study will consist of open-label dosing of 1 mg/kg administered by IV infusion once qow for at least 12 weeks. After evaluation of 12 week safety, tolerability and PD data in individual subjects a dose increase to 3 mg/kg may be implemented. Subsequent modifications to the dosing schedule, or dose increases or decreases, may be considered by the Sponsor, after consultation with the PI, for each subject throughout the study based on a review of safety, tolerability, and PD data for that subject and other available safety data from the SBC-103 program. Infusions will be administered every 14 days ± 5 days and must be administered at least 10 days apart.
Reference Therapy	There is no standard reference therapy against which the investigational product is being compared.
Criteria for Evaluation – Primary Endpoint	**Primary Endpoint** The primary endpoint of this study is safety and tolerability of SBC-103 in subjects with MPS IIIB. The safety assessments will include the following: • Incidence of AEs, serious adverse events (SAEs), and infusion-associated reactions (IARs). • Changes from baseline in clinical laboratory tests (haematology, serum chemistry, and urinalysis) and CSF findings (cell counts, glucose, and protein). • Changes from baseline in 12-lead ECGs. • Changes in vital signs during and post-infusion, relative to pre-infusion values. • Physical examination findings. • Use of concomitant medications/therapies. • Incidence of anti-drug antibodies (ADAs), including seroconversion rate, time to seroconversion, and ADA titre by time point, peak ADA titre, and ADA titre status (positive/negative), and the effect of ADAs on the safety of SBC-103, including the relationship between ADA-positive subjects and the incidence of IARs.

Criteria for Evaluation – Secondary and Exploratory Endpoints	**Secondary Endpoints**
	The secondary endpoints of this study are:
	• PK profile of SBC-103 after single and multiple doses as measured by:
	  • Serum maximum concentration (C_{max}).
	  • Time to maximum concentration (T_{max}).

	• Area-under-the-concentration-time curve extrapolated to infinity (AUC_{∞}). • Half-life ($T_{1/2}$). • Clearance (Cl). • Apparent volume of distribution at steady state (V_{ss}). • Onset and magnitude of changes in levels of total HS in CSF, serum, and urine following dosing with SBC-103 administered IV. • Change from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period) in CSF, serum, and urine HS in the absence of treatment. • Changes from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period) in the following: • Clinical laboratory tests (haematology, serum chemistry, and urinalysis) and CSF findings (cell counts, glucose, and protein). • 12-lead ECGs. • Vital signs. • Physical examination. • Use of concomitant medications/therapies. • Change in neurocognitive and developmental function during the NGLU-CL01-T study (on treatment), as determined by Vineland Adaptive Behavior Scales, Second Edition (Vineland-II). • Change in neurocognitive and developmental function from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period), as determined by Vineland-II. • Change in neurocognitive and developmental function during the NGLU-CL01-T study (on treatment) as determined by the subject's age-appropriate scores, the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) or Kaufman Assessment Battery for Children, Second Edition (KABC-II), Bruininks-Oseretsky Test of Motor Proficiency, Second Edition, Brief Form (BOT-2 Brief Form), and Children's Communication Checklist, Second Edition (CCC-2). • Changes in brain structure, as measured by the relative proportion of grey and white matter volume, and indices of microstructural integrity, as assessed by MRI of the brain, during the NGLU-CL01-T study (on treatment). • Changes in brain structure, as measured by the relative proportion of grey and white matter volume, and indices of microstructural integrity, as assessed by MRI of the brain, from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period).

	• Changes in BBB integrity during the NGLU-CL01-T study (on treatment), as determined by CSF-AI.
	• Changes in BBB integrity from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period), as determined by CSF-AI.
	Exploratory Endpoints
	Onset and magnitude of changes in biomarkers, SBC-103 concentration in CSF, MPS IIIB disease characteristics and symptoms, and QOL after administration of SBC-103:
	• Biomarkers:
	  • Change in non-reducing end (NRE) HS derivatives in CSF, serum, and urine.
	  • Changes in serum ferritin and chitotriosidase.
	  • Changes in CSF disease-related biomarkers including, but not limited to, hepatocyte growth factor, calbindin D, Tau, pTau, amyloid β, albumin, immunoglobulin G (IgG), glutamic acid, and glycine.
	  • Changes in glutamic acid and glycine in relation to plasma (carrier-mediated excitatory amino acids that are markers of transport function).
	  • Changes in CSF IgG Index ([CSF/serum IgG ratio] / [CSF-AI]). CSF IgG Index is a measure of IgG synthesis within the central nervous system.
	  • Changes in inflammatory markers in serum.
	  • Changes in other blood or urine biomarkers of interest that are identified during the course of this study based on emerging data from the scientific literature or the Sponsor's MPS IIIB development program (if there is sufficient sample volume and if local regulations permit).
	• Disease characteristics and symptoms, and QOL.
	• Coarsening of facial features, as determined by Facial Dysmorphology Novel Analysis (FDNA).
	• SBC-103 concentration in CSF.
	• Changes in measures of sleep disorders or dysfunction, as assessed by the Children's Sleep Habits Questionnaire (CSHQ).
	• Changes in measures of behaviour, as determined by the Sanfilippo Behavior Rating Scale (SBRS).
	• Changes in subjective QoL measures, as determined by the Short Form Health Survey for Children (SF-10).
	• Changes in measures of caregiver QOL, as determined by the Zarit Burden Interview (ZBI) 12-item short form.

	Onset and magnitude of changes in biomarkers and MPS IIIB disease characteristics and symptoms from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period):
	• Biomarkers:
	  • Change in NRE HS derivatives in CSF, serum, and urine.
	  • Changes in serum ferritin and chitotriosidase.
	  • Changes in CSF disease-related biomarkers including, but not limited to, hepatocyte growth factor, calbindin D, Tau, pTau, amyloid β, albumin, IgG, glutamic acid, and glycine.
	  • Changes in glutamic acid and glycine in relation to plasma (carrier-mediated excitatory amino acids that are markers of transport function).
	  • Changes in inflammatory markers in serum.
	• Disease characteristics and symptoms.
	• Coarsening of facial features, as determined by FDNA.

Statistical Methods	**General Considerations** Descriptive summary statistics will be provided for baseline demographics, disease characteristics, and drug exposure (overall and by dose). Disposition including number of subjects screened, enrolled, and percentage of subjects who discontinued from the study, along with reasons for discontinuations will be tabulated and described in listings. Continuous data will be summarised using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) and, where appropriate, graphic representation and 2-sided 95% confidence interval (CI) estimates; categorical data will be summarised by number of subjects, proportions, and 2-sided 95% CI estimates where possible. The sample size of up to 5 subjects is based on clinical and not statistical consideration. The data from this study, along with data from other NGLU studies, will inform future development decisions for SBC-103. **Analysis Datasets** The Full Analysis Set (FAS), defined as all subjects for whom informed consent has been obtained, who have a confirmed diagnosis of MPS IIIB, and who have received any amount of SBC-103, will be used to summarise safety and tolerability data. Analysis will include datasets based on the following study periods: • Observational Period: the NGLU-CL01 study visit to baseline (pre-dose) of the NGLU-CL01-T study. • On-Treatment Period: baseline of the NGLU-CL01-T study to end of the NGLU-CL01-T study. • Overall Study (Observational+On-Treatment Period): the NGLU-CL01 study visit to end of the NGLU-CL01-T study.

	To facilitate the descriptive summarisation of the above described data sets, data contained in the NGLU-CL01 study database for these subjects, including medical history, demographics, concomitant medications, physical examination, safety laboratory assessments, CSF, serum, and urine HS, biomarkers, Vineland-II, and data from structural and diffusion MRI, will be copied and entered in the NGLU-CL01-T study database. On-study data from subjects in the NGLU-CL01 study for endpoints including NAGLU enzyme activity, concomitant medications, physical examination, vital signs, weight, ECG, Vineland-II, haematology, clinical chemistry, urinalysis, CSF, serum and urine HS, serum albumin, serum ferritin and chitotriosidase, plasma glutamic acid and glycine, CSF: calbindin, Tau, pTau, albumin, IgG, glutamic acid and glycine, routine analysis – cell counts, glucose and protein, and structural and diffusion MRI that are contained in the NGLU-CL01 study database will also be copied and entered in the NGLU-CL01-T study database. Also, any additional assessments (e.g., neurocognitive and developmental assessments, laboratory data including serum and urine HS, biomarker data, and concomitant medication) available in these subjects since the NGLU-CL01 study visit until baseline of the NGLU-CL01-T study will be copied and entered in the NGLU-CL01-T database. All available observational period data from subjects enrolled in the NGLU-CL01 study for assessments also performed in the NGLU-CL01-T study will be copied and entered in the NGLU-CL01-T study database to facilitate analysis of changes in these assessments over the untreated and treated periods. Details of the planned analyses will be provided in the statistical analysis plan (SAP). **Safety Analysis** Descriptive statistics will be computed for safety parameters as per FAS, as appropriate. Number and percentage of subjects who discontinued from the study because of AEs, will be tabulated across doses; severity and frequency of AEs and SAEs will also be tabulated across doses. All other safety data will be provided in listings. Baseline (as described above), within study, end-of-study, and change from baseline in physical examination findings, ECG, clinical laboratory values, and vital signs will be summarised by dose. The number and proportion (percentage) of subjects with measurable antibodies to SBC-103 will be displayed. In addition, incidence of IARs will be tabulated by dose and overall. Medications to treat IARs, including any pre-treatment medications, will also be presented by dose and for the entire study period. SBC-103 infusions in which the rate was slowed or discontinued due to IARs will be detailed in a separate data listing. Additional statistical evaluations may be carried out for select endpoints, if warranted. All baseline and safety data collected during the study will be included in subject listings.

	Pharmacokinetic Analysis PK analysis will be performed using non-compartmental analysis method. Graphs of PK concentration over time will be generated for each subject and also for all subjects by dose group. Serum PK parameter (C_{max}, T_{max}, AUC_{∞}, $T_{1/2}$, Cl and V_{ss}) assessments will be summarised descriptively for each subject, as well as for each dose group, using non-compartmental analysis method. SBC-103 concentration in CSF will be summarised at available time points. Additional analysis of PK data, including assessment of the impact of ADA, may be performed as appropriate. Further details will be provided in the PK section of the SAP or in a separate clinical pharmacology analysis plan. **Pharmacodynamic/Efficacy Analyses** Parameters describing total HS and exploratory disease-related biomarkers including NRE HS derivatives, will be provided in listings and may be tabulated as described previously. Parameters describing disease characteristics and symptoms, and QOL of subjects with MPS IIIB, including neurodegeneration (MRI), CSF-AI, neurocognitive and QOL (Vineland-II, BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, SF-10, ZBI 12-item) will be provided in listings and may be tabulated as appropriate. Pharmacodynamic, disease characteristics and symptoms, and QOL outcomes analyses will be performed for the FAS. Observed measurements and changes or percent changes from baseline in HS and NRE HS derivatives and disease-related biomarkers will be summarised overall and by dosing regimen for each time point. Change in relative proportion of grey and white matter volume and microstructural integrity will be summarised descriptively. Scores and changes from baseline in neurocognitive function, disease characteristics and symptoms, and QOL questionnaires will be summarised by time point. Graphs of actual values and changes over time may be created as appropriate. Parameters describing facial features of subjects with MPS IIIB will be provided in listings and may be tabulated as appropriate. Further details of the pre-specified analyses will be provided in the SAP. **Summaries of Data Prior to Study Completion** Interim data may be summarised for presentation to Regulatory Authorities or to the scientific community to facilitate development of SBC-103. Details of the pre-specified statistical analyses will be provided in a separate SAP.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{∞}	Area-under-the-concentration-time curve extrapolated to infinity
BBB	Blood brain barrier
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency, Second Edition
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
CCC-2	Children's Communication Checklist, Second Edition
CFR	Code of Federal Regulations
CI	Confidence interval
Cl	Clearance
C_{max}	Maximum concentration
CNS	Central nervous system
CRF	Case report form
CSF	Cerebrospinal fluid
CSF-AI	Cerebrospinal fluid/serum albumin index
CSHQ	Children's Sleep Habits Questionnaire
CSR	Clinical study report
ECG	Electrocardiogram
ERT	Enzyme replacement therapy
EU	European Union
FAS	Full Analysis Set
FDNA	Facial Dysmorphology Novel Analysis
FIH	First-in-human
GAG	Glycosaminoglycan
GCP	Good Clinical Practice
HED	Human equivalent dose
HGF	Hepatocyte growth factor
HS	Heparan sulphate
IAR	Infusion-associated reaction
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgE	Immunoglobulin E

Abbreviation	Definition
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International normalised ratio
IRB	Institutional Review Board
IT	Intrathecal
IV	Intravenous(ly)
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LLN	Lower limit of normal
LSD	Lysosomal storage disorder
M6PR	Mannose-6-phosphate receptor
MMR	Macrophage mannose receptor
MPS	Mucopolysaccharidoses
MPS I	Mucopolysaccharidosis I
MPS II	Mucopolysaccharidosis II
MPS IIIB, Sanfilippo B	Mucopolysaccharidosis III, type B
MRI	Magnetic resonance imaging
NAGLU	Alpha-N-acetylglucosaminidase
NOAEL	No-observed-adverse-effect level
NRE	Non-reducing end
NVI	Non-verbal index
PAD	Pharmacologically active dose
PD	Pharmacodynamic(s)
PET	Positron emission tomography
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT	Prothrombin time
QOL	Quality of life
qow	Every other week
qw	Once every week
rhNAGLU	Recombinant human alpha-N-acetylglucosaminidase
SAE	Serious adverse event
SAP	Statistical analysis plan
SBRS	Sanfilippo Behavior Rating Scale
SF-10	Short Form Health Survey for Children
sMRI	Structural magnetic resonance imaging
SOA	Schedule of Assessments

Abbreviation	Definition
SRC	Safety Review Committee
$T_{1/2}$	Half-life
T_{max}	Time to maximum concentration
ULN	Upper limit of normal
US	United States (of America)
Vineland-II	Vineland Adaptive Behavior Scales, Second Edition
V_{ss}	Apparent volume of distribution at steady state
ZBI	Zarit Burden Interview 12-item short form

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1 INTRODUCTION

This document is a protocol for a human research study. This study will be conducted according to Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and the ethical principles underlying European Union (EU) Directives 2001/20/EC and 2005/28/EC; the United States (US) Code of Federal Regulations (CFR), Title 21, Parts 50 and 312 (21 CFR 50, 21 CFR 312); and all applicable government regulations and institutional research policies and procedures.

1.1 Background

1.1.1 Mucopolysaccharidosis Type IIIB

The mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders (LSDs) caused by a deficiency of enzymes catalysing the degradation of glycosaminoglycans (GAGs, also known as mucopolysaccharides). The majority of LSDs share a propensity for a chronic and progressive disease course with multi-system involvement, although each MPS may present with unique clinical features (Neufeld, 2012, *The Metabolic and Molecular Bases of Inherited Disease*). The type III MPS, referred to as Sanfilippo syndromes, are clinically very similar and demonstrate somatic complications that are commonly observed in the other MPS; however, MPS III is also characterised by severe degeneration of the central nervous system (CNS) which dominates the clinical picture (Heron, 2011, *Am J Met Genet A*; Neufeld, 2012, *The Metabolic and Molecular Bases of Inherited Disease*). The MPS III syndromes are all characterised by the accumulation of heparan sulphate (HS) due to mutations in 1 of the 4 enzymes required for the degradation of HS. Heparan N-sulfatase is deficient in type A, alpha-N-acetylglucosaminidase (NAGLU) in type B, acetyl-CoA:alpha-glucosaminide acetyltransferase in type C, and N-acetyl glucosamine 6-sulfatase in type D.

Mucopolysaccharidosis III, type B (MPS IIIB), also known as Sanfilippo B syndrome (OMIM #252920), is a very rare LSD associated with significant morbidity and mortality in affected patients. Birth prevalence estimates for MPS IIIB, based on the available literature and defined as the number of diagnosed cases per 100,000 live births over 1 year, range from 0.12 to 0.78 per 100,000 (Nelson, 1997, *Hum Genet*; Poorthuis, 1999, *Hum Genet*; Nelson, 2003, *Am J Med Genet*; Pinto, 2004, *Eur J Hum Genet*; Baehner, 2005, *J Inherit Metab Dis*; Heron, 2011, *Am J Met Genet A*). Regional variances may exist with respect to prevalence or the relative proportion of MPS IIIB to the other MPS subtypes. The disease is caused by mutations in the NAGLU gene. MPS IIIB patients typically have a normal to near-normal development during the first 2 years of life, followed by a slowing and full stagnation of development at around 3 to 4 years, and finally regression of cognitive capabilities. Patients usually become fully dependent on care early in their teenage years. Death typically occurs at the end of the second or the beginning of the third decade of life. However, as with other LSDs, a broader spectrum of disease severity may exist. An attenuated form of MPS IIIB has been described in a Dutch cohort of patients in which the progression of some disease manifestations appears to be slower, but progression still occurs with loss of functions such as speech and walking (Valstar, 2010, *J Inherit Metab Dis*; Wijburg, 2013, *Acta Paediatr*). Patients with the attenuated phenotype may have a stable intellectual disability for many years. These patients also appear to have a longer preservation of motor functions and may live into adulthood (Valstar, 2011, *Orphanet J Rare Dis*).

There are currently no safe or effective therapies for the treatment of MPS IIIB. Supportive therapies are used in an attempt to mitigate some of the effects of the disease. Options for management of clinical symptoms are limited, and include the use of CNS medications to control seizures, behavioural problems, and sleep problems.

1.1.2 Medical Rationale for Enzyme Replacement Therapy for MPS IIIB

The medical rationale of enzyme replacement therapy (ERT), and specifically the potential medical benefit of intravenously (IV)-administered recombinant enzyme for MPS IIIB, is supported by the successful use of ERT, with favourable benefit/risk profiles, to treat other LSDs. Furthermore, nonclinical data have demonstrated the benefit of substrate (HS) reduction in the CNS on CNS manifestations in LSDs, including the MPS III syndromes, and nonclinical data have also demonstrated the ability of IV-administered SBC-103, a recombinant human alpha-N-acetylglucosaminidase (rhNAGLU), to reduce substrate levels in the liver and the brain in the MPS IIIB animal model following once weekly (qw) as well as once every other week (qow) dosing. In addition, the medical rationale for additional clinical study of SBC-103 is supported by available safety, tolerability and preliminary pharmacodynamics data in the currently ongoing first-in-human (FIH) study, NGLU-CL02 (see Section 1.4).

The successful treatment of Gaucher's disease with placental glucocerebrosidase in the 1990s, with the follow-on enzyme produced by recombinant deoxyribonucleic acid technology, established the medical value and long-term safety of ERT for LSDs (Barton, 1990, *Proc Natl Acad Sci USA*; Barton, 1991, *N Engl J Med*). The scientific concepts established by these initial studies have now been extended to a broad range of disorders including: Pompe disease (van der Beek, 2006, *Acta Neurol Belg*), Fabry disease (Wilcox, 2004, *Am J Hum Genet*), MPS I (Wraith, 2004, *J Pediatr*), and MPS II (Muenzer, 2007, *Mol Genet Metabol*). As a result, there is now extensive clinical experience with long-term ERT in subjects with LSDs (Desnick, 2012, *Annu Rev Genomics Hum Genet*).

Early intervention with IV-administered ERT in other LSDs with CNS manifestations in sibling pair studies appears to modify disease progression. In MPS II, 2 siblings, aged 3 years and 4 months, respectively, initiated treatment by IV administration of the ERT idursulphase and outcomes were compared (Tajima, 2013, *Mol Genet Metab*). At the start of treatment, the older brother showed typical neurodegenerative features of MPS II, including intellectual disability. After 34 months of treatment with idursulphase, his somatic disease was stable or improved; however, he continued to decline cognitively. By comparison, after 32 months of treatment with idursulphase, his younger brother manifested only exudative otitis media, but remained free from most of the somatic features that appeared in his brother at the same age. Of relevance to considerations for MPS IIIB, although the younger brother's developmental quotient trended downward over time to just below the normal range, his intellectual disability at 3 years of age was not as severe as the brother who started treatment later.

Nonclinical studies with a variety of experimental therapeutic modalities have demonstrated that substrate reduction in the CNS in LSDs including the MPS III syndromes, is accompanied by improvements in CNS manifestations. (Kim, 2009, *Eur J Neurosci*; Ou, 2014, *Mol Genet Metab*; Higuchi, 2012, *Mol Genet Metab*). In addition, brain NAGLU enzyme levels required to maintain normal phenotype in wild type or

heterozygote carriers are substantially lower (> 50×) than enzyme activity levels in normal liver (Li, 1999, *Proc Natl Acad Sci USA*). Furthermore, nonclinical studies with SBC-103 have demonstrated that IV administration of SBC-103 following qw as well as qow dosing reduces substrate levels in both systemic tissues (liver/kidney) and in the brain in the MPS IIIB animal model (Leavitt, 2013, LDN WORLD Conference; SBC103-P013 [data on file]).

In summary, this knowledge and the precedent established for other LSDs, available safety, tolerability and preliminary pharmacodynamics (PD) data in the currently ongoing FIH study, (NGLU-CL02), provide a rationale that ERT with SBC-103 may benefit patients with MPS IIIB.

This interventional study will provide data on the effects of treatment with SBC-103, as well as observational data in the same study subjects from NGLU-CL01.

Developing a more complete understanding of the pharmacokinetics (PK), and PD/efficacy relationship of SBC-103 via this study and other studies in the SBC-103 Phase I/II program will further inform the development of SBC-103 as an ERT for MPS IIIB, a disease with devastating CNS complications.

1.2 Investigational Medicinal Product (SBC-103)

SBC-103, rhNAGLU, is manufactured using transgenic *Gallus,* produced in egg white. SBC-103 is a highly purified recombinant human enzyme intended to be used as ERT for the treatment of MPS IIIB.

The rhNAGLU transgene encodes the same amino acid sequence as reported for the native human enzyme (Weber, 1996, *Hum Mol Genet*; Zhao, 1996, *Proc Natl Acad Sci USA*). Purified rhNAGLU is a glycoprotein that contains up to 7 potential N-linked glycosylation sites. Specific glycans, including mannose-6-phosphate containing glycans, are thought to be critical for biodistribution and uptake of SBC-103 into the lysosomes of key target cells involved in pathogenesis of the disease. NAGLU catalyses the hydrolysis of N-acetylglucosamine (GlcNAc)alpha(1-4))n to (GlcNAc alpha(1 4))n-1 and 2 (acetylamino)-2-deoxy-beta-D-glucopyranose.

SBC-103 is supplied as an aqueous solution which is essentially free of visible foreign particulate matter.

1.3 Nonclinical Data

In vitro studies with SBC-103 using NAGLU-deficient human fibroblasts have demonstrated efficient mannose-6-phosphate dependent cellular uptake with correction of intracellular enzyme deficiency. In addition, mannose receptor-mediated uptake of SBC-103 by cells of macrophage lineage has also been demonstrated.

Several nonclinical studies demonstrated a reduction in total HS in NAGLU-deficient mice following qw as well as qow IV administration of SBC-103 (4 to 6 repeated doses of 0.3 to 27 mg/kg) for up to 6 weeks. The results demonstrated dose-dependency. Reductions in HS concentrations were accompanied by increases in measured NAGLU concentration. Following SBC-103 administration, clinical signs such as lethargy, and ataxia were observed. The majority of the observations occurred after the third or fourth dose. These observations were not considered to be directly related to the pharmacological effect of SBC-103. In these studies, hypersensitivity reactions, which

were sometimes fatal, were attributed to the repeat IV administration of a human recombinant protein to a heterologous species and are consistent with published literature (SBC103-P004, SBC103-P007, SBC103-P009, SBC103-P010, Hovland, 2007, *Toxicol Pathol;* Flaherty, 2012, *Toxicological Sciences;* Finkelman, 2007, *J Allergy Clin Immunol;* Khodoun, 2011, *PNAS*). Pre-treatment with diphenhydramine was used to minimise the effects, but did not completely block the reactions. This finding is consistent with the existence of two distinct pathways of anaphylaxis in mice; either by immunoglobulin E (IgE)-mediated histamine release from mast cells or by immunoglobulin G (IgG)-mediated platelet-activating factor release from macrophages (Finkelman, 2007, *J Allergy Clin Immunol).*

In the study SBC103-P010, the potential for CNS uptake and activity following IV administration of SBC-103 was evaluated in NAGLU-deficient mice. These mice were administered SBC-103 at doses of 0.3, 1, 3, 5, or 10 mg/kg qw for 4 weeks. A statistically significant decrease in HS was demonstrated in both brain and liver following IV dosing with a pharmacologically active dose (PAD; the lowest dose tested with the intended pharmacologic activity) established at a dose level of 3 mg/kg (0.075 mg dose for a 25 gram mouse) IV in the brain and 0.3 mg/kg (0.0075 mg dose) in the liver (SBC103-P010).

Several biodistribution studies were performed in rats and monkeys using ^{124}I-labelled SBC-103 and ^{89}Zr-labelled SBC-103 administered IV (SBC103-K004, SBC103-K005). All studies in the rat and monkey demonstrated IV delivery of SBC-103 to the brain and showed that the major fraction of the injected dose accumulated in the liver.

Consistent with ICH guidelines (ICH S6 [Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals] and Addendum to ICH S6 [Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6{R1}]) the potential toxicity of SBC-103 was evaluated in two species, the Sprague-Dawley rat (4 weeks) and the Cynomolgus monkey (4 weeks and 3 months). Since monkeys of 0.5 to 3 years of age correspond to a human child of 2 to 12 years (Barrow, 2007, *FDA News;* Tassisnari, 2013, *Wiley)*, and the MPS IIIB patient population includes children, juvenile Cynomolgus monkeys were studied in the 3-month toxicology study of SBC-103. The monkey is considered the most relevant species for the toxicological assessment of SBC-103.

The potential toxicity of SBC-103 was evaluated in Sprague-Dawley rats following repeated IV doses of SBC-103 (1, 3, or 10 mg/kg qw) for 4 weeks with a 2-week recovery period (SBC103-T007). Overall, the IV administration of SBC-103 qw at a dose of 10 mg/kg resulted in transient clinical observations of decreased activity, decreased muscle tone and/or prostration generally after the third and fourth doses. Microscopically, findings of minimal to mild inflammation were observed in the liver at all doses and in the heart and lungs of individual animals at 10 mg/kg. Most of these findings showed partial reversibility at the end of the recovery period. The incidence of anti-SBC-103 IgG antibodies in samples collected at study termination was 100% in SBC-103 treated animals (irrespective of the dose) and no anti-SBC-103 antibody formation was detected in any control animals. Based on the observed vascular/perivascular inflammation in the heart and lungs in the Sprague-Dawley rat, a no-observed-adverse-effect level (NOAEL) was established at a dose level of 3 mg/kg.

The potential toxicity of SBC-103 was evaluated in Cynomolgus monkeys following repeated IV doses of SBC-103 (1, 3, 10 or 20 mg/kg qw) for 4 weeks with a 2-week recovery period (SBC103-T008). There were no changes in clinical observations, macroscopic, organ weight or microscopic findings that were considered SBC-103-related. The incidence of anti-SBC-103 IgG antibodies in samples collected at study termination was approximately 80% in SBC-103 treated animals (irrespective of the dose). No anti-SBC-103 antibody formation was detected in any control animals. The administration of SBC-103 at these IV dose levels was well tolerated. Consequently, the NOAELs in this study were considered to be 10 mg/kg/dose qw and 20 mg/kg/dose qow.

The potential toxicity of SBC-103 was evaluated in juvenile Cynomolgus monkeys following repeated qw IV doses of 3 and 10 mg/kg or qow at 20 mg/kg during a 3-month dosing period with a 4-week recovery period (SBC103-T009). There were no SBC-103-related mortalities and no macroscopic, organ weight, or microscopic changes that were considered SBC-103-related. Transient clinical signs were noted but there were no correlating findings in any of the other parameters evaluated. The transient clinical signs included, but were not limited to, decreased activity, hunched posture, lying on side, abnormal gait, uncoordination, excessive scratching/cage manipulation and/or repetitive behaviour. The presence of anti-SBC-103 IgG antibodies was confirmed in 87%, 60% and 87% animals from 3 mg/kg, 10 mg/kg, and 20 mg/kg dose respectively and no animals in the control group were confirmed positive for anti-SBC-103 antibody. Antibody titres did not increase with dose level administered. Consequently, the NOAELs were considered to be 10 mg/kg/dose (qw) and 20 mg/kg/dose (qow) in this study.

Overall, the findings in two different toxicology species and data from NAGLU disease model at relevant IV doses suggest a hypersensitivity reaction to a foreign protein with some species differences. This is generally supported by the high incidence of anti-SBC-103 IgG antibodies in SBC-103 treated animals across species, and laboratory/clinical indicators of inflammation. While this is consistent with previous studies, it should be noted that nonclinical studies are not predictive of potential immunogenicity of humans (Garcia, 2007, *Mol Genet Metab*; Hemsley, 2007, *Mol Genet Metab*; McVie-Wylie, 2008, *Mol Genet Metab*; Hovland, 2007, *Toxicol Pathol*; Flaherty, *2012, Toxicological Sciences*; Finkelman, 2007, *J Allergy Clin Immunol*; Khodoun, 2011, *PNAS*; Brinks, 2011, *Pharm Res*; Ponce, 2009, *Reg Toxicol Pharmacol*). Additionally, it is important to note that high-dose IV SBC-103 resulted in microscopic findings in both the rat and Cynomolgus monkey in numerous tissues, presumably reflecting an exaggerated hypersensitivity reaction to a human protein.

Refer to the Investigator Brochure for further information regarding the nonclinical studies with SBC-103.

1.4 Clinical Data

An FIH study with SBC-103 (NGLU-CL02) is currently enrolling subjects. This study is entitled: *A Phase I/II Open Label Study in MPS IIIB Subjects to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics/Efficacy of SBC-103 Administered Intravenously (NGLU-CL02).* Approximately 9 MPS IIIB subjects (≥ 2 and < 12 years of age) will participate in the study which will investigate the safety, PK, and PD/efficacy of SBC-103 administered IV. Approximately 9 subjects will be treated, 3 subjects in each of 3 sequential dose groups (0.3, 1, and 3 mg/kg SBC-103). The total duration of the

NGLU-CL02 study is approximately 164 weeks. This includes a screening period that will last up to 4 weeks, an initial study treatment period that includes 24 weeks on therapy and a 4-week period of time off therapy (Part A), an extended treatment period that will last up to 128 weeks (Part B), and a 4-week follow-up period after the last dose is administered.

As of 30 April 2015, the NGLU-CL02 study is currently ongoing and 3 patients have been enrolled and treated with SBC-103 in each of the first 2 cohorts. The available safety data for Cohort 1 (0.3 mg/kg SBC-103) and Cohort 2 (1.0 mg/kg SBC-103) have been reviewed by the Safety Review Committee (SRC) and the Sponsor. The SRC has approved continued dosing of subjects in Cohorts 1 and 2. The available preliminary safety data from the study to date show that SBC-103 has been administered without any remarkable safety observations that have led to changes in how the product is administered or how patients are monitored for safety. Preliminary PD data show a decrease from baseline in serum HS.

In addition, there is extensive human experience with ERTs for the treatment of other LSDs including: Gaucher's, Pompe, and Fabry diseases, MPS I and II (see Section 1.1.2). While these diseases have distinct clinical manifestations and demonstrate differences in the targeting and biological effects of the ERT, there are relevant data from these studies that inform the use of investigational products in this class. Substrate reduction, as evidenced by decreases in cerebrospinal fluid (CSF) GAG levels, has been demonstrated following intrathecal (IT) dosing in MPS IIIA and MPS II in ongoing clinical studies (Breen, 2013, *ASHG*, Wijburg, 2013, *Acta Paediatr,* Wijburg, 2013, *ACMHGM,* Muenzer, 2014*, LDN poster*). No new significant safety findings have emerged to date from these studies based on publically available data. Most of the adverse events (AEs) associated with clinical use of ERTs are comprised of infusion-associated reactions (IARs), which typically occur either during, or within 2 hours following completion of the infusion. Given the propensity for IARs with ERT administration, measures have been incorporated in this protocol to minimise risk to subject safety from such events (see Section 7.1.3).

1.4.1 Assessment of Neurodegeneration by Structural and Diffusion MRI

Neurodegenerative diseases such as Alzheimer's disease, multiple sclerosis, and multiple system atrophy are characterised by slow progressive loss of neurons in the CNS, which leads to deficits in specific brain functions. Neurodegenerative diseases usually extend over a decade, and the actual onset of neurodegeneration may precede clinical manifestations by many years. MPS III is also a neurodegenerative disorder, and it shares similar characteristics with the more traditional neurodegenerative diseases.

In recent years, multimodal neuroimaging has become the most widely used approach to evaluate the pathophysiology of the diseased brain and these methods allow quantification of single or combined weight magnetic resonance imaging (MRI) parameters, to describe neurodegenerative processes. Measurement of MRI parameters sensitive to complementary tissue characteristics (e.g., volume atrophy, iron deposition, and microstructural damage) has great potential for evaluating pathological changes in neurologic/psychiatric diseases. Structural and diffusion MRI can provide indices of grey and white matter volume reductions and microstructural and white matter connection integrity, and may be used to assess neurodegeneration.

Structural magnetic resonance imaging (sMRI) obtains high resolution structural images that are useful for brain morphometry investigation. In sMRI scans, two types of brain tissue - grey matter and white matter - are clearly perceptible and distinguishable. Thus, sMRI allows for simultaneous analysis of these two tissues, which have most often been analysed separately in studies of both healthy and diseased brain (Preuss, 2005, *Schizophr Res*; Mitelman, 2007, *Neuroimage*; Hazlett, 2008, *Schizophr Res*). This is an important advance, given the complex relationship between grey and white matters. Grey matter is composed predominantly of cell bodies, while white matter is composed mainly of axons connecting cell bodies; both tissues are highly integrated within cerebral cortex and subcortical structures, and it has been proposed that spatial expansion of one could be associated with contraction of the other (Pfefferbaum, 1994, *Arch Neurol*; Cicchetti, 2006, *Ann N Y Acad Sci*). Therefore, it is reasonable to expect that morphometric changes in one tissue may result in, or be related to, disturbance of the other (Xu, 2012, *Neurol Res Int*).

Diffusion MRI is routinely employed for the diagnosis and management of stroke and other diseases (e.g., tumours, multiple sclerosis, and epilepsy). Diffusion MRI is a quantitative imaging technique that is sensitive to changes in the microstructure of tissues, meaning that it is influenced by alterations in cell packing, cell size and membrane permeability to water. Most biomarkers derived by this modality are therefore sensitive to subtle alterations in tissue structure and are good biomarker candidates for early detection of pathological changes and for monitoring subtle changes over time. Accordingly, diffusion MRI has proven useful for obtaining information about the underlying mechanisms of neurodegenerative disorders (e.g., Alzheimer's disease and other dementias, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, hereditary ataxias), and has potential utility to confirm diagnoses and predict prognoses and therapeutic response in patients with neurodegenerative disease.

A structural and diffusion MRI will, therefore, be performed at baseline to assess neurodegeneration prior to treatment with SBC-103 and will also be used as a comparison to evaluate changes after extended treatment with SBC-103. This structural and diffusion MRI, performed at baseline, will also be used as a comparison to evaluate changes from the time of the MRI performed for the NGLU-CL01 study (natural history data).

1.4.2 Assessment of Blood Brain Barrier Integrity

In addition, blood brain barrier (BBB) integrity will be assessed by calculating the CSF/serum albumin index (CSF-AI) before and after treatment with SBC-103. The BBB partly prevents proteins from peripheral blood from entering the brain and the CSF, resulting in markedly lower concentrations of proteins in CSF than in serum (Davson, 1969, *The Cerebrospinal Fluid Handbook of Neurochemistry*). Albumin in CSF originates in the serum as it is synthesised only in the liver (Fishman, 1980, *Adv Neurol*). The relationship between the concentration of albumin in CSF and serum, that is the CSF-AI, is the most common method for evaluating BBB function (Ganrot, 1974, *Clin Chem*; Tibbling, 1977, *Scand J Clin Lab Invest*). The CSF-AI performed at baseline will also be used as a comparison to evaluate changes from the time of the CSF-AI assessment performed for the NGLU-CL01 study (natural history data).

The Sponsor has conducted a non-interventional/observational study in MPS IIIB entitled *Evaluation of Blood Brian Barrier Integrity and Structural Abnormalities in MPS IIIB*

Patients Using Multimodal Magnetic Resonance Imaging (Study NGLU-CL01, data on file). In this study, BBB integrity and structural brain abnormalities were evaluated in 5 MPS IIIB patients using CSF-AI and multimodal MRI. Top-line data indicate that in MPS IIIB patients, there is evidence of mild BBB leakage based on the CSF-AI findings; these findings are reflected in the absence of clear evidence for BBB leakage on MRI. MRI volumetric measurements showed global and tissue-specific atrophy in these patients.

The 5 subjects who participated in the NGLU-CL01 study will be eligible to participate in NGLU-CL01-T.

1.5 Dose Rationale and Risk/Benefits

1.5.1 Study Dose Rationale

This study consists of open label dosing, with an opportunity for dose escalation after a minimum of 12-weeks dosing. The intent is for 2 dose levels of SBC-103 (1 mg/kg and 3 mg/kg) to be administered by IV infusion once qow. If subjects are unable to tolerate these doses, the dose may be reduced from 3 mg/kg to 1.0 mg/kg or from 1.0 mg/kg to 0.3 mg/kg. All subjects will be dosed with a starting level of 1 mg/kg.

The dose scaling across species for SBC-103 has used body weight. This is based on reviews of the approach taken for other therapeutic proteins (Tang, 2004, *J Pharm Sci*; Mahmood, 2004, *J Pharm Sci*), particularly ERTs such as Elaprase®.

The selection of the starting dose for SBC-103 of 1 mg/kg administered through IV infusion is based on available human safety, tolerability and PD data from the currently ongoing FIH study in MPS IIIB subjects (NGLU-CL02); PK/PD modelling; the pharmacological effects of SBC-103 in a highly relevant NAGLU-deficient nonclinical mouse model of MPS IIIB following qw as well as qow IV dosing; and the NOAEL defined in the Cynomolgus monkey (including a 3-month study in juvenile Cynomolgus monkey) and the Sprague-Dawley rat when SBC-103 was administered through IV infusion.

Overall, as of 30 April 2015, there have been no remarkable safety observations with the doses administered in the first 2 cohorts of the NGLU-CL02 study (0.3 mg/kg and 1 mg/kg) that have led to changes in how the product is administered or how subjects are monitored for safety.

Pharmacological effects were seen in a highly relevant nonclinical mouse model of MPS IIIB (NAGLU deficient) with IV bolus doses of 0.3, 1, 3, 5, or 10 mg/kg of SBC-103 qw for 4 weeks (SBC103-P010). Total HS in the brain was reduced following IV administration at 3 mg/kg dose establishing the PAD at 3 mg/kg IV (human equivalent dose [HED] = 3 mg/kg based on body weight). HS in the liver was reduced following IV administration at 0.3 mg/kg establishing the PAD in the liver at 0.3 mg/kg (HED = 0.3 mg/kg based on body weight). Similar pharmacological effects were also seen in NAGLU-deficient mice after qow IV bolus doses of SBC-103. PK/PD modelling data supports a qow dose interval. In addition, modelling data predict that the PAD for both brain and liver following IV infusion will be lower than the anticipated PAD following the IV bolus injection.

In the Sprague-Dawley rat, a NOAEL was defined as 3 mg/kg based on the observed vascular/perivascular inflammation in the heart and lungs; this represents a 3.0 fold

margin over the proposed starting dose (1 mg/kg) on a mg/kg basis. Transient clinical signs attributable to SBC-103 infusions were observed at a dose of 10 mg/kg, generally after the third and fourth doses (see Section 1.3). Given the nature of the findings and the frequent presence of anti-SBC-103 antibodies, these likely reflect hypersensitivity to the administration of a human protein to a rat.

In the juvenile Cynomolgus monkeys, which are considered the most relevant species, transient clinical signs attributable to SBC-103 IV infusions were observed (see Section 1.3). However, there were no correlating findings in any of the other parameters evaluated. A NOAEL was defined as 10 mg/kg/dose qw and 20 mg/kg/dose qow. This represents a 10 and 20 fold safety margin over the proposed starting dose (1 mg/kg) on a mg/kg body weight basis.

Preclinical and human PD data after qow dosing, PK modelling data and affinity data for SBC-103 binding to the macrophage mannose receptor (MMR)- and the mannose-6-phosphate receptor (M6PR)-mediated delivery to lysosomes supports the qow dosing frequency that is planned in this study. Based on available human safety, tolerability and PD data from the currently ongoing FIH study (NGLU-CL02), PK/PD modelling, the planned starting dose of 1 mg/kg is expected to provide possible therapeutic effect in this Phase I/II study. The increment between the two doses in this study is approximately 3 fold, allowing for the assessment of safety, tolerability, PK, and PD/efficacy in MPS IIIB patients across a relevant 3 fold range of doses on a mg/kg basis (1 and 3 mg/kg).

1.5.2 Risk/Benefit Assessment

As discussed in Section 1.1.1, MPS IIIB is a very rare disease that is associated with significant morbidity and mortality in affected patients. Currently, there are no safe or effective therapies for MPS IIIB.

Nonclinical studies conducted in the Sprague-Dawley rat and Cynomolgus monkey (including a 3-month study in juvenile monkeys) by IV route were generally well tolerated at the doses planned in this study. Minimal/mild microscopic findings were noted in the liver in some animals, and these changes appear to be limited and were seen at doses higher than planned in this study. Clinical observations such as decreased activity, drowsiness/sluggishness, decreased muscle tone, abnormal gait, and repetitive behaviour were noted generally after the third or fourth dose of SBC-103. These observations generally lasted for a short period of time and did not have any relationship with several tests performed using the blood and tissues (see Section 1.3). These findings along with anti-SBC-103 IgG antibodies are suggestive of hypersensitivity, which is not unexpected when administering a recombinant human protein to a heterologous species. It should be noted that nonclinical studies are not predictive of potential immunogenicity of humans (Brinks, 2011, *Pharm Res;* Ponce, 2009, *Reg Toxicol Pharmacol*).

Subjects in this clinical study will be monitored closely to identify any potential safety concerns, including monitoring liver parameters and antibody development. See Sections 5.2 and 6.2 for more details regarding laboratory assessments and subject stopping rules, respectively.

Extensive clinical experience with approved ERTs for other LSD indications is relevant for risk evaluation of SBC-103. The main AEs associated with administration of

approved ERTs (including but not limited to Cerezyme®, VPRIV®, Fabrazyme®), are related to IARs (Cerezyme® prescribing information, 2011; VPRIV® prescribing information, 2013; Fabrazyme® prescribing information, 2010; Desnick, 2012, *Annu Rev Genomics Hum Genet*). The observed IARs are usually mild and can be managed by changes in infusion rate and/or the administration of antipyretics and antihistamines. While severe infusion reactions, including anaphylaxis, and serious adverse events (SAEs) related to ERT administration rarely occur, medications and equipment for the treatment of hypersensitivity reactions will be available for immediate use. They include, but are not limited to, oxygen, acetaminophen, antihistamines (e.g., diphenhydramine, parenteral and oral), corticosteroids, epinephrine (adrenaline), and cardiopulmonary resuscitation devices. Anti-drug antibodies (ADAs) have also been reported with approved ERTs and may be associated with altered response to treatment and/or increased risk of IARs.

As described in Section 1.1.2 and Section 1.3, pharmacologic activity has been observed following qw and qow IV dosing of SBC-103 in NAGLU-deficient mice including increased enzyme activity and reduction of the accumulated substrate (HS). Although examination of the effects of long-term IV dosing on CNS manifestations in the mouse model has not been possible because of clinical symptoms related to the apparent hypersensitivity, there is a substantial body of data linking substrate reduction in brain tissue in MPS IIIB and other MPS disorders with improvements in CNS manifestations (Calias, 2012, *PloS One*; Hemsley, 2009, *Int J Clin Pharmacol Ther*).

The design of this study is based on available human safety, tolerability and PD data from the currently ongoing FIH study (NGLU-CL02)*; in vivo* pharmacology data in a relevant disease model supporting the potential for CNS activity following qw and qow IV administration (SBC103-P004, SBC103-P007, SBC103-P009, SBC103-P010, SBC103-P013 [data on file]), with supportive information from *in vivo* pharmacology data in a relevant disease model supporting the potential for CNS activity following IV/IT administration (SBC103-P011); tissue specific differences in NAGLU enzyme levels required to maintain normal phenotype (Li, 1999, *Proc Natl Acad Sci USA*); positron emission tomography (PET)/computed tomography investigations of the PK of radiolabelled SBC-103 in non-human primates (IV administration and IT administration) indicating access to the CNS following IV administration (SBC103-K004); and PK modelling data and affinity data for SBC-103 binding to MMR and M6PR.

As described in Section 1.1.2, early IV administration of enzyme to an MPS II patient partially stabilised cognitive function and prevented the somatic complications seen in his affected older brother who started treatment later in life (Tajima, 2013, *Mol Genet Metab*). There is extensive clinical evidence supporting the safety of ERT with known AEs for which to monitor. Furthermore, based on available human safety, tolerability and PD data from the currently ongoing FIH study (NGLU-CL02), there is a reasonable basis to conclude that extended dosing of SBC-103 in this study may have beneficial effects on disease activity in MPS IIIB patients. The data obtained on the effects of treatment with SBC-103 in this study, as well as the observational data in the same study subjects from NGLU-CL01, combined with data from the other Phase I/II studies with SBC-103, will guide and inform the development of SBC-103.

In addition to potential risks associated with Investigational Medicinal Product (IMP) administration, this study entails procedures that incur incremental risks that are critical for a thorough evaluation of the effects of SBC-103 on MPS IIIB. Given the devastating complications associated with MPS IIIB and the inability to obtain important disease relevant information using other approaches, the risks are considered to be acceptable in this patient population. Risk assessment for selected study procedures are described below.

1.5.2.1 Risk Assessment for Selected Study Procedures

Anaesthesia

Disease progression in patients with MPS IIIB is associated with cognitive decline and behavioural disturbances. Conscious subjects will not be able to comply with study assessment requirements, including maintenance of appropriate positioning during MRI and lumbar puncture. Thus subjects will receive general anaesthesia prior to, and during the MRI procedure (and lumbar puncture, as appropriate). Sedation of children is associated with risks of hypoxaemia, inadequate sedation, and failed sedation. General anaesthesia is a safe alternative to facilitate MRI scans in children perceived to be at increased risk for sedation-related AEs as for those with a history of failed sedation (Malviya, 2000, *Br J Anaesth*).

Lumbar Puncture

A lumbar puncture is necessary to determine if SBC-103 administration is able to reduce HS within the CNS. A subject may experience discomfort or bruising of the skin at the site where the needle was inserted (similar to blood collection). Mild headache is reported in less than 10% of cases.

In rare instances, more severe headaches may occur, which usually respond quickly to treatment with over-the-counter pain relievers. A very rare occurrence is infection from the sample collection itself. The risk for such infection is less than that of a regular blood draw.

Subjects will receive general anaesthesia prior to the lumbar puncture, if clinically appropriate. See above regarding risks associated with anaesthesia.

Magnetic Resonance Imaging

The primary risks of MRI in patients with MPS IIIB are those associated with the administration of anaesthesia and the potential interference of MRI with metallic foreign objects in the body. Subjects will be screened by MRI personnel, according to local guidelines, for any medical contraindications to MRI, including the presence of metallic foreign bodies in the brain or eye or cardiac pacemaker. See above regarding risks associated with anaesthesia.

In conclusion, the risks to subjects in this study from both exposure to IMP and the required procedures are reasonable in relation to the seriousness of the disease and the anticipated benefits and/or knowledge that can be expected from the results. Appropriate measures have been incorporated into the protocol to minimise risk and to monitor subject safety.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the safety and tolerability of IV administration of SBC-103 in previously studied, SBC-103 treatment-naïve subjects with mucopolysaccharidosis III, type B (MPS IIIB, Sanfilippo B) who participated in the NGLU-CL01 study. The NGLU-CL01 study was a non-interventional study that evaluated structural brain abnormalities and BBB integrity by MRI and CSF-AI.

2.2 Secondary Objectives

- To characterise the PK profile of SBC-103 administered IV.
- To determine the effects of dosing with SBC-103 administered IV on the levels, onset and magnitude of changes in levels of total HS in CSF, serum, and urine.
- To evaluate the PD/efficacy of treatment with SBC-103 administered IV as measured by neurocognitive and developmental function, changes in brain structure, and BBB integrity.
- To evaluate change from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period) in the following where available: clinical laboratory tests including HS in CSF, in serum, and in urine, electrocardiograms (ECGs), physical examination, vital signs, concomitant medications, neurocognitive and developmental function, brain structure and microstructural integrity, and BBB integrity.

2.3 Exploratory Objectives

- To examine the onset and magnitude of changes in biomarkers, SBC-103 concentration in CSF, MPS IIIB disease characteristics and symptoms, and quality of life (QOL) after IV administration of SBC-103.
- To evaluate the change in biomarkers and MPS IIIB disease characteristics and symptoms from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period).

3 INVESTIGATIONAL PLAN

3.1 Overall Design and Plan of the Study

This study (NGLU-CL01-T) is designed to evaluate the safety and tolerability of IV administration of SBC-103 for the treatment of MPS IIIB. Up to 5 subjects, previously enrolled in the NGLU-CL01 study at 1 centre in the United Kingdom, will be eligible to participate in this study. This interventional study will provide data on effects of treatment with SBC-103, and observational data in the absence of treatment in the same study subjects from study NGLU-CL01 to baseline of NGLU-CL01-T will be included in the analysis.

All subjects will initially receive 1 mg/kg SBC-103 IV qow. All subjects will be monitored in an in-patient setting for safety and tolerability for 24 hours following the first dose of SBC-103. The decision to continue dosing in each subject will be made by the Sponsor in consultation with the Principal Investigator (PI) after review of 24-hour safety data from that subject and available safety data from all other subjects.

With the intent of treating subjects with the lowest dose that is safe and tolerable and which has potential for efficacy, dose modification (either an increase to 3 mg/kg or a decrease to 0.3 or 1 mg/kg) may be proposed for individual subject(s) throughout the study, following ongoing evaluation of safety and tolerability data as well as biomarker and response to treatment data. Dose reductions can be made at any point during the study, but dose escalation cannot occur before completion of at least 12 weeks of dosing.

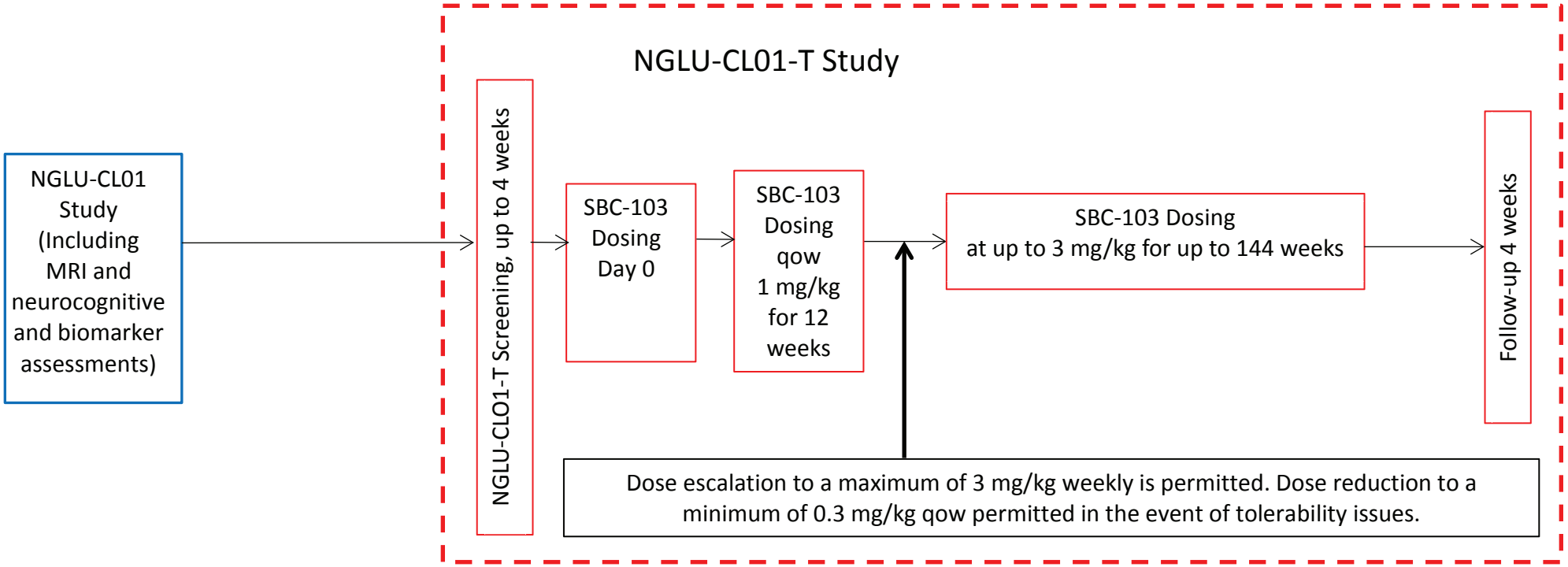
After a minimum of 12 weeks of dosing at 1 mg/kg, a review of safety, tolerability, and PD data from each subject will be conducted by the Sponsor in consultation with the PI to determine whether it is appropriate to escalate the dose to 3 mg/kg for that individual subject. Dose frequency (e.g., weekly) modifications may also be considered by the Sponsor after consultation with the SRC and PI, based a review of safety, tolerability, and response to treatment data and with consideration of any other available data on SBC-103.

Safety, PK and PD/efficacy assessments will be performed in all subjects throughout the study.

At least 4 weeks after a subject's last dose of SBC-103 is administered in this study, the subject (or the subject's parent or caregiver) will receive a follow-up phone call to assess AEs and concomitant medications unless the subject has a scheduled follow-up study visit.

As indicated in Figure 1, the planned total duration of the study is approximately 164 weeks. This will include a Screening period that will last up to 4 weeks, an initial study treatment period of 12 weeks at 1 mg/kg, 144 weeks of treatment at up to 3 mg/kg, and a 4-week follow-up period after the last dose is administered.

Figure 1: NGLU-CL01-T Study Schematic



Key: qow = every other week; MRI = magnetic resonance imaging.

Observational Period (~18 months)	Treatment Period (3 years)

3.2 Rationale for Study Design

This study (NGLU-CL01-T) will be conducted in MPS IIIB patients who participated in the NGLU-CL01 study. The NGLU-CL01 study was a single time point evaluation of BBB integrity by Dynamic Contrast-Enhanced MRI and CSF-AI, and assessment of structural brain abnormalities by Structural and Diffusion MRI.

All subjects in the NGLU-CL01 study were ≥ 5 years of age with rapidly progressing MPS IIIB. All subjects had a definitive diagnosis of MPS IIIB, as determined by documented deficiency in NAGLU enzyme activity of < 10% of the lower limit of normal (LLN) or documented functionally-relevant mutations in both alleles of the NAGLU gene.

The five subjects who participated in the NGLU-CL01 study, entered the study between 27 December 2013 and 06 May 2014. The NGLU-CL01-T study provides an opportunity to follow up these subjects and understand both the longitudinal stability and progression of important disease parameters (e.g., MRI and CSF-AI), over approximately 12 to 18 months between these assessments in addition to the specific study objectives of this interventional study with SBC-103.

This study will evaluate safety and tolerability of IV administration of SBC-103 in up to 5 subjects with MPS IIIB for up to 3 years (156 weeks).

Safety and tolerability is the primary objective of this study but PD/efficacy assessments will be conducted at regular intervals throughout the study and will include, but not be limited to, CSF, blood and urine samples for biomarkers including HS, BBB integrity, neurocognitive and developmental function assessments, structural and diffusion MRI, and routine clinical assessments. To reduce the burden on subjects, and as there was no clear evidence of BBB leakage shown by Dynamic Contrast-Enhanced MRI from the NGLU-CL01 study, BBB integrity will be assessed by CSF-AI in the NGLU-CL01-T study.

Safety will be assessed by monitoring AEs, safety haematology and clinical chemistry, vital signs, and presence of ADA. Stopping rules have been put in place for IARs and for liver enzyme abnormalities. Regular data reviews, including after the first dose in each subject prior to continuing dosing, prior to consideration of a dose escalation after 12 weeks, and throughout the study have been incorporated to minimise risk, to monitor subject safety and to assess PD data (see Sections 3.1 and 3.3).

In light of the paediatric patient population intended for enrolment, it is important (and often required by regulation) to provide some prospect for benefit with the investigational treatment. For an ERT for a chronic disease such as MPS IIIB, extended treatment is generally required to offer any prospect of benefit. Nonclinical data, including a 3 month toxicology study in juvenile Cynomolgus monkeys, supports both chronic dosing and intra-subject dose escalation based on safety, tolerability and evidence of biological activity. Therefore, this study design includes chronic dosing as well as intra-subject dose escalation, to assess the long term safety, tolerability and effects of treatment with SBC-103 on the somatic and neurological components of MPS IIIB.

Based on the experience with neurodegenerative diseases, it is anticipated that clinical response to treatment, specifically on the neurological component of the disease, may not be observed sooner than 6 months after initiating treatment with SBC-103. For this reason this study is designed with efficacy evaluations with MRI and neurocognitive and

developmental assessments starting after 6 months of treatment. Effect of treatment on the biomarker HS is expected to be observed earlier and is assessed in CSF from 12 weeks and from 4 weeks in serum and urine.

There are emerging data on the advantages of earlier treatment with ERTs in other MPS subtypes particularly with regard to impact on disease manifestations which are eventually irreversible (Tajima, 2013, *Mol Genet Metab*; Gabrielli, 2010, *Pediatrics*; McGill, 2010, *Clin Genet*; Furujo, 2011, *Mol Genet Metab*). Given the inevitable neurodegenerative manifestations of MPS IIIB, early intervention is an important consideration to avoid irreversible disease progression and, therefore, paediatric subjects have been included in this study.

Data from a nonclinical disease model (NAGLU-deficient mice) demonstrate reductions in brain HS and increases in brain enzyme activity following IV dosing of SBC-103. Evaluating the accumulation of HS in the CSF via lumbar puncture in this clinical study and in the NGLU-CL02 study will provide important insights into the utility of SBC-103 administered IV in MPS IIIB patients.

Important manifestations of MPS IIIB disease include developmental and cognitive delay and regression as well as sleep and behaviour disturbances. This study includes periodic assessments to evaluate any changes in these parameters after treatment with SBC-103 administered by IV infusion.

As noted in Section 1.5.1, structural and diffusion MRI can provide indices of grey and white matter volume reductions and microstructural and white matter connection integrity. For these reasons, structural and diffusion MRI will be used to assess neurodegeneration and any changes after treatment with SBC-103 administered by IV infusion.

For the PD/efficacy variable MRI and for neurocognitive assessments, changes from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study will be evaluated (observational period).

Changes in BBB integrity will be evaluated by measuring CSF-AI after treatment with SBC-103; these data will enable evaluation of changes from time points when CSF-AI was measured during the NGLU-CL01 study.

The data obtained on the effects of treatment with SBC-103 in this study, as well as the observational data in the same study subjects from NGLU-CL01, combined with data from the other Phase 1/2 studies with SBC-103 will guide and inform the development of SBC-103.

3.3 Rationale for Dose and Escalation Timing

In this study all subjects will initially be administered 1 mg/kg SBC-103 qow by IV infusion, see Section 1.5.1 for dose justification.

3.3.1 Decision for Continued Dosing after the First Dose in Each Subject

Due to the relatively limited experience with SBC-103 in humans (as of 30 April 2015), 24-hour in-patient safety monitoring following the first dose for each subject will be conducted in this study. The Sponsor and PI will review safety data from the first dose in each subject prior to continuation of dosing in that subject.

3.3.2 Decision for Dose Escalation Within a Subject after 12 Weeks of Treatment

Considering the potential for immunogenicity with a protein product, evaluation of the safety and tolerability following multiple rather than single doses prior to escalation is important (see Section 1.3). Therefore, the decision to escalate to 3 mg/kg will be made by the Sponsor and PI only after review of safety, tolerability and PD data from each subject after they have completed a minimum of 12 weeks of treatment. This data review will include HS data from CSF evaluation at 12 weeks and the HS data from serum and urine samples every 4 weeks, along with multiple dose safety and tolerability data.

3.3.3 Additional Dose Adjustment During the Study

Additional dose modifications (including reductions in dose) may be considered by the Sponsor after consultation with the PI, based on review of safety and tolerability data as well as biomarker and response to treatment data.

Dose modification of increasing the dose to 3 mg/kg can only occur after 12 weeks of treatment and review of data as described above.

Dose modification of decreasing the dose to 1 mg/kg or 0.3 mg/kg can occur for individual subjects at any point in the study to manage subject safety and/or response to treatment data. The independent SRC for the SBC-103 program will continue to provide oversight of subject safety through periodic reviews of safety data. Dose frequency (e.g., weekly) modifications may be considered by the Sponsor after consultation with the SRC and PI, based on a review of safety, tolerability, and response to treatment data.

During the study the SRC, Sponsor or PI may request a pause in dosing in individual, multiple or all subjects based on review of reported events and available data. Dosing will resume only after the review of data and agreement to do so by the SRC, Sponsor and PI.

3.4 Study Endpoints

3.4.1 Primary Endpoint

The primary endpoint of this study is safety and tolerability of SBC-103 in subjects with MPS IIIB. The safety assessments will include the following:

- Incidence of AEs, SAEs, and IARs.
- Changes from baseline in clinical laboratory tests (haematology, serum chemistry, and urinalysis) and CSF findings (cell counts, glucose, and protein).
- Changes from baseline in 12-lead ECGs.
- Changes in vital signs during and post-infusion, relative to pre-infusion values.
- Physical examination findings.
- Use of concomitant medications/therapies.

- Incidence of ADAs, including seroconversion rate, time to seroconversion, and ADA titre by time point, peak ADA titre, and ADA titre status (positive/negative), and the effect of ADAs on the safety of SBC-103, including the relationship between ADA-positive subjects and the incidence of IARs.

3.4.2 Secondary Endpoints

The secondary endpoints of this study are:

- PK profile of SBC-103 after single and multiple doses as measured by:
  - Serum maximum concentration (C_{max}).
  - Time to maximum concentration (T_{max}).
  - Area-under-the-concentration-time curve extrapolated to infinity (AUC_{∞}).
  - Half-life ($T_{1/2}$).
  - Clearance (Cl).
  - Apparent volume of distribution at steady state (V_{ss}).
- Onset and magnitude of changes in levels of total HS in CSF, serum, and urine following dosing with SBC-103 administered IV.
- Change from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period) in CSF, serum, and urine HS in the absence of treatment.
- Changes from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period) in the following:
  - Clinical laboratory tests (haematology, serum chemistry, and urinalysis) and CSF findings (cell counts, glucose, and protein).
  - 12-lead ECGs.
  - Vital signs.
  - Physical examination.
  - Use of concomitant medications/therapies.
- Change in neurocognitive and developmental function during the NGLU-CL01-T study (on treatment), as determined by Vineland Adaptive Behavior Scales, Second Edition (Vineland-II).
- Change in neurocognitive and developmental function from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period), as determined by Vineland-II.
- Change in neurocognitive and developmental function during the NGLU-CL01-T study (on treatment) as determined by the subject's age-appropriate scores, the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) or Kaufman Assessment Battery for Children, Second Edition (KABC-II), Bruininks-Oseretsky Test of Motor Proficiency, Second Edition, Brief Form (BOT-2 Brief Form), and Children's Communication Checklist, Second Edition (CCC-2).

- Changes in brain structure, as measured by the relative proportion of grey and white matter volume, and indices of microstructural integrity, as assessed by MRI of the brain during the NGLU-CL01-T study (on treatment).
- Changes in brain structure, as measured by the relative proportion of grey and white matter volume, and indices of microstructural integrity, as assessed by MRI of the brain, from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period).
- Changes in BBB integrity during the NGLU-CL01-T study (on treatment), as determined by CSF-AI.
- Changes in BBB integrity from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period), as determined by CSF-AI.

3.4.3 Exploratory Endpoints

Onset and magnitude of changes in biomarkers, SBC-103 concentration in CSF, MPS IIIB disease characteristics and symptoms, and QOL after administration of SBC-103 (on treatment):

- Biomarkers:
    - Change in NRE HS derivatives in CSF, serum, and urine.
    - Changes in serum ferritin and chitotriosidase.
    - Changes in CSF disease-related biomarkers including, but not limited to, hepatocyte growth factor, calbindin D, Tau, pTau, amyloid β, albumin, IgG, glutamic acid, and glycine.
    - Changes in glutamic acid and glycine in relation to plasma (carrier-mediated excitatory amino acids that are markers of transport function).
    - Changes in CSF IgG Index ([CSF/serum IgG ratio] / [CSF-AI]). CSF IgG Index is a measure of IgG synthesis within the CNS.
    - Changes in inflammatory markers in serum.
    - Changes in other blood or urine biomarkers of interest that are identified during the course of this study based on emerging data from the scientific literature or the Sponsor's MPS IIIB development program (if there is sufficient sample volume and if local regulations permit).
- Disease characteristics and symptoms, and QOL.
- Coarsening of facial features, as determined by Facial Dysmorphology Novel Analysis (FDNA).
- SBC-103 concentration in CSF.
- Changes in measures of sleep disorders or dysfunction, as assessed by the Children's Sleep Habits Questionnaire (CSHQ).

- Changes in measures of behaviour, as determined by the Sanfilippo Behavior Rating Scale (SBRS).
- Changes in subjective QoL measures, as determined by the Short Form Health Survey for Children (SF-10).
- Changes in measures of caregiver QoL, as determined by the Zarit Burden Interview (ZBI) 12-item short form.

Onset and magnitude of changes in biomarkers and MPS IIIB disease characteristics and symptoms from the NGLU-CL01 study visit to baseline of the NGLU-CL01-T study (observational period):

- Biomarkers:
    - Change in NRE HS derivatives in CSF, serum, and urine.
    - Changes in serum ferritin and chitotriosidase.
    - Changes in CSF disease-related biomarkers including, but not limited to, hepatocyte growth factor, calbindin D, Tau, pTau, amyloid β, albumin, IgG, glutamic acid, and glycine.
    - Changes in glutamic acid and glycine in relation to plasma (carrier-mediated excitatory amino acids that are markers of transport function).
    - Changes in inflammatory markers in serum.
- Disease characteristics and symptoms.
- Coarsening of facial features, as determined by FDNA.

4 STUDY POPULATION

4.1 Target Population

The target population for this study is male and female subjects with documented MPS IIIB between 2 and 12 years old, who participated in the NGLU-CL01 study.

4.2 Number of Subjects

Up to 5 subjects may be recruited to this study.

4.3 Eligibility Criteria

4.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for participation in this study:

1. Previous participation in the NGLU-CL01 study.
2. Subject consents or subject's parent or legal guardian (if applicable) grants consent for the subject to participate in the study and provides informed consent prior to any study procedures being performed. If the subject is of minor age, he/she is willing to provide assent where required per local regulations, and if deemed able to do so.
3. Female subjects who are of childbearing potential at the time of consent or who become of childbearing potential during participation on study (a) must have a negative urine pregnancy test at Screening, (b) cannot be breast feeding, and (c) must use a highly reliable method of birth control (expected failure rate less than 5% per year) for the duration of the study and for 30 days after last dose of SBC-103. For acceptable contraceptive methods, refer to Section 7.2.5 of the protocol.Women may be considered of non-childbearing potential if they have not started their menses or are surgically sterile (i.e. hysterectomy, bilateral salpingectomy or bilateral oophorectomy).
4. Male subjects must use a highly reliable method of birth control (expected failure rate less than 5% per year) during any sexual contact with females of childbearing potential while participating in the study and for 30 days following discontinuation from this study even if he has undergone a successful vasectomy. For acceptable contraceptive methods, refer to Section 7.2.5 of the protocol.
5. Willingness and ability to comply with protocol requirements to the extent that may be expected of a subject with cognitive impairment.

4.3.2 Exclusion Criteria

Subjects meeting any of the following criteria will not be eligible for participation in this study:

1. Received treatment with gene therapy at any time, or any investigational drug (including high dose genistein > 150 mg/kg/day) or device intended as a treatment for MPS IIIB within 30 days prior to Screening, or is currently being treated in another study that involves an investigational drug or device.
2. Has any internal or non-removable external metal items that may present a safety risk for study assessments that utilise magnetic fields, or any other medical condition or

circumstance in which an MRI is contraindicated according to local institutional policy.

3. Previous hematopoietic stem cell or bone marrow transplant.
4. Known or suspected hypersensitivity to anaesthesia or the use of a sedative is contraindicated for any other reason.
5. History of poorly controlled seizure disorder.
6. A bleeding disorder, or any other medical condition or circumstance in which a lumbar puncture (for collection of CSF) is contraindicated according to local institutional policy.
7. Known hypersensitivity to eggs. Subjects at high risk for food allergy that may include eggs should be tested according to local guidelines.
8. Other medical conditions or comorbidities (e.g., alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3 x the upper limit of normal [ULN], confirmed by repeat testing, analysed locally and based on the standardised reference range provided in the laboratory manual), or other markers of clinically significant liver dysfunction (e.g. elevated bilirubin, [with the exception of subjects with confirmed Gilbert's disease] confirmed by repeat testing, or elevated prothrombin time [PT]/international normalised ratio [INR] confirmed by repeat testing analysed locally and based on the standardised reference range provided in the laboratory manual) which in the opinion of the Investigator, in consultation with the Sponsor, would interfere with study compliance, or confound data interpretation.

4.4 Concomitant Medications and Treatments

Concomitant medications include prescription and over-the-counter medications, prophylactic and therapeutic vaccines, herbal medications, vitamins, and dietary/nutritional supplements, as well as any investigational medications the subject may have received. Concomitant treatments include diagnostic, palliative, or interventional procedures (e.g., hematopoietic stem cell transplant, bone marrow transplant).

At the Screening visit, information on all medications and treatments received by the subject within the preceding 4 weeks will be recorded in the case report form (CRF). Thereafter, reasonable efforts will be made to ascertain all changes in concomitant medications and treatments from Screening until the subject completes the safety follow-up phone call. Particular attention will be given to any changes in the dose or dosing regimen of genistein or melatonin, antihistamines, chloral hydrate, benzodiazepines, thioridazine, carbamazepine, and sodium valproate. Note that subjects who are on a stable dosing regimen for any of the listed medications at the time of Screening, including a low dose of genistein (≤ 150 mg/kg/day), should remain on the dosing regimen during the study. Dose adjustments or discontinuation of these medications should occur only when there is a clear medical reason and should be pre-approved by the Sponsor. Information on all concomitant medications and treatments will be recorded in the CRF and will include the name of the medication (brand or generic) or therapy, reason for use, start date, stop date, dose, route of administration (if applicable), and frequency of administration.

4.5 Discontinuation of Subjects

4.5.1 Premature Withdrawal from Study Participation

Subjects have the right to withdraw from the study at any time for any reason, without prejudice to further treatment.

The Investigator and Sponsor also have the right to withdraw subjects from the study at any time. Specific reasons for discontinuation may include, but are not restricted to, the following:

- Intercurrent illness.
- AEs, including severe infusion reactions.
- Pregnancy.
- Clinically important protocol deviation or non-compliance.
- Termination of the study by the Sponsor.

4.5.2 Procedures for Discontinuation

If a subject discontinues at any time after being dosed with SBC-103, all efforts should be made to have the subject complete follow-up visit procedures, including End of Study/Early Withdrawal Visit per Schedule of Assessments (SOA) (refer to Section 14.1, Appendix A). All subjects who withdraw should be asked about the reason(s) for their discontinuation and about the presence of AEs. The date and the reason for discontinuation will be recorded.

When a subject fails to return for scheduled assessments, the following efforts should be made to contact him/her (this would generally apply to the parent/caregiver) to determine a reason for the failure to return: 3 phone attempts, including the date and time, to be documented in the subject's chart. If there is no response to the telephone calls, a certified letter should be sent. After these efforts have been exhausted, a subject should be identified as lost to follow-up.

4.6 Subject Replacement Policy

Subjects will not be replaced.

4.7 Subject Re-screening

Subjects who were unable to complete all Screening procedures within the 28-day Screening window may be re-screened. Safety laboratory tests (chemistry, haematology and urinalysis) and weight as well as assessments scheduled to be performed on Day 0 will be repeated if performed more than 28 days prior to dosing. The subject will be re-consented and Screening procedures will be repeated at the discretion of the Investigator after discussion with the Medical Monitor.

5 STUDY PROCEDURES

5.1 Study Assessments

A Schedule of Study Assessments is presented in Section 14.1. The SOA provides detailed information regarding the time points for all of these assessments.

5.1.1 Informed Consent/Assent

The subject (or the subject's parent or legal guardian) will be given a consent form as well as a verbal explanation of the study, including information about the study procedures, and will have all questions adequately addressed. The subject (or the subject's parent or legal guardian) must sign and date a consent form that has been approved by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) within 90 days before Screening procedures are initiated, and will be given a copy of the signed and dated informed consent form. Subjects will need to be re-consented if the consent form was signed and dated more than 90 days from first Screening assessment. In addition, age and comprehension-appropriate assent will be obtained from subjects below the age of consent, as required by local regulations.

5.1.2 Subject Eligibility

All subjects will be assessed for eligibility against the inclusion and exclusion criteria described in Section 4.3.

5.1.3 Medical History

Any new medical history occurring since the screening date of the NGLU-CL01 study will be recorded.

Medical history to be recorded includes, but is not limited to, the following:

- Historical results of NAGLU enzyme activity testing and genetic mutation analysis, as applicable.
- Presence (and date of onset, if known) of the following clinical manifestations or disorders as applicable:
    - Cognitive delay/difficulties.
    - Abnormal facial features (flat nasal bridge, enlarged lips, enlarged mouth and tongue, abnormal thickening/darkening/coarseness of eyebrows).
    - Hepatomegaly.
    - Language delay/difficulties or regression of language skills .
    - Abnormal behaviours (hyperactivity, aggressiveness, irritability, endangering behaviours).
    - Autism spectrum disorder.
    - Epilepsy.
    - Motor function delay/difficulties, including loss of independent walking.

- Sleep disturbances (settling difficulties, early awakening, complete reversal of day-night rhythm, obstructive sleep apnoea).
- Ear-nose-throat problems (recurrent ear infections, adenoidectomy or tonsillectomy, grommets, documented history of hearing loss).
- Difficulty swallowing.

Data on family medical history will be obtained from the NGLU-CL01 database. Any changes in family medical history since the subject's participation in that study (such as new siblings, death of a sibling, or new diagnosis of MPS in a sibling) will be recorded.

Refer to Section 4.4 for details on collection of medication history and concomitant medications/treatments.

5.1.4 Demographic Information

Demographic data collected for all subjects during their participation in the NGLU-CL01 study.

5.1.5 Physical Examination

Complete, age-appropriate physical examinations will be performed by the Investigator or qualified designee at the time points specified in the SOA. These examinations will include an assessment of the subject's general appearance; skin; head, eyes, ears, nose, throat, and head circumference; heart; lungs; abdomen; extremities/joints; and neurological status. Abnormal findings will be recorded in the CRF.

5.1.6 Height and Weight

Height and weight will be measured at the time points specified in the SOA. Weight-for-age, weight-for-height, height-for-age, and body mass index-for-age will be derived during data analysis, and percentiles or z-scores will be determined for each of these derived parameters by standardization to age- and gender-appropriate Centers for Disease Control growth charts.

5.1.7 Vital Signs and Electrocardiogram

Vital signs, including pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature will be taken at the time points specified in the SOA in accordance with local institutional procedures. On Day 1, vital signs will be taken prior to hospital discharge. During dosing visits, vital signs will be taken within approximately 30 minutes before dosing with SBC-103, approximately every 15 minutes during infusion and approximately every 15 minutes for 2 hours after completion of the infusion. Vital signs should also be obtained after the lumbar puncture is completed as per the standard of care. The duration of post-infusion vital signs monitoring may be shortened to 1 hour starting with Week 54, provided that there is no occurrence of IARs during the infusion.

Every effort will be made to collect a 12-lead ECG during the time points specified in the SOA in accordance with local institutional procedures. 12-lead ECGs will be collected in triplicate for the first 6 months. ECGs will be reviewed by the Investigator, or designee, and any abnormalities will be specified as clinically significant or not clinically significant.

Vital signs and ECG monitoring during general anaesthesia prior to the MRI scan will be performed in accordance with local institutional procedures.

Due to the behavioural issues typical of subjects with MPS IIIB, ECG assessments may not be able to be completed, but should be attempted whenever possible.

5.1.8 Neurocognitive, Developmental and Quality of Life (QOL) Assessments

Neurocognitive, developmental, and QOL assessments are presented in Section 14.2 (Appendix B) and will be performed at time points specified in the SOA. The BSID-III, KABC-II, and BOT-2 Brief Form are administered to the subject. All other assessments are administered to the parent or caregiver.

The Investigator or designee should use clinical judgement to decide whether subject hearing or vision problems may preclude developmental testing. Assessment of vision and hearing may be collected from medical history, parent report, or based on evaluation during Screening physical examination. Assessment of hearing should be documented in the CRF.

Assessments to be performed will include the Vineland-II, BSID-III and/or KABC-II, BOT-2 Brief Form and CCC-2, CSHQ, SBRS, ZBI, and the SF-10. The Vineland-II, BSID-III or KABC-II, and BOT-2 Brief Form should be administered face to face by appropriately qualified professionals. Assessments may be conducted over more than 1 day.

The selection of the appropriate neurocognitive test instrument administered to the child is normally dependent on the calendar age of the child. However, since MPS IIIB patients are likely to show delayed development, the choice of test instrument at the Screening visit will be based on a subject's Vineland-II age equivalent (developmental age) assessed using the survey interview form. The BSID-III will be administered to subjects with a mean Vineland-II age-equivalent of < 3 years 6 months, and the KABC-II, BOT-2 Brief Form, and CCC-2 will be administered to subjects with a Vineland-II age-equivalent of ≥ 3 years 6 months.

During the initial administration of the BSID-III or KABC-II, BOT-2 Brief Form, and CCC-2 at Screening, if the test administrator determines that the chosen test instrument appears unfit for the subject, he/she may switch to the alternate test instrument. However, after the Screening visit, the KABC-II should be first attempted. If the subject appears to be failing the KABC-II, they may revert to the BSID-III. If the subject passes the BSID-III, the KABC-II should be continued. See Section 5.1.8.3 and Section 5.1.8.4 for details.

5.1.8.1 Vineland Adaptive Behavior Scales, Second Edition (Vineland-II)

The Vineland-II supports the diagnosis of cognitive and developmental disabilities in subjects from birth through age 90 years. The Vineland-II assesses a subject's abilities across 5 domains: communication, daily living skills, socialization, motor skills, and maladaptive behaviours. In this study, all sections except for the critical items in the Maladaptive Behaviour domain will be used. Standardised scores, percentile ranks, and adaptive levels are provided for each domain, as well as for an adaptive behaviour

composite measure. Additionally, the Vineland-II allows for determination of V-scale scores, adaptive levels, and age equivalents for subdomains of each of the 5 adaptive behaviour domains. Administration of the Vineland-II Survey Interview Form with the parent/caregiver takes approximately 20 to 60 minutes.

For this study, the mean age equivalent is calculated by taking the average of all age equivalents of the subdomains under communication, daily living skills, socialization, and motor skills. Maladaptive behaviour is not included in this calculation.

The age equivalent and developmental quotient will be calculated for all Vineland-II domains and their subdomains. This quotient is calculated as (Age equivalent/Calendar age)*100.

5.1.8.2 Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)

The BSID-III has been validated for children aged less than 3.5 years and takes approximately 25 to 60 minutes to administer (Connolly, 2012, *Pediatr Phys Ther*). The test is administered to the subject and was designed to identify young children with developmental delays. The BSID-III assesses developmental function across 5 domains: cognition; language (expressive and receptive); motor (fine and gross motor functioning); and social, emotional, and adaptive behaviour.

In this study, cognition, language, and motor functioning will be assessed. The social, emotional, and adaptive behaviour domains are not being used due to overlap with the Vineland scale.

The age equivalent and developmental quotient will be calculated for the BSID-III domains and their subtests. This quotient is calculated as (Age equivalent/Calendar age)*100.

Switching from BSID-III to the Kaufman ABC-II (KABC-II)

At the Screening visit, a child may perform better than expected based on the Vineland-II test. If the score on the first subdomain (cognition) is higher or equal to 79, the KABC-II should be used in combination with BOT-2 Brief Form and CCC-2.

During future study visits, the KABC-II should be attempted first as it was the assessment completed at the first visit. If the subject appears to be failing the KABC-II, they may revert to the BSID-III.

5.1.8.3 Kaufman Assessment Battery for Children, Second Edition (KABC-II)

The KABC-II has been validated for children aged 3 to 18 years and takes approximately 35 to 70 minutes to administer (Malda, 2010, *Assessment*). The test is administered to the subject and was designed to identify strengths and weaknesses in cognitive ability and mental processing. The KABC-II is comprised of 18 subtests, although not all subtests are required to be administered, and is typically used in conjunction with other cognitive or neuropsychological assessments.

Order of completion of the subtests by MPS IIIB subjects

Children with MPS IIIB may not be able to complete all subtests, due to a limited attention span and behavioural problems. Therefore, we only require completion of the

non-verbal index (NVI) battery as appropriate for the developmental age of the child. Other skills (language and motor skills) will be assessed by the CCC-2 and BOT-2 Brief Form, respectively. Priority should be given to the most informative domains, the NVI and the BOT-2 Brief Form. The CCC-2 is completed by the parents. After completion of the NVI and BOT-2 Brief Form, the rater can complete the optional domains in order of importance, and thus, relevance. The NVI and BOT-2 Brief Form should be administered first. The optional domains include Sequential/Gsm, Simultaneous/Gv, Learning/Glr, Planning/Gf (only for developmental ages 7 to 18 years), and Knowledge/Gc.

The age equivalent and developmental quotient will be calculated for the KABC-II subtests. This quotient is calculated as (Age equivalent/Calendar age)*100.

Switching from KABC-II to the BSID-III

At the Screening visit, a child may perform poorer than expected on the KABC-II. In this case the BSID-III should be used. It is likely that these children will have started with the NVI subtests for children aged 3 to 5 years. The first tests for the NVI are Conceptual thinking and Face recognition. If the raw scores for both these first 2 tests are ≤ 5 then the KABC-II should be discontinued and the BSID-III should be used.

During future study visits, the KABC-II should be attempted first. If the subject appears to be failing the KABC-II, they may revert to the BSID-III. If the subject passes the BSID-III, the KABC-II should be continued at this visit when practical and subject compliance allows.

5.1.8.4 Bruininks-Oseretsky Test of Motor Proficiency, Second Edition, Brief Form (BOT-2 Brief Form)

The BOT-2 Brief Form is an individually administered test that uses engaging, goal-directed activities to measure a wide array of motor skills in children aged 4 through 21 years (Bruininks, 2010, *NCS*). The BOT-2 Brief Form contains 12 items to assess fine motor precision, fine motor integration, manual dexterity, bilateral coordination, balance, running speed and agility, upper-limb coordination, and strength. The BOT-2 Brief Form will be administered to subjects who are also completing the KABC-II and takes approximately 20 minutes to complete.

If the subject does not obtain any points in the first 2 tasks, the motor scales of the BSID-III should be used, even if the subject's cognition was assessed by KABC-II.

5.1.8.5 Children's Communication Checklist, Second Edition (CCC-2)

The CCC-2 is a 70-item questionnaire that was designed to rate aspects of communication in children including speech vocabulary, sentence structure, and social language skills. Within the 2 domains of language and pragmatics, the following subdomains are evaluated: speech, syntax, semantics, coherence, initiation, scripted language, context, non-verbal communication, social relations, and interests (Volden, 2010, *Am I Speech Lang Pathol*). The CCC-2 takes approximately 5 to 15 minutes to administer to the parent/caregiver and has been validated for use in children between the ages of 4 to 16 years. In this study, the CCC-2 will be administered to parents/caregivers who are assessed by the KABC-II in order to get an estimation of language and communication development of the subject. Since language development assessment is already part of the BSID-III, the CCC-2 should not be completed by parents/caregivers of

the children who are assessed by BSID-III, unless as specified in Sections 5.1.8.3 and 5.1.8.4.

5.1.8.6 Children's Sleep Habits Questionnaire (CSHQ)

The CSHQ is a comprehensive, parent-reported screening survey that has been validated for children aged 4 to 10 years (Owens, 2000, *Sleep*); however, it will be completed, if possible, for all subjects treated in the study. The design of the CSHQ is based on common clinical symptom presentations of the most prevalent paediatric diagnoses as described in the *International Classification of Sleep Disorders* (Thorpy, 1990, *American Sleep Disorder Association*). The CSHQ takes approximately 20 minutes to complete and consists of 45 questions administered across 8 sleep-wake functions including bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night awakenings, sleep-disordered breathing, parasomnias, and daytime sleepiness.

5.1.8.7 Sanfilippo Behavior Rating Scale (SBRS)

The SBRS is a parent-reported assessment developed at the University of Minnesota specifically to assess patients with Sanfilippo syndrome or MPS III disease. The SBRS assesses communication and expression as well as behaviour and is administered as 3 sections. The initial assessment includes Section I (Communication), Section II (Temper Tantrums), and Section III (Behavior), which evaluates 15 areas of function that are important for or unique to children with Sanfilippo Syndrome. The 96 questions included in the initial assessment will take approximately 45 minutes to complete. The follow-up assessments include a specific follow-up version of Sections I, II, and III of the SBRS. This section will assess if there have been any changes since the last visit (increased, stayed the same, decreased). It will take approximately 45 minutes for the parent to complete the 96 questions during the follow-up assessments.

5.1.8.8 12-item Zarit Burden Interview (ZBI)

The 12-item ZBI is a caregiver self-report measure that is used to evaluate levels of stress for caregivers of patients with Alzheimer's disease or other forms of dementia. The 12-item ZBI, validated for use in cross-sectional, longitudinal, and interventional studies (Bédard, 2001, *Gerontologist*), represents a truncated form of the original 22-item ZBI thus enabling easier administration. The assessment takes approximately 5 minutes to complete and measures the caregiver's overall level of burden enabling physicians to identify caregivers who may be at high risk of developing physical and/or emotional problems.

5.1.8.9 10-item Short Form Health Survey for Children (SF-10)

The SF-10 is a parent-completed survey that contains 10 questions adapted from the Child Health Questionnaire and takes less than 5 minutes to complete. The SF-10 has been validated in children aged 5 to 18 years (Zhang, 2008, *Health Qual Life Outcomes*); however, it will be completed, if possible, for all subjects treated in the study under the age of 5. The SF-10 provides coverage across a wide range of domains, and is scored to produce physical and psychosocial health summary measures. The survey provides a quick and efficient means to measure health status. Due to its brevity, the SF-10 can be easily integrated and administered within a broader assessment, and is particularly applicable to large-scale child population surveys.

5.2 Clinical Laboratory Assessments

5.2.1 Routine Assessments and Biomarkers

A list of all clinical laboratory tests that will be performed is provided in Table 1; the time points for sample collection are specified in the SOA.

Blood collected for standard haematology and serum chemistry (including coagulation parameters) will be analysed locally.

During Screening, if a subject's ALT or AST is greater than 3 x ULN, or a subject has elevated bilirubin or PT/INR, confirmatory testing will be completed. Abnormal safety labs at Screening can be repeated within 1 to 2 weeks. The difference between these 2 pre-treatment values for each abnormal laboratory parameter should differ by < 20% for each subject.

Efforts should be made by the Investigator to review subject medical history, concomitant medications and health status so that a clear explanation for the elevation is established. The Investigator, in consultation with the Sponsor, shall make a determination of subject eligibility based on review of Exclusion Criterion 8.

During the study, after treatment with SBC-103, in the event that a subject's ALT or AST is 2 x ULN (when baseline ALT or AST was within normal limits) or 3 x ULN (when baseline ALT or AST was greater than 1.5 x ULN), or when a subject has an elevation in bilirubin or PT/INR a confirmatory test should be completed at the earliest possible time point, but not later than the next scheduled visit. Upon positive confirmation of the elevated transaminases as described above, dosing will be paused until AST and ALT have returned to baseline or to study nadir (nadir values may be confirmed by additional laboratory sampling at the discretion of the Investigator, using the same laboratory for analysis of each sample), or normalised if the baseline level was within normal limits. See Section 6.2 for stopping rules.

Every effort will be made to collect urine for urinalysis testing. If urine can be collected, a urine pregnancy test will be performed and analysed locally for females of child-bearing potential. If a urine sample is not able to be provided, a serum pregnancy test will be performed and analysed locally.

Serum, and where possible, urine, will be collected for analysis of MPS IIIB substrate (total HS) and other disease-related biomarkers including NRE HS derivatives. CSF will be collected via lumbar puncture for analysis of total HS and other disease-related biomarkers including NRE HS derivatives. All efforts will be made to obtain a blood sample to evaluate serum albumin and serum IgG at the same time as the CSF sample, as reflected in the SOA. The CSF-AI will be calculated as the CSF albumin (mg/mL)/serum albumin (g/L). IgG index will be calculated as the ([CSF/serum IgG ratio] / [CSF-AI]). Refer to Section 5.2.1.3 for details regarding the lumbar puncture.

A specific sample for biomarker analysis is being collected in this study; however, remaining blood and urine samples collected in this study may also be used to analyse additional biomarkers of potential clinical interest, if there is sufficient sample and where local regulations permit. As subjects with MPS IIIB may be incontinent, urine samples for routine assessments and biomarkers may not be able to be collected, but should be attempted whenever possible.

Due to the limitations on the volume of blood collection that is considered to be acceptable in young children with very small total circulating blood volumes; see Committee for Medicinal Products for Human Use and Paediatric Committee guidance (EMEA/536810/2008, adopted 25 June 2009), the blood laboratory tests will be ranked by tier. Per individual, the study-related blood loss should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 mL/kg body weight; 3% corresponds to about 2.4 to 2.7 mL blood per kg body weight.

Tier 1 assessments (see Table 1) are considered mandatory and all efforts should be made to collect these samples in all subjects. Samples for the Tier 2 or Tier 3 assessments will be collected if permitted based on the blood or CSF volume threshold for a subject's weight, as well as the subject's clinical status. All tests will be performed by a qualified laboratory.

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

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

Table 1: Clinical Laboratory Tests

Laboratory Parameter Panel	Tier	Local or Central Analysis	Matrix	Tests
Haematology	1	Local Lab	Whole blood	White blood cell count; red blood cell count; haemoglobin; haematocrit; MCV, MCH, MCHC; platelet count; neutrophils; lymphocytes; monocytes; eosinophils; basophils
Serum Chemistry	1	Local Lab	Serum	ALT, AST, alkaline phosphatase, GGT, albumin, total bilirubin, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus), glucose, creatinine, bicarbonate, total protein, blood urea nitrogen
Coagulation	1	Local Lab	Plasma	PT, INR
Urinalysis	N/A	Local Lab	Urine	pH, clarity, colour, specific gravity, glucose, ketones, blood, protein, nitrite, and leukocytes (microscopic examination will only be done if urinalysis is positive for blood, nitrite, or leukocytes, or if protein is > 1+)
Pregnancy test[a]	N/A	Local Lab	Urine	
MPS IIIB Diagnostics	1	Central Lab	Dried blood spot	NAGLU enzyme activity
PK	1	Central Lab	Serum	PK profile
PK	3	Central Lab	CSF	SBC-103 concentration
ADA	1	Central Lab	Serum	Anti-SBC-103 antibodies (IgM, IgG, and IgE). Subjects who experience a moderate or severe IAR should have a serum sample collected for ADA during the next study visit (≥ 4 days after the IAR) prior to the infusion.
Biomarkers	1	Central Lab	Serum	HS (total and NRE)
	2	Central Lab	Serum	Ferritin and chitotriosidase
	2	Central Lab	Plasma	Glutamic acid and glycine
	2	Central Lab	Serum	IgG, inflammatory markers, and biomarkers

Table 1: Clinical Laboratory Tests

Laboratory Parameter Panel	Tier	Local or Central Analysis	Matrix	Tests
	N/A	Central Lab	Urine	HS (total and NRE)
	1	Central Lab	CSF	HS (total and NRE)
	2	Central Lab	CSF	HGF, calbindin D, Tau, pTau, amyloid β, albumin, IgG, glutamic acid and glycine
	1	Central Lab	CSF/ Serum[b]	CSF/Serum Albumin Index (CSF-AI) and IgG index ([CSF/serum IgG ratio] / [CSF-AI])
	2	Local Lab	CSF	Routine findings (cell counts, glucose, protein)
Serum Tryptase	*If clinically indicated*	Central Lab	Serum	Subjects who experience a moderate or severe IAR should have a serum sample collected for analysis of tryptase 1-3 hours after the IAR onset and another serum sample for tryptase and ADA during the next study visit (≥ 4 days after the IAR) prior to the infusion.

Key: ADA = anti-drug antibodies; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CSF = cerebrospinal fluid; CSF-AI = cerebrospinal fluid/serum albumin index; GGT = gamma-glutamyl transpeptidase; HGF = hepatocyte growth factor; HS = heparan sulphate; IAR = infusion-associated reaction; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin M; INR= international normalised ratio; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; MCV = mean corpuscular volume; N/A = not applicable; NAGLU = alpha-N-acetylglucosaminidase; NRE = non-reducing end; PK = pharmacokinetics; PT = prothrombin time.

[a] Test performed by a local laboratory for all female subjects of child-bearing potential. If a urine sample is not able to be provided, a serum pregnancy test will be performed by a local laboratory.

[b] Ensure that serum albumin is collected at each time point a CSF sample is collected. If a serum chemistry is not scheduled at the same study visit, a serum albumin should be drawn.

5.2.1.1 Biomarkers

Blood samples for serum isolation will be obtained at the time points specified in the SOA for exploratory analyses to identify and evaluate disease-related biomarkers, where local regulations and blood volume threshold permits. A specific sample for biomarker analysis is being collected in this study; however, remaining blood or urine samples collected in this study may also be used to analyse additional biomarkers of potential clinical interest, if there is sufficient sample and where local regulations permit. These samples will be used to identify baseline disease and dynamic markers that will help the Sponsor to better understand the pathogenesis of MPS IIIB and related comorbidities and response to treatment. Given the rarity of MPS IIIB, the definitive list of analytes remains to be determined.

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

Samples will be stored by the Sponsor, or designee, in a secure and controlled environment until analysis, and will be destroyed by the Sponsor or designee after all worldwide obligations have been met, or sooner if required by local regulations. Biomarker assays will be performed by a central laboratory or, as appropriate, by academic research laboratories with expertise in the analysis of specific biomarkers.

Refer to the laboratory manual for further details regarding the collection, processing, and storage of these samples.

5.2.1.2 Pharmacokinetic Assessments

As described in Table 2 and the SOA, blood samples will be collected to determine SBC-103 serum concentrations using an enzyme-based PK assay. PK samples collected concurrently with vital sign assessments will be taken prior to collection of blood pressure on the non-infusion arm. PK samples collected at all other time points will be taken at least 5 minutes following deflation of the blood pressure cuff. PK samples should not be taken from the same extremity where the infusion catheter is in place.

CSF samples for determination of SBC-103 concentration in the CSF may also be collected from subjects if CSF volume limitations based on subject's age and weight have not been exceeded.

Table 2: Pharmacokinetic Sampling

	Day 0	Week 12	Week 24
Pre-infusion (within 30 minutes)	X	X	X
During Infusion			
5 minutes (±2 minutes)	X		
10 minutes (±2 minutes)	X		
30 minutes (±5 minutes)	X	X	X
50 minutes (±5 minutes)	X		
70 minutes (±5 minutes)	X		
90 minutes (±5 minutes)[a]	X	X	X
120 minutes/End of Infusion[b] (±5 minutes)	X	X	X
After Completion of Infusion			
5 minutes (±2 minutes)	X		
15 minutes (±2 minutes)	X	X	X
30 minutes (±5 minutes)	X	X	X
60 minutes (±5 minutes)	X	X	X
90 minutes (±5 minutes)	X	X	X
120 minutes (±5 minutes)	X	X	X
4 hours (±5 minutes)	X	X	X
6 hours (±5 minutes)		X	
8 hours (±15 minutes)	X		X
12 hours (±15 minutes)	X		X
24 hours (±15 minutes)[a]	X		X

[a] Time points may be omitted, if necessary, to avoid exceeding blood volume limitations.
[b] After the infusion bag has been emptied, but prior to the flush.

Table 2 (continued): Pharmacokinetic Sampling

	Week 52	Week 78	Week 104	Week 130	Week 156
Pre-infusion (within 30 minutes)	X	X	X	X	X
During Infusion					
30 minutes (±5 minutes)	X		X		X
90 minutes (±5 minutes)[a]	X		X		X
120 minutes/End of Infusion[b] (±5 minutes)	X		X		X
After Completion of Infusion					
30 minutes (±5 minutes)	X		X		X
2 hours (±5 minutes)	X		X		X
4 hours (±15 minutes)	X		X		X
6 hours (±15 minutes)	X		X		X

[a] Time points may be omitted, if necessary, to avoid exceeding blood volume limitations.
[b] After the infusion bag has been emptied, but prior to the flush.

5.2.1.3 Lumbar Puncture (Cerebrospinal Fluid)

Lumbar punctures will be performed for the collection of CSF at the time points specified in the SOA. The lumbar puncture may be performed under general anaesthesia, if clinically appropriate, or under light sedation and will be performed as per local practices by a qualified professional in accordance with local institutional procedures. The first 10 mL of CSF will be collected and mixed gently to avoid gradient effects. The actual volume may be adjusted based on subject age or size and local institutional guidelines. If CSF volume is limited, the analysis of CSF HS (total and NRE) should be prioritised as noted in Table 1.

Routine CSF findings will also be documented (e.g., cell counts, glucose, and protein levels), and MPS IIIB substrate (HS) and other CSF biomarkers will be analysed (see Table 1 for details).

Per the SOA, collection of serum chemistry will not always coincide with the collection of CSF. In order to measure the CSF-AI at each possible time point, a serum albumin sample should be collected at time points where a serum chemistry sample is not being collected at the same day as the CSF sample.

After the lumbar puncture is completed, the subject should be observed as per institution standard practice. Vital signs should be obtained prior to discharge. Any AEs or changes to concomitant medications should also be assessed.

5.2.2 Facial Dysmorphology Novel Analysis

Facial photographs will be obtained for FDNA at the time points specified in the SOA. This technology enables automatic detection and evaluation of subtle craniofacial dysmorphology associated with multiple rare diseases, by processing and analysing standard 2-dimensional facial photos. The FDNA system uses proprietary computer algorithms to recognise and describe subtle craniofacial malformations (out of a list of clinically relevant anatomical facial features) in mathematical terms. A ranked score, representing the probability of the genetic syndrome, is produced based on analysis of the severity of the facial alterations relative to variations in a normal population, as well as recognition of the face "gestalt" associated with certain rare diseases. FDNA offers potential as a tool for screening large populations for MPS IIIB, which may enable wider and earlier diagnosis of MPS IIIB patients, as well as providing a means for monitoring progression of disease in patients diagnosed with MPS IIIB. This study will evaluate FDNA technology as a means to evaluate both clinical characteristics and course of disease progression in MPS IIIB. FDNA assessment will be optional based on subject/parent consent to participate. A subject/caregiver may refuse this assessment and still participate in this study. Once a subject/caregiver consents to this assessment, all attempts should be made to collect data at each study time point.

5.2.3 General Anaesthesia/Sedation

Subject compliance and maintenance of appropriate and stable positioning during the MRI procedure is complicated due to the anticipated behaviour disturbances characteristic of MPS IIIB subjects. A key advantage of general anaesthesia is that it minimises any potential for stress or anxiety during the procedure and is independent of a subject's ability to cooperate, which is critical with MPS IIIB subjects. The whole process, including preparation and scan time, is more predictable, and the scan quality will benefit as a result of the subject being immobilised.

Thus, subjects will receive general anaesthesia prior to the MRI procedure. In principle all types of general anaesthesia techniques can be used as long as the subject is kept asleep during the MRI procedure. The decision should depend on comorbidities, anatomy, and fasting status in the individual case and the procedures and practices of the institution. In clinical practice and in earlier studies with subjects with MPS III, propofol sedation was used together with a laryngeal mask to guarantee a secure airway and to not unnecessarily prolong the procedure. The IV properties of propofol make it an ideal anaesthetic for subjects undergoing imaging assessments. An IV anaesthetic without endotracheal intubation allows for careful titration of sedation to achieve a clinical effect. Propofol provides the ability to titrate an anaesthetic level rapidly and maintain stable drug concentrations during the procedure, thus ensuring that anaesthesia is administered in a timely and consistent manner. Recovery from this type of anaesthesia is rapid and not accompanied by nausea or vomiting. Often the anaesthetic can be delivered allowing the subject to breathe spontaneously. Competency of airway is accomplished by the insertion of a laryngeal mask airway which allows ventilation of the subject in the cases required. Appropriate local procedures should be utilised under supervision of a paediatric anaesthesiologist, however, in subjects aged 1 to 10 years, a dose of 100 mcg/kg/min will be sufficient to keep the subject asleep with no movement during the scan. If the subject has an IV in place, then a bolus of 2 to 10 mg/kg (depending on age) can be given initially, followed by a continuous infusion of propofol.

If no IV is in place, then anaesthesia can be induced with an inhalative narcotic such as halothane or sevoflurane (with N_2O and oxygen), and IV can be inserted, and then continuous infusion of propofol started (Schulte-Uentrop, 2010, *Curr Opin Anaesthesiol*).

As indicated in Section 5.2.1.3, if clinically appropriate, lumbar punctures may also be performed under general anaesthesia in accordance with local institutional procedures. When applicable, the lumbar puncture should be performed just prior to the MRI scan and prior to dosing. Lumbar puncture, when not performed alongside the MRI scan, may also be performed under light sedation.

If clinically indicated, subjects may also receive general anaesthesia or sedation for central line placement for long-term vascular access, in accordance with institutional guidelines. When possible, the procedure to place the central line should be performed while the subject is already anaesthetised or sedated for another study procedure.

5.2.4 Structural and Diffusion MRI

MRI will be performed at the time points specified in the SOA.

High-resolution whole-brain T1-weighted and T2-weighted images will be acquired in order to enable measurements of brain volume and relative volumes of grey and white matter.

Whole-brain diffusion MRI will also be acquired with multiple diffusion sensitization orientations, *b* value $\geq$ 1000 s/mm^2. This will enable measurement of diffusion tensor parameters, including mean diffusivity (mean apparent diffusion coefficient) and fractional anisotropy, as well as anatomical connectivity mapping.

The estimated total scan time will be approximately 5 to 10 minutes for structural MRI sequences and 15 minutes for diffusion MRI sequences. All imaging scans will be read centrally. Detailed instructions on image acquisition and analysis will be provided in the Imaging Manual.

5.2.5 Telephone Calls

A follow-up telephone call will be made to each subject (or the subject's parent or caregiver) within 24 hours after each of the subject's second, third, and fourth doses to assess AEs.

At least 4 weeks after a subject's last dose of SBC-103 is administered, the subject (or the subject's parent or caregiver) will receive a follow-up phone call to assess AEs and concomitant medications unless the subject has a scheduled follow-up study visit.

6 STUDY TREATMENTS

6.1 Treatments Administered

All subjects in the study will receive qow (every 14 days ± 5 days) IV SBC-103 for 156 weeks. Infusions must be administered at least 10 days apart. All study visits will be scheduled relative to Day 0. Each subject will receive 1 mg/kg for at least 12 weeks prior to consideration for a dose escalation. After evaluation of an individual subject's safety, tolerability, and PD data, a dose increase to 3 mg/kg may be implemented for that subject if the 1 mg/kg dose is well tolerated.

Subsequent modifications to the dosing schedule, or dose increases or decreases, may be considered by the Sponsor, after consultation with the PI, for each subject throughout the study based on a review of safety, tolerability, and PD data for that subject and other available safety data from the SBC-103 program.

6.1.1 Dose Adjustments

The maximum planned dose to be evaluated in this study is 3 mg/kg administered by IV infusion. In the event of poor tolerability at any time during the study the dose may be reduced or paused. If a subject cannot tolerate the lowest dose (0.3 mg/kg qow) despite measures taken to manage any IARs or other significant safety events, the subject will be discontinued from treatment. See Section 7.1.3 for guidelines for diagnosis and management of IARs and Section 6.2 for stopping rules for individual and multiple subjects.

6.1.2 Non-compliance with Study Treatment

If during the 156-week treatment period a subject misses ≥ 3 consecutive infusions, additional assessments will be required prior to resuming dosing, including safety labs (haematology, chemistry, coagulation, urinalysis and pregnancy test, where applicable), and serum and urine HS. If ≥ 6 consecutive infusions are missed, additional assessments, including lumbar puncture for CSF collection, may be required prior to resuming dosing as determined by the Sponsor in consultation with the Investigator. The next scheduled lumbar puncture would not be necessary if ≤ 2 months have elapsed since the previous lumbar puncture.

6.2 Stopping Rules

6.2.1 Stopping Rules in Individual Subjects

During the study, subjects who experience a severe IAR, an AE considered related to SBC-103, or significant elevation in specific laboratory values, will have SBC-103 dosing paused based on the rules described below.

For IARs:

- Subjects who develop a severe IAR as defined in Section 7.1.3, must stop treatment until their information is reviewed by the Sponsor and PI. Dosing with alterations to the infusion regimen (e.g., pre-treatment or slowing the rate of infusion) may resume once the Sponsor and PI approve.

- Subjects with mild or moderate IARs can continue receiving SBC-103 in the study. The Sponsor, in consultation with the PI, may recommend alterations to the infusion regimen (e.g., pre-treatment or slowing the rate of infusion).

For all other AEs (i.e., AEs that are not characterised as IARs):

- Any event considered related to SBC-103 which is either serious or severe will result in pausing additional dosing in an individual subject. The Sponsor and PI will review the data and will resume dosing only after review and agreement.
- Subjects with mild or moderate non-serious AEs can continue receiving SBC-103 in the study.

For laboratory values:

- Dosing will be paused based on confirmed elevations in ALT or AST under the following circumstances:
    - In the event that a subject's ALT or AST is ≥ 2 x ULN (when baseline ALT or AST was within normal limits).
    - In the event that a subject's ALT or AST is ≥ 3 x ULN (if baseline ALT or AST greater than 1.5 x ULN).

Dosing will only resume after ALT or AST have returned to baseline or to study nadir (nadir values may be confirmed by additional lab sampling at the discretion of the Investigator, using the same lab for analysis of each sample), or normalised if the baseline level was within normal limits.

When dosing is resumed it should be restarted at a reduced dose. For example, if a subject was receiving a dose of 3 mg/kg, he/she would be restarted at 1 mg/kg. If a subject was receiving a 1 mg/kg dose, he/she would be restarted at 0.3 mg/kg. In the event that the subject was receiving a dose of 0.3 mg/kg, he/she may resume at the 0.3 mg/kg dose. Dosing in an individual subject will be resumed only after ALT or AST have returned at least to baseline or to study nadir (nadir values may be confirmed by additional lab sampling at the discretion of the Investigator, using the same lab for analysis of each sample), or normalised if the baseline level was within normal limits.

If after resuming treatment at the lower dose, the ALT or AST elevation recurs at greater than or equal to 2 x ULN (for those with ALT or AST within normal limits at baseline) or 2 times the baseline value (for those with abnormal ALT or AST at baseline) study drug should be stopped and not resumed.

Dosing will also be paused based on confirmed elevations in ALT or AST with accompanying elevations in any of the following:

- Confirmed bilirubin > 1.5 x ULN.
- Confirmed INR > 1.5 .
- Eosinophilia (> 5%), rash, or fever.

If bilirubin and INR values normalise and the Sponsor and PI believes that it is safe to resume dosing, the subject may resume dosing with the dose reduced by 1 level (e.g., those previously receiving 3 mg/kg would reduce the dose to 1 mg/kg and patients receiving 1 mg/kg would reduce the dose to 0.3 mg/kg). However, in this scenario, any subject developing recurrent elevations in ALT or AST (with or without elevations in total bilirubin, INR, eosinophilia [more than 5%], rash, or fever) should not be restarted on the study drug.

6.2.2 Stopping Rules for Multiple Subjects

If 2 subjects experience a similar severe event or SAE, or any subject experiences a life threatening AE that is considered to be at least possibly related to SBC-103, dosing will be stopped for this study. The independent Safety Review Committee and the Sponsor will evaluate the data and will resume dosing only after review and agreement, including review and approval by local regulatory authorities, where required.

Detailed information regarding the composition of the SRC, the safety data to be reviewed, and the data review process will be included in the SRC charter.

Either of the SRC and Sponsor may request a pause in dosing of all subjects based on review of reported events and all available data from this and other studies in the program. Dosing will resume only after the review of data and agreement to do so by the SRC and Sponsor.

6.3 Description of SBC-103

The reference document for SBC-103 is the Investigator Brochure. SBC-103 must be administered under close supervision of the Investigator, or designee.

The study drug will be provided in a 10-mL glass vial containing approximately 10.5 mL (including 5% overfill) of a buffered solution of SBC-103 at a concentration of 2 mg/milk The study drug contains no preservatives and vials are single use only.

6.4 Method for Assigning Subjects to Treatment Groups

Not applicable as there is only 1 treatment group in this study.

6.5 Storage and Disposition of SBC-103

6.5.1 Receipt of Drug Supplies

Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable SBC-103 in a given shipment will be documented in the study files. The Investigator must notify study Sponsor of any damaged or unusable study treatments that were supplied to the Investigator's site.

6.5.2 Storage

All SBC-103 vials must be stored at a controlled temperature of 2°C to 8°C. Vials should not be frozen and should be protected from light during storage.

The infusion bag or syringe containing SBC-103 diluted in 0.9% saline should be prepared immediately before infusion. Dilution should occur under controlled and validated aseptic conditions. The prepared diluted infusion bag (or syringe) may be stored at room temperature (20°C to 25°C) for no more than 8 hours, although it is preferable that prepared solution be used within 4 hours of dilution. Shaking or other forms of agitation of vials or infusion bags should be avoided. Refer to the IMP Manual for detailed instructions.

6.5.3 Disposition

The Investigator or designee (e.g., a licensed pharmacist) will be responsible for maintaining accurate records for all supplies used. Opened vials of SBC-103 containing residual volume will be stored at room temperature for SBC-103 accountability. Following SBC-103 accountability, the Sponsor will provide authorisation to the Investigator to return or destroy any remaining investigational product as instructed.

Under no circumstances will SBC-103 be used other than as directed in the protocol. Refer to the IMP Manual for additional details.

6.6 Preparation and administration of Study Drug

6.6.1 Preparation of Study Drug

Dose preparation and administration should be performed using sterile, non-pyrogenic disposable materials including, but not restricted to syringes, needles, transfer tubing, and stopcocks.

The infusion bag (or syringe) containing SBC-103 should be prepared just prior to the start of IV infusion. It is preferable that the prepared diluted infusion is used within 4 hours of dilution, although it may be stored at room temperature for up to 8 hours.

Prior to preparation of the infusion, the vials of study drug should be visually inspected. The solution should not be used if it contains foreign particulate matter or is discoloured. The solution may be used if a small number of visible translucent to opalescent or white amorphous or threadlike particles are present in the vial. The contents should NOT be warmed using a microwave or other heat source. SBC-103 is a protein and should be not be shaken but should be handled and mixed gently to prevent foaming.

The subject's most recent protocol-scheduled weight measurement, rounded to the nearest 0.1 kg, will be used for calculating the volume of study drug to be withdrawn from the vial(s) to prepare the IV infusion. Study drug will be diluted in 0.9% saline for injection.

Refer to the IMP Manual for detailed instruction regarding the preparation of the IV infusion.

6.6.2 Administration of Study Drug

All infusions must be administered under close supervision of the Investigator, or designee. Study drug should not be infused with other products in the same infusion tubing, as the compatibility of SBC-103 in solution with other products has not been evaluated. It is recommended that all infusions of study drug be administered using in-line filtration with a low protein binding 0.2 μm filter.

The recommended duration of the infusion is 2 hours at a constant rate. The protocol allows for a change in rate should the subject experience an IAR. At the discretion of the Investigator, and in consultation with the Sponsor, in circumstances such as a prior IAR or other like situations where subject safety is a concern, an extended duration of infusion or a variable rate is acceptable. If the infusion is not well tolerated, the infusion rate may be decreased or interrupted as noted in Section 7.1.3 and Section 6.2. All changes to infusion rate must be carefully recorded in the CRF, including the start and stop time of each rate change.

Refer to the IMP Manual for detailed instruction on the administration of SBC-103.

6.7 Blinding of SBC-103

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

6.8 Destruction of SBC-103

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

7 ASSESSMENT OF SAFETY

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

7.1 Adverse Events and Laboratory Abnormalities

7.1.1 Clinical Adverse Events

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

All AEs occurring during the clinical study will be reported in the AE page of the CRF.

The Investigator will assess the severity, causality (relationship to study drug), and seriousness of each AE.

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

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

Causality: AEs will be assessed as not related, unlikely related, possibly related, or related to study drug. Table 3 provides general guidance on the assessment of causality. For data reporting purposes, AEs assessed as not related or unlikely related will be classified as unrelated to study drug, and AEs assessed as possibly related or related will be classified as related to study drug. Assessment of causality should be based on the Investigator's medical judgment and the observed symptoms associated with the event.

Table 3: Assessment of Causality

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

Seriousness: AEs will be classified as serious or non-serious according to the definitions provided below.

An SAE is any AE that is or leads to any of the following:

- Death.
- Immediately life threatening. An AE is considered "life threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Requires in-patient hospitalisation or prolongation of existing hospitalization.
- Congenital anomaly/birth defect.
- Persistent or significant disability or incapacity.
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

A planned hospitalization to accommodate a study procedure is not considered an SAE. However, during the hospitalization, AEs will be collected and assessed for seriousness and reported appropriately (i.e., important medical event or prolonged hospitalization).

All AEs that do not meet any of the criteria for an SAE should be regarded as ***non-serious AEs***.

All SAEs and IARs must be reported to the Sponsor as described in Section 7.4.1.

7.1.2 Laboratory Test Abnormality

Laboratory test results will be recorded, or appear on the laboratory reports submitted directly from the laboratory. Out-of-range laboratory test values should not be reported as AEs unless they are considered to be clinically significant abnormalities by the Investigator.

7.1.3 Adverse Events of Special Interest (Infusion-Associated Reactions)

IARs will be considered AEs of special interest. Any AE that occurs during the infusion or within 4 hours after the infusion is completed and is assessed by the Investigator as at least possibly related to study drug will be designated as an IAR. In addition, if, at any time during the study, the Investigator observes symptoms that he/she considers to be consistent with an IAR or hypersensitivity reaction related to administration of study drug, the symptoms should be recorded as an AE(s) and designated as an IAR(s). Individual AE terms should be recorded rather than the terms IAR or Infusion Associated Reaction.

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

General guidelines for classifying the severity of a reaction are provided in Section 7.1.1.

For similar biological products, most acute IARs occur within 2 hours of the infusion. Signs of a possible acute IAR may include:

- Hyperemia, flushing, fever and/or chills, nausea, pruritus, urticaria, gastro-intestinal symptoms (vomiting, diarrhoea, abdominal cramping), cardiopulmonary reactions, including chest pain, cardiac arrhythmias, dyspnoea, wheezing, stridor, hypotension, or hypertension.

Table 4 includes dose modifications required for all IARs and general guidance for the diagnosis and management of IARs in accordance with the institution's standard of care. The Investigator should use clinical judgement in the management of IARs in individual subjects participating in this study. In the case of a severe life-threatening reaction, current medical standards for emergency treatment are to be followed.

Table 4: Guidelines for the Management of Infusion-associated Reactions (IARs)

Symptoms	Action
Mild Reaction Common • Hyperemia (flushing) • Flushing • Lightheadedness • Nausea • Mild chest discomfort (tightness) Less Common • Fever and/or shivering • Palpitations • Headache • Irritability (especially in young children)	• Slow infusion rate by 50% • Administer antipyretic and/or antihistamine • Decrease infusion rate by a further 25% if symptoms persist • If the event resolves, the infusion should continue at a reduced rate for a minimum of 30 minutes before the infusion is increased to 75% of original rate. If the subject tolerates the infusion at 75% of the original rate for at least 30 minutes the original rate may be restored for the remainder of the infusion. • If reactions persist despite rate reduction, stop infusion • Pre-treat with antihistamine and antipyretic prior (approximately 1.5 hours) to next infusion • e.g., diphenhydramine (1 mg/kg) by mouth and acetaminophen (15 mg/kg) by mouth
Moderate Reaction • Hyperemia (flushing) • Chest discomfort • Itching and/or raised urticarial rash • Severe headache • Gastrointestinal symptoms, vomiting, diarrhoea, abdominal cramping	• Stop infusion • Give antihistamine IV and consider IV or oral steroids in accordance with institutional standard of care • Consider giving a beta-adrenergic inhaler treatment if appropriate • If the event resolves, the infusion may continue at a reduced rate of 50% of the original for a minimum of 30 minutes before the infusion is increased to 75% of the original rate. If the subject tolerates the infusion at 75% of the original rate for at least 30 minutes the original rate may be restored for the remainder of the infusion. • If reaction persists despite rate reduction stop infusion • Pre-treat with oral antihistamine and antipyretic prior to next infusion • Collect serum for analysis of tryptase 1-3 hours after the IAR onset and another serum sample for tryptase and ADA during the next study visit (≥ 4 days after the IAR) prior to the infusion. • Consider skin testing

Table 4: Guidelines for the Management of Infusion-associated Reactions (IARs)

Symptoms	Action

Severe Reaction
• Clinically significant cardiovascular effects: e.g., hypertension or hypotension defined as a decline approaching 20-30% of their preinfusion value without alternative aetiology (agitation, pain, fluid overload, dehydration)
• Respiratory symptoms: Significant shortness of breath, stridor, wheezing, laryngeal oedema, swelling of tongue
• Cardiac arrhythmias
• Anaphylactic/anaphylactoid shock with hypotension and circulatory collapse
	• Stop infusion
	• Give oxygen, if available
	• Give epinephrine (adrenaline)
	• Give antihistamines IV and steroids IV
	• Consider giving a beta-adrenergic inhaler treatment if appropriate
	• Collect serum sample for tryptase 1-3 hours after the IAR onset and another serum sample for tryptase and ADA during the next study visit (≥ 4 days after the IAR) prior to the infusion
	• Consider skin testing
	• Dosing of the subject will be suspended until the SRC has completed review of the IAR, and any other relevant safety data and any other relevant safety data (Section 6.2)
	• In the event subject is approved by the SRC for resumption of dosing:
	  • Pre-treat with antihistamine and antipyretic prior to next infusion
	  • Slowly up-titrate the infusion rate during the subsequent infusion: e.g., if previous rate was 50 mL/h, begin at 0.25 x previous rate (12.5 mL/h) x 15 min, then increase to 0.5 x rate (25 mL/h) x 15 min, then increase to 0.75 x rate (37.5 mL/h) x 15 min, then increase to full rate (50 mL/h) for the remainder of the infusion

Key: ADA = anti-drug antibodies; IAR = infusion-associated reaction; IV = intravenously; SRC = Safety Review Committee.

7.2 Handling of Safety Parameters

7.2.1 Serious Adverse Events and Infusion-Associated Reactions (Immediately reportable to the Sponsor)

All SAEs **and** all IARs (serious and non-serious), irrespective of the treatment received by the subject, must be reported to the Sponsor or designee immediately and no later than 24 hours of the Investigator's first knowledge of the event (expedited reporting).

The definition and reporting requirement are in accordance with ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting (Topic E2, 1995).

7.2.2 Adverse Event Reporting Period

The study period during which AEs must be reported is defined as the period from signature of the informed consent to the end of the study treatment follow-up. AEs occurring after signing the informed consent but prior to the first dose of study medication will only be recorded if assessed as related to protocol procedures or requirements. For this study, the study treatment follow-up is defined as a minimum of 30 days following the last administration of study treatment. If a subject experiences an SAE that is considered to be related to study treatment at any time after the study, it must be reported to the Sponsor.

7.2.3 Treatment and Follow-up of Adverse Events

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

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

7.2.4 Follow-up of Abnormal Laboratory Test Values

In the event of unexplained clinically significant abnormal laboratory values, the tests should be repeated immediately and followed up until they have returned to baseline values and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded. All subjects showing possible drug-induced liver injury should be evaluated by a hepatologist for other causes of elevated hepatic function tests and followed until all abnormalities return to normal or baseline, or are deemed not to be related to the study drug.

See Sections 5.2.1 and 6.2.1 regarding pausing rules for subjects with significantly elevated transaminases.

7.2.5 Pregnancy

Female subjects who are of childbearing potential at the time of consent or who become of childbearing potential during participation on study must agree to use a highly reliable method of birth control (expected failure rate less than 5% per year) for the duration of the study and for 30 days after the last dose of SBC-103.

Male subjects and their partners, must use a highly reliable method of birth control (expected failure rate less than 5% per year) for the duration of the study and for 30 days after last dose of SBC-103.

As described in the *Clinical Trial Facilitation Group Recommendations related to contraception and pregnancy testing in clinical trials dated 2014-09-13*, acceptable contraceptive methods which may be considered as highly effective are summarized in Table 5.

Table 5: Acceptable Contraceptive Methods Which May Be Considered Highly Effective

Contraceptive Methods	Notes
Oral, intravaginal or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation	Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method. Implantable progestogen-only hormonal contraception is a contraceptive method that is considered to have low user dependency.
Oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation	
Intrauterine device (IUD)	These contraceptive methods are considered to have low user dependency.
Intrauterine hormone-releasing system (IUS)	
Bilateral tubal occlusion	
Vasectomised partner	A vasectomized partner is a contraceptive method that is considered to have low user dependency. In addition a vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
Sexual abstinence	Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Reference: Clinical Trial Facilitation Group; Recommendations related to contraception and pregnancy testing in clinical trials, FINAL VERSION 2014-09-13

A female subject must immediately inform the Investigator if she becomes pregnant during the study and must not receive further SBC-103 infusions. Pregnancies occurring up to 90 days after the completion of the last infusion must be reported to the Investigator. The Investigator must report all pregnancies to the Sponsor within 24 hours of notification. The Investigator should counsel the subject discussing the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy.

Pregnancy occurring in the partner of a subject participating in the study within 90 days of completion of the last infusion must also be reported to the Investigator and Sponsor. The partner should be counselled and followed as described above.

7.3 Recording of Adverse Events

At each contact with the subject (and the subject's parent or caregiver), the Investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs should be recorded immediately in the source documentation and in the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded under a single diagnosis.

AEs will be recorded from the time of signing of the informed consent until completion of the last scheduled visit, i.e., the follow-up visit. AEs occurring after signing the informed consent but prior to the first dose of study medication will only be recorded if assessed as related to protocol procedures or requirements. Any AEs remaining unresolved should be recorded as ongoing. Ongoing AEs/SAEs should continue to be followed up for the period specified in Section 7.2.2 but without further recording in the CRF. However, follow-up information on SAEs must be reported to the Sponsor or designee as described in Section 7.4.1. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

Any AE that occurs within 24 hours of the infusion will be recorded by time and date. AEs occurring more than 24 hours after the infusion will be recorded by date only. The date and time, or the date when the AE started and stopped, as well as the intensity, seriousness, action taken with regard to the SBC-103, causality assessment and outcome of the event will be recorded for each AE.

7.4 Reporting of Serious Adverse Events, Infusion-Associated Reactions, and Unanticipated Problems

Investigators and the Sponsor must conform to the AE reporting timelines, formats, and requirements of the various entities to which they are responsible (§13 GCP-V; Detailed guidance on the collection, verification and presentation of AE/reaction reports arising from clinical trials on medicinal products for human use ['CT-3']; US CFR Title 21, §312.32, Investigational New Drug [IND] safety reporting). The Sponsor or designee will report all reportable events to all Regulatory Authorities, IECs or IRBs, and Investigators as required by local regulations.

All SAEs and IARs, and other reportable events (see Section 7.4.3) must be reported to the Sponsor or designee in an expedited manner according to timelines described in Section 7.4.1.

7.4.1 Investigator Reporting: Notifying the Sponsor

Periodic safety reporting to Regulatory Authorities will be done by the Sponsor according to national and local regulations. Any SAE, IAR, or unanticipated problem posing risk of harm to subjects, must be reported to the Sponsor or designee immediately and no later than 24 hours after the Investigator's first knowledge of the event. To report such events, an SAE/IAR form must be completed by the Investigator and sent within 24 hours. The Investigator will keep a copy of this SAE/IAR form on file at the study site.

The Investigator will provide any additional information within 24 hours of becoming aware of this information. This should include a copy of the completed SAE or IAR form, and any other information that will assist with the understanding of the event. Significant new information on ongoing SAEs or IARs must be reported to the Sponsor or designee immediately and no later than 24 hours after the Investigator's becomes aware of this information.

Report SAEs and IARs by fax to:

PPD Pharmacovigilance Fax	
EU	+44 1223 374102

7.4.2 Investigator Reporting: Notifying the IRB/IEC

Unanticipated problems posing risks to subjects or others as noted above will be reported to the IRB/IEC according to local regulations. Copies of each report and documentation of IRB/IEC notification and receipt will be kept in the Investigator's study file.

7.4.3 Sponsor Reporting: Notifying Regulatory Authorities

The Sponsor is required to report certain study events in an expedited manner to the US Food and Drug Administration, the European Medicines Agency, and to all country Regulatory Authorities where the study is being conducted. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- Immediately and within 7 calendar days
    - Any suspected adverse reaction that is: associated with the use of the study drug, unexpected, and fatal or life threatening.
    - Follow-up information must be reported in the following 8 calendar days.
- Immediately and within 15 calendar days
    - Any suspected adverse reaction that is: associated with the use of the study drug, unexpected, and serious, but not fatal or life threatening.
    - Any finding from tests in laboratory animals that: suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
    - Any event in connection with the conduct of the study or the development of the IMP that may affect the safety of the study subjects.
    - Follow-up information must be reported within 15 calendar days.

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

7.4.4 Sponsor Reporting: Notifying Participating Investigators

It is the responsibility of the Sponsor or designee to immediately notify all participating Investigators of any AE associated with the use of the drug that is both serious and

unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects.

7.5 Independent Safety Review Committee (SRC)

It will be the responsibility of the PI to oversee the safety of the study at his/her site. Additional oversight of the subject safety in the study will be provided by an independent SRC composed of individuals with pertinent medical expertise, who will serve in advisory capacity to the Sponsor, to provide an additional level of scrutiny to minimise the chance that clinical study participants are exposed to unreasonable or unnecessary risks. The SRC will provide additional oversight for safety through a bi-annual review of safety data, and will also be available for consultation on modification of dosing frequency, stopping of dosing in individual subjects or all subjects in accordance with the stopping rules (see Section 6.2). The composition of the SRC and their specific activities will be outlined in the SRC Charter which will be ratified during the initial meeting, prior to commencement of dosing of the study subjects. The SRC will be tasked with ongoing review of safety data in order to advise the Sponsor regarding continued dosing and dose escalation decisions for the study (see Section 3.3.3). These safety monitoring functions and the oversight of such activities will be distinct from the requirement for study review and IRB/IEC approvals.

Core members of the SRC will not participate in the study as Investigators or sub-Investigators, as members of any team otherwise participating in the study, or in any other capacity that may compromise their privileged activities on the SRC. Neither members of the SRC nor their immediate family members will have a direct financial interest in the Sponsor or an interest that is dependent of the outcome of the study. To be considered for SRC membership, all candidates must disclose all actual or potential conflicts of interest, including any financial interest in, or research activity on a competing product. SRC members will be compensated at an appropriate market rate for time spent reviewing, discussing, and attending the meetings. The Sponsor will also reimburse SRC members for any out-of-pocket travel expenses required for attendance at the meetings. Aside from the above, SRC members will receive no additional compensation for their membership on the committee as outlined in the SRC Charter.

8 STATISTICAL PLAN

8.1 General Considerations

Descriptive summary statistics will be provided for baseline demographics, disease characteristics, and drug exposure. Subject disposition including number of subjects screened, enrolled, dosed, and percentage of subjects who discontinued from the study, along with reasons for discontinuations will be tabulated and described in listings.

Continuous data will be descriptively summarised (by number of subjects, mean, standard deviation, median, minimum, and maximum), and, where appropriate, graphic representation and 2-sided 95% confidence interval (CI) estimates. Categorical data will be summarised by sample size, proportions, and 2-sided 95% CIs where possible.

Descriptive summaries of data will be presented overall for all treated subjects and by dose cohort.

8.2 Determination of Sample Size

The sample size of up to 5 subjects is determined by the number of subjects enrolled in the prior NGLU-CL01 study, based on clinical and not statistical consideration. Along with data from other NGLU studies this data, including PD/efficacy data, will inform dose selection, regimen, and study design for future studies.

8.3 Analysis Sets

The Full Analysis Set (FAS), defined as all subjects for whom informed consent has been obtained, who have a confirmed diagnosis of MPS IIIB, and who have received any amount of SBC-103, will be used to summarise safety and tolerability data.

Analysis will include datasets based on the following study periods:

- Observational Period: the NGLU-CL01 study visit to baseline (pre-dose) of the NGLU-CL01-T study.
- On-Treatment Period: baseline of the NGLU-CL01-T study to end of the NGLU-CL01-T study.
- Overall Study (Observational+On-Treatment Period): the NGLU-CL01 study visit to end of the NGLU-CL01-T study.

To facilitate the descriptive summarisation of the above described data sets, baseline data contained in the NGLU-CL01 study database for these subjects, including medical history, demographics, concomitant medications, physical examination, safety labs, CSF, serum and urine HS, biomarkers, Vineland-II, and data from structural and diffusion MRI, will be transferred to and merged with the NGLU-CL01-T study database.

On-study data from subjects in the NGLU-CL01 study for endpoints including NAGLU enzyme activity, concomitant medications, physical examination, vital signs, weight, ECG, Vineland-II, haematology, clinical chemistry, urinalysis, CSF, serum and urine HS, serum albumin, serum ferritin and chitotriosidase, plasma glutamic acid and glycine, CSF: calbindin, Tau, pTau, albumin, IgG, glutamic acid and glycine, routine analysis-cell counts, glucose and protein, structural and diffusion MRI that are contained in NGLU-CL01 database will also be copied and merged with NGLU-CL01-T database.

Also any additional assessments (e.g., neurocognitive and developmental assessments, lab data including serum and urine HS, biomarker data and concomitant medication) available in these subjects since the NGLU-CL01 study visit until the baseline of NGLU-CL01-T will also be captured in the NGLU-CL01-T database.

All available observational period data from subjects enrolled in the NGLU-CL01 study for assessments also performed in the NGLU-CL01-T study will be copied and merged with the NGLU-CL01-T study database in order to facilitate analysis of changes in these assessments over both the untreated and treated periods.

Details of the planned analyses will be provided in the statistical analysis plan (SAP).

8.4 Safety Analysis

Descriptive statistics will be computed for safety parameters as per FAS, as appropriate. Number and percentage of subjects who discontinued from the study because of AEs, will be tabulated across doses; severity and frequency of AEs and SAEs will also be tabulated across doses. All other safety data will be provided in listings. Baseline (as described in Section 8.3), within study, end of study, and change from baseline in physical examination findings, ECG, clinical laboratory values, and vital signs will be summarised by dose.

The number and proportion (percentage) of subjects with measurable antibodies to SBC-103 will be displayed. In addition, incidence of IARs will be tabulated by dose and overall. Medications to treat IARs, including any pre-treatment medications, will also be presented by dose and for the entire study period. SBC-103 infusions in which the rate was slowed or discontinued due to IARs will be detailed in a separate data listing.

Additional statistical evaluations may be carried out for select endpoints, if warranted. All baseline and safety data collected during the study will be included in subject listings.

8.5 Pharmacokinetic Analysis

PK analysis will be performed using non-compartmental analysis method. Graphs of PK concentration over time will be generated for each subject and also for all subjects in a dose group. Serum PK parameter (C_{max}, T_{max}, AUC_{∞}, $T_{1/2}$, Cl, and V_{ss}) assessments will be summarised for each subject, as well as for each dose group, using non-compartmental analysis method. SBC-103 concentration in CSF will be summarised at available time points. Additional analysis of PK data, including assessment of the impact of ADA, may be performed as appropriate.

Further details will be provided in the PK section of the SAP or in a separate clinical pharmacology analysis plan.

8.6 Pharmacodynamic/Efficacy Analyses

Parameters describing total HS and exploratory disease-related biomarkers including NRE HS derivatives, will be provided in listings and may be tabulated as described previously.

Parameters describing disease characteristics, symptoms, and QOL of subjects with MPS IIIB, including neurodegeneration (MRI), CSF-AI, neurocognitive and QOL (Vineland-II, BSID-III, KABC-II, BOT-2 Brief Form, CCC-2, SBRS, CSHQ, SF-10, ZBI 12-item) will be provided in listings and may be tabulated as appropriate.

PD, disease characteristics, symptoms, and QOL outcomes analyses will be performed for the FAS. Observed measurements and changes or percent changes from baseline in HS and NRE HS derivatives and disease-related biomarkers will be summarised overall and by dosing regimen for each time point. Change in relative proportion of grey and white matter volume and microstructural integrity will be summarised.

Scores and changes from baseline in the neurocognitive, disease characteristics, symptoms and QOL questionnaires will be summarised by time point.

Graphs of actual values and changes over time may be created as appropriate.

Parameters describing facial features of subjects with MPS IIIB will be provided in listings and may be tabulated as appropriate.

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

8.7 Summaries of Data Prior to Study Completion

Interim data may be summarised for presentation to Regulatory Authorities or to the scientific community to facilitate the development of SBC-103.

Details of the pre-specified statistical analyses will be provided in a separate SAP.

9 SUBJECT DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of applicable local regulations.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments.

The MRI images plus auxiliary information will be stored locally but also transmitted to the Sponsor in Digital Imaging and Communications in Medicine format for potential further internal analyses and for generation of illustrative images.

9.3 Case Report Forms

Required data for this study will be captured on CRFs via electronic data capture unless otherwise specified in this document. Except for data points for which the protocol indicates that the CRF may serve as source documentation, data are to be obtained from the subject's source documents and then entered into the CRF by authorised personnel. Clinical data that are not recorded on the CRF will be captured and transferred to the Sponsor or its designee.

9.4 Records Retention

It is the Investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application for SBC-103 in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of SBC-103. These documents should be retained for a longer period if required by the local legislation requirements or an agreement with the Sponsor. In such an instance, it is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

10 STUDY MONITORING, AUDITING, AND INSPECTING

10.1 Study Monitoring Plan

This study will be monitored according to the study monitoring plan. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study-related facilities (e.g., diagnostic laboratory), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The Investigator will permit study-related monitoring, audits, and inspections by the IRB/IEC, the Sponsor (or their designee), government regulatory bodies, and quality assurance groups of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g., diagnostic laboratory).

Participation as an Investigator in this study implies acceptance of potential inspection by government Regulatory Authorities and applicable compliance and quality assurance offices.

11 ETHICAL CONSIDERATIONS

This study is to be conducted in accordance with international standards of GCP (ICH, EU Directives 2001/20/EC and 2005/28/EC, and US 21 CFR 50 and 21 CFR 312), as well as all other applicable government regulations and institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted IRB/IEC, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/IEC concerning the conduct of the study will be made in writing to the applicant and a copy of this decision will be provided to the Sponsor before commencement of this study. The IRB/IEC will be requested to provide a list of IRB/IEC members. A member who is affiliated with the Sponsor should not participate in voting on the IRB/IEC opinion.

Each subject (or the subject's parent or legal guardian) will be given a consent form describing this study and providing sufficient information to allow the subject (or the subject's parent or legal guardian) to make an informed decision about the subject's participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB/IEC for the study. The formal consent of a subject (or a subject's parent or legal guardian), using the IRB/IEC-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject (or the subject's parent or legal guardian), and the Investigator-designated research professional obtaining the consent.

Any changes in the study protocol, such as changes in the study design, objectives or endpoints, inclusion and exclusion criteria, and/or procedures (except to eliminate an immediate hazard) will be implemented only after the mutual agreement of the Investigator and the Sponsor or designee. All protocol changes must be documented in protocol amendment(s). Protocol amendment(s) must be signed by the Investigator and approved (if applicable) by the IRB/IEC prior to implementation. Any changes in study conduct that result from a pending amendment will be considered protocol deviations until IRB/IEC approval is granted. Documentation of IRB/IEC approval must be returned to the Sponsor or designee.

12 CLINICAL STUDY REPORT AND DATA DISCLOSURE

A clinical study report (CSR) will be produced upon completion of the study. A coordinating Investigator will be designated to review and sign the completed CSR.

Information about this study will be posted on the http://clinicaltrials.gov and https://www.clinicaltrialsregister.eu websites and, where applicable, on other websites required by the local Regulatory Authorities of participating countries.

It is intended that the results from this research will be submitted to a peer-reviewed medical publication, once the study is completed.

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14 APPENDICES

14.1 Appendix A: Schedule of Study Assessments

Assessments	Screening	Day 0	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24	Week 26
Visit Window (Days)	-28 to 0	-5 to 0 days		±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
Informed Consent/Assent*	X															
Inclusion/Exclusion Criteria	X															
Medical History (review of changes from NGLU-CL01)	X															
Physical Examination	X	X[P]	X		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	
Height and Weight	X	X[P]			X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (Triplicate)	X	X[P]							X[P]						X[P]	
FDNA	X														X	
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CCC-2, SBRS,CSHQ, ZBI, SF-10[2]	X														X[P]	
Haematology, Serum Chemistry (including Coagulation), Urinalysis[3]	X	X[P]	X		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	
Pregnancy Test (Urine)[4]	X	X[P]			X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	

Assessments	Screening	Day 0	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24	Week 26
Visit Window (Days)	-28 to 0	-5 to 0 days		±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
Serum and Urine Heparan Sulphate (Total and NRE)	X	X^P			X^P		X^P		X^P		X^P		X^P		X^P	
Serum Ferritin and Chitotriosidase	X	X^P			X^P		X^P		X^P		X^P		X^P		X^P	
Plasma Glutamic Acid and Glycine	X	X^P			X^P		X^P		X^P		X^P		X^P		X^P	
NAGLU enzyme activity	X															
Serum Biomarkers (Exploratory including IgG, inflammatory markers)		X^P			X^P		X^P		X^P		X^P		X^P		X^P	
Serum Pharmacokinetic Profile[5]		X							X						X	
SBC-103 ADA[6]		X^P			X^P		X^P		X^P		X^P		X^P		X^P	
General Anaesthesia/Sedation[7]		X^P							X^P						X^P	
Lumbar Puncture[7,8]		X^P							X^P						X^P	
Heparan Sulphate (Total and NRE) in CSF		X^P							X^P						X^P	
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF		X^P							X^P						X^P	
Glutamic Acids and Glycine in CSF		X^P							X^P						X^P	

Assessments	Screening	Day 0	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24	Week 26
Visit Window (Days)	-28 to 0	-5 to 0 days		±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
Routine Findings (Cell Counts, Glucose, Protein) in CSF[3]		X[P]							X[P]						X[P]	
SBC-103 in CSF		X[P]							X[P]						X[P]	
Structural and Diffusion MRI[7]		X[P]													X[P]	
Telephone call				X	X	X										
SBC-103 Dosing		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[10]	CONTINUOUS															
Concomitant Medications[11]	CONTINUOUS															

Assessments	Week 28	Week 30	Week 32	Week 34	Week 36	Week 38	Week 40	Week 42	Week 44	Week 46	Week 48	Week 50	Week 52
Visit Window (Days)	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
Physical Examination	X[P]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
Height and Weight	X[P]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[1]													X[P]
FDNA													X
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI, SF-10[2]													X[P]
Haematology, Serum Chemistry (incl. Coagulation), Urinalysis[3]	X[P]				X[P]				X[P]				X[P]
Pregnancy Test (Urine) [4]	X[P]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
Serum and Urine Heparan Sulphate (Total and NRE)	X[P]				X[P]				X[P]				X[P]
Serum Ferritin and Chitotriosidase	X[P]				X[P]				X[P]				X[P]
Plasma Glutamic Acid and Glycine	X[P]				X[P]				X[P]				X[P]
Serum Biomarkers (Exploratory including IgG, inflammatory markers)	X[P]				X[P]				X[P]				X[P]
Serum Pharmacokinetic Profile[5]													X
SBC-103 ADA[6]	X[P]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
General Anaesthesia/Sedation[7]					X[P]								X[P]

Assessments	Week 28	Week 30	Week 32	Week 34	Week 36	Week 38	Week 40	Week 42	Week 44	Week 46	Week 48	Week 50	Week 52
Visit Window (Days)	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
Lumbar Puncture[7,8]					X^P								X^P
Heparan Sulphate (Total and NRE) in CSF					X^P								X^P
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF					X^P								X^P
Glutamic Acids and Glycine in CSF					X^P								X^P
Routine Findings (Cell Counts, Glucose, Protein) in CSF[3]					X^P								X^P
SBC-103 in CSF					X^P								X^P
Structural and Diffusion MRI[7]													X^P
SBC-103 Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[10]	CONTINUOUS												
Concomitant Medications[11]	CONTINUOUS												

Assessments	Week 54	Week 56	Week 58	Week 60	Week 62	Week 64	Week 66	Week 68	Week 70	Week 72	Week 74	Week 76	Week 78
Visit Window (Days)	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
Physical Examination		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	
Height and Weight		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	
Vital Signs[12]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[1]													X[P]
FDNA													X
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI, SF-10[2]													X[P]
Haematology, Serum Chemistry (including Coagulation), Urinalysis[3]				X[P]				X[P]					X[P]
Pregnancy Test (Urine) [4]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	
Serum and Urine Heparan Sulphate (Total and NRE)				X[P]				X[P]					X[P]
Serum Ferritin and Chitotriosidase				X[P]				X[P]					X[P]
Plasma Glutamic Acid and Glycine				X[P]				X[P]					X[P]
Serum Biomarkers (Exploratory including IgG, inflammatory markers)				X[P]				X[P]					X[P]

Assessments	Week 54	Week 56	Week 58	Week 60	Week 62	Week 64	Week 66	Week 68	Week 70	Week 72	Week 74	Week 76	Week 78
Visit Window (Days)	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
Serum Pharmacokinetic Profile[5]													X
SBC-103 ADA[6]		X^P		X^P		X^P		X^P		X^P		X^P	
General Anaesthesia/Sedation[7]								X^P					X^P
Lumbar Puncture[7,8]								X^P					X^P
Heparan Sulphate (Total and NRE) in CSF								X^P					X^P
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF								X^P					X^P
Glutamic Acids and Glycine in CSF								X^P					X^P
Routine Findings (Cell Counts, Glucose, Protein) in CSF[3]								X^P					X^P
SBC-103 in CSF								X^P					X^P
SBC-103 Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[10]	CONTINUOUS												
Concomitant Medications[11]	CONTINUOUS												

Assessments	Week 80	Week 82	Week 84	Week 86	Week 88	Week 90	Week 92	Week 94	Week 96	Week 98	Week 100	Week 102	Week 104
Visit Window (Days)	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
Physical Examination	X[P]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
Height and Weight	X[P]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
Vital Signs[12]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[1]													X[P]
FDNA													X
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI, SF-10[2]													X[P]
Haematology, Serum Chemistry (including Coagulation), Urinalysis[3]				X[P]				X[P]					X[P]
Serum albumin sample						X[P]							
Pregnancy Test (Urine)[4]	X[P]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
Serum and Urine Heparan Sulphate (Total and NRE)				X[P]		X[P]		X[P]					X[P]
Serum Ferritin and Chitotriosidase				X[P]				X[P]					X[P]
Plasma Glutamic Acid and Glycine				X[P]				X[P]					X[P]
Serum Biomarkers (Exploratory including IgG, inflammatory markers)				X[P]				X[P]					X[P]

Assessments	Week 80	Week 82	Week 84	Week 86	Week 88	Week 90	Week 92	Week 94	Week 96	Week 98	Week 100	Week 102	Week 104
Visit Window (Days)	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
Serum Pharmacokinetic Profile[5]													X
SBC-103 ADA[6]	X^P		X^P		X^P		X^P		X^P		X^P		X^P
General Anaesthesia/Sedation[7]						X^P							X^P
Lumbar Puncture[7,8]						X^P							X^P
Heparan Sulphate (Total and NRE) in CSF						X^P							X^P
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF						X^P							X^P
Glutamic Acids and Glycine in CSF						X^P							X^P
Routine Findings (Cell Counts, Glucose, Protein) in CSF[3]						X^P							X^P
SBC-103 in CSF						X^P							X^P
Structural and Diffusion MRI[7]													X^P
SBC-103 Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[10]	CONTINUOUS												
Concomitant Medications[11]	CONTINUOUS												

Assessments	Week 106	Week 108	Week 110	Week 112	Week 114	Week 116	Week 118	Week 120	Week 122	Week 124	Week 126	Week 128	Week 130	Week 132
Visit Window (Days)	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
Physical Examination		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
Height and Weight		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
Vital Signs[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[1]													X[P]	
FDNA													X	
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI, SF-10[2]													X[P]	
Haematology, Serum Chemistry (including Coagulation), Urinalysis[3]				X[P]				X[P]					X[P]	
Pregnancy Test (Urine) [4]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]
Serum and Urine Heparan Sulphate (Total and NRE)				X[P]				X[P]					X[P]	
Serum Ferritin and Chitotriosidase				X[P]				X[P]					X[P]	
Plasma Glutamic Acid and Glycine				X[P]				X[P]					X[P]	
Serum Biomarkers (Exploratory including IgG, inflammatory markers)				X[P]				X[P]					X[P]	
Serum Pharmacokinetic Profile[5]													X	
SBC-103 ADA[6]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]

Assessments	Week 106	Week 108	Week 110	Week 112	Week 114	Week 116	Week 118	Week 120	Week 122	Week 124	Week 126	Week 128	Week 130	Week 132
Visit Window (Days)	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
General Anaesthesia/Sedation[7]								X^P					X^P	
Lumbar Puncture[7,8]								X^P					X^P	
Heparan Sulphate (Total and NRE) in CSF								X^P					X^P	
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF								X^P					X^P	
Glutamic Acids and Glycine in CSF								X^P					X^P	
Routine Findings (Cell Counts, Glucose, Protein) in CSF[3]								X^P					X^P	
SBC-103 in CSF								X^P					X^P	
SBC-103 Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[10]	CONTINUOUS													
Concomitant Medications[11]	CONTINUOUS													

Assessments	Week 134	Week 136	Week 138	Week 140	Week 142	Week 144	Week 146	Week 148	Week 150	Week 152	Week 154	Week 156/ End of Treatment/ Early Termination	Week 160
Visit Window (Days)	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
Physical Examination		X^P		X^P		X^P		X^P		X^P		X^P	
Height and Weight		X^P		X^P		X^P		X^P		X^P		X^P	
Vital Signs[12]	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[1]												X^P	
FDNA												X	
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI, SF-10[2]												X^P	
Haematology, Serum Chemistry (including Coagulation), Urinalysis[3]			X^P				X^P					X^P	
Serum Albumin sample					X								
Pregnancy Test (Urine) [4]		X^P		X^P		X^P		X^P		X^P		X^P	
Serum and Urine Heparan Sulphate (Total and NRE)			X^P		X^P		X^P					X^P	
Serum Ferritin and Chitotriosidase			X^P				X^P					X^P	
Plasma Glutamic Acid and Glycine			X^P				X^P					X^P	
Serum Biomarkers (Exploratory including IgG, inflammatory markers)			X^P				X^P					X^P	
Serum Pharmacokinetic Profile[5]												X	

Assessments	Week 134	Week 136	Week 138	Week 140	Week 142	Week 144	Week 146	Week 148	Week 150	Week 152	Week 154	Week 156/ End of Treatment/ Early Termination	Week 160
Visit Window (Days)	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days
SBC-103 ADA[6]		X^P		X^P		X^P		X^P		X^P		X^P	
General Anaesthesia/Sedation[7]					X^P							X^P	
Lumbar Puncture[7,8]					X^P							X^P	
Heparan Sulphate (Total and NRE) in CSF					X^P							X^P	
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF					X^P							X^P	
Glutamic Acids and Glycine in CSF					X^P							X^P	
Routine Findings (Cell Counts, Glucose, Protein) in CSF[3]					X^P							X^P	
SBC-103 in CSF					X^P							X^P	
Structural and Diffusion MRI[7]												X^P	
Telephone call[9]													X
SBC-103 Dosing	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events[10]	CONTINUOUS												
Concomitant Medications[11]	CONTINUOUS												

Assessments	Week 134	Week 136	Week 138	Week 140	Week 142	Week 144	Week 146	Week 148	Week 150	Week 152	Week 154	Week 156/ End of Treatment/ Early Termination	Week 160
Visit Window (Days)	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days

Key: ADA = anti-drug antibodies; BOT-2 Brief Form = Bruininks-Oseretsky Test of Motor Proficiency, Second Edition, Brief Form; BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; CCC-2 = Children's Communication Checklist, Second Edition; CSF = cerebrospinal fluid; CSHQ = Children's Sleep Habits Questionnaire; D = day; ECG = electrocardiogram; FDNA = Facial Dysmorphology Novel Analysis; HGF = hepatocyte growth factor; IgG = immunoglobulin G; KABC-II = Kaufman Assessment Battery for Children, Second Edition; NAGLU = alpha-N-acetylglucosaminidase; MRI = magnetic resonance imaging; NRE = non-reducing end; SBRS = Sanfilippo Behavior Rating Scale; SF-10 = Short Form Health Survey for Children; Vineland-II = Vineland Adaptive Behavior Scales, Second Edition; Wk = week; ZBI = Zarit Burden Interview, 12-item.

*All study visits will be scheduled relative to Day 0. Infusions will be administered every 14 days ± 5 days and must be administered at least 10 days apart. Informed consent may be granted before the beginning of the screening period. All screening assessments other than informed consent should be completed within a 28-day window.

X^P Assessments to be performed pre-dose

[1] ECG assessments after 6 months do not need to be performed in triplicate.

[2] The Vineland-II, BSID-III or KABC-II, BOT-2 Brief Form, and CCC-2 should be administered in-person by an appropriately qualified professional.

[3] Local lab ranges will be used for those labs analysed locally. If samples are taken within 3 days of Day 0, samples do not need to be repeated on Day 0. However, a Day 0 serum sample for albumin should be collected at the same time as the CSF collection, to enable calculation of CSF-AI. Central laboratory parameter reference ranges will be used throughout the study, including in the event that laboratory parameters are analysed locally. All attempts should be made to draw laboratory samples for central laboratory analysis when samples are needed for local analysis. Day 1 samples will be analysed locally, all other samples may be analysed centrally.

[4] If a urine sample is not able to be provided, a serum pregnancy test will be performed by a local laboratory.

[5] Refer to Section 5.2.1.2 for directions and timing of PK sampling.

[6] In addition to time points indicated, obtain a sample for ADA determination anytime subject experiences a moderate-to-severe IAR during the next study visit (≥ 4 days after the IAR) and prior to the infusion.

[7] Lumbar puncture and MRI procedures may be performed under general anaesthesia or light sedation, as clinically appropriate in accordance with local institutional procedures. If clinically indicated, subjects may also receive general anaesthesia or sedation for central line placement for long-term vascular access, in accordance with institutional guidelines. When possible, the procedure to place the central line should be performed while the subject is already anaesthetised or sedated for another study procedure. After the lumbar puncture is completed, the subject should be observed as per institution standard practice. Vital signs, adverse events, and concomitant medications should be assessed before the subject is discharged from the site.

[8] During study visits where CSF is collected, and no serum chemistry sample is indicated per the SOA, a serum albumin sample should be collected to assess CSF-AI. After the lumbar puncture is completed, the subject should be observed as per institution standard practice.

Assessments	Week 134	Week 136	Week 138	Week 140	Week 142	Week 144	Week 146	Week 148	Week 150	Week 152	Week 154	Week 156/ End of Treatment/ Early Termination	Week 160
Visit Window (Days)	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	±5 days

[9] A telephone follow-up call will be made 4 weeks after the last dose received of SBC-103 after Week 156 End of Treatment or after the Early Termination visit.

[10] All AEs should be followed until they have returned to baseline values or stabilised or until the Investigator and Sponsor or designee agree that follow-up is no longer necessary.

[11] Information on all medications and treatments received by the subject within the 4 weeks preceding the Screening visit through the final visit will be recorded in the CRF.

[12] Starting at Week 54, vital signs may be taken pre-dose (within approximately 30 minutes), approximately every 15 minutes during infusion and approximately every 15 minutes for 1 hour after completion of the infusion, provided there is no occurrence of IARs during the infusion. Vital signs will be obtained after any lumbar puncture as per site standard of care.

14.2 Appendix B: NGLU-CL01-T Neurocognitive, Developmental and QOL Assessments

Assessment*	Administered to	Special Instructions
Vineland-II	Parent/Caregiver	Must be administered prior to the other developmental tests at Screening (i.e., BSID-III, KABC-II, BOT-2 Brief Form, CCC-2). Administered in-person
BSID-III[1]	Subject	At Screening, administered to subjects with Vineland-II age equivalent of < 3 years, 6 months). Administered in-person
KABC-II[1]	Subject	At Screening, administered to subjects with Vineland-II age equivalent of ≥ 3 years, 6 months. Administered in-person
BOT-2 Brief Form[2]	Subject	Administered only to subjects who complete the KABC-II.
CCC-2[2]	Parent/Caregiver	Administered only to subjects completing the KABC-II.
ZBI, 12-item	Parent/Caregiver	
SF-10	Parent/Caregiver	
SBRS	Parent/Caregiver	
CSHQ	Parent/Caregiver	

* All neurocognitive, developmental and QOL assessments are administered during the Screening visit. Assessments can be performed over multiple days.

[1] Either the BSID-III or KABC-II will be administered to the subject depending on the mean age equivalent determined by the Vineland-II at Screening.

[2] Administered only to subjects completing the KABC-II