A Phase I/II Open Label Study in MPS IIIB Subjects to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics/Efficacy of SBC-103 Administered Intravenously

Unique Protocol ID:	NGLU-CL02
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EudraCT Number:	2013-003400-39
Date of Protocol:	21 January 2016

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

Protocol Number:	NGLU-CL02
Amendment Number:	7
Date of Protocol:	21 January 2016
EudraCT Number:	2013-003400-39
IND Number:	IND 118402
Product:	SBC-103
Sponsor:	Alexion Pharmaceuticals, Inc. 352 Knotter Drive Cheshire, CT 06410 UNITED STATES

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

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REVIEWED/APPROVED BY:

PPD		PPD	22 Jan 2016
Alexion Pharmaceuticals, Inc.		Signature	Date

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 enrollment in 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 MPS IIIB Subjects to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics/Efficacy of SBC-103 Administered Intravenously
Protocol Number	NGLU-CL02
EudraCT Number	2013-003400-39
IND Number	IND 118402
Objectives	**Primary Objective** • To evaluate the safety and tolerability of intravenous (IV) administration of SBC-103 in subjects with mucopolysaccharidosis III, type B (MPS IIIB, Sanfilippo B) with evaluable signs or symptoms of developmental delay. **Secondary Objectives** • To characterize the pharmacokinetic (PK) profile of SBC-103 administered IV. • To determine the effects of SBC-103 administered IV on the levels, onset and magnitude of changes total heparan sulfate (HS) in cerebrospinal fluid (CSF), serum, and urine. • To evaluate the pharmacodynamics (PD)/efficacy of SBC-103 administered IV as measured by neurocognitive and developmental function and change in brain structures. • To evaluate the impact of temporary interruption of SBC-103 therapy (between Parts A and B) on safety, tolerability, and select PD/efficacy markers, including the reversibility of changes in levels of total HS in CSF, serum, and urine. **Exploratory Objectives** • To examine the onset, magnitude, and reversibility of changes in exploratory biomarkers, SBC-103 concentration in CSF, MPS IIIB disease characteristics, symptoms, and quality of life (QOL) after IV administration of SBC-103.
Methodology	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. This study will be conducted in 3 parts: Part A (Initial Therapy), Part B (Therapy at 1 and/or 3 mg/kg), and Part C (Therapy at 5 and/or 10 mg/kg). All subjects who participate in Part A may continue SBC-103 dosing in Part B if they qualify for continued dosing, and all subjects who participate in Part B are eligible for dose escalation in Part C providing that they qualify for dose escalation. **Part A (Initial Therapy)** In Part A, following completion of screening assessments to confirm study eligibility, approximately 9 subjects will be treated in 1 of 3 different dosing cohorts (0.3, 1, or 3 mg/kg). In the event that more than 3 subjects in a cohort have entered Screening and are determined to be eligible to participate in the

	study, an additional subject may be dosed with SBC-103 within the intended dose cohort. This will be acceptable provided the following conditions are met: 1) the Safety Review Committee (SRC) has met and approved the continued dosing of the 1st subject in the cohort and the first dose of the 2nd subject and 2) the Sponsor has reviewed safety information of the 2nd subject in the cohort and has approved the 3rd subject to be dosed. Each subject in each cohort will be dosed sequentially with SBC-103 administered by IV infusion once every other week (QOW) for 24 consecutive 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 at least 24 hours following the first dose of SBC-103 in Part A. To evaluate safety, follow-up phone calls will be made to each subject (or the subject's parent or caregiver) within 24 hours after the subject's second, third, and fourth doses in Part A. After receiving SBC-103 QOW for 24 consecutive weeks, subjects will have a 4-week temporary interruption of therapy prior to being considered for participation in Part B. If a subject will not participate in Part B of the study, an additional follow-up phone call will be made 4 weeks after the subject's last administered dose in Part A unless the subject has a scheduled follow-up visit. **Criteria for Dosing and Dose Escalation in Part A:** The decision to **continue dosing in the 1st subject** in the 1st, 2nd, and 3rd cohorts will be made by the Sponsor based on SRC recommendations after review of 24-hour safety data from that subject and available safety data from all other subjects. The decision to **initiate dosing in the 2nd subject** of each cohort will be made by the Sponsor based on SRC recommendations after review of 24-hour safety data from Subject 1 in the same cohort and available safety data from all other subjects. The decision to **initiate dosing in the 3rd subject** of each cohort will be made by the Sponsor based on 24-hour safety data from Subject 2 in the same cohort and available safety data from all other subjects. The decision to **escalate into the next dose cohort** will be made by the Sponsor based on SRC recommendations after review of safety data from the 1st subject who completes the first 4 doses in the dose cohort, 24-hour safety data after the first dose from the 3rd subject of the same cohort, and available safety data from all other subjects. **Part B (Therapy at 1 and/or 3 mg/kg):** Subjects who meet qualifying criteria may commence Part B (Therapy at 1 and/or 3 mg/kg) after completing Part A, after the SRC and Sponsor have evaluated an individual subject's available safety data, and deemed it acceptable for that subject to initiate continued therapy in Part B. Only subjects who meet eligibility criteria for Part B will re-initiate SBC-103 dosing in Part B. Eligible subjects may re-initiate SBC-103 dosing in Part B no sooner than 4 weeks after

	the subject's last dose in Part A. In Part B, dose or dosing frequency (eg, QOW or weekly) modifications may be considered by the Sponsor after consultation with the SRC, based a review of safety, tolerability, and treatment response data. With the intent of treating patients with the lowest dose that is safe and tolerable and which has potential for efficacy, dose modification (either an increase to 1 or 3 mg/kg or a decrease to 0.3 or 1 mg/kg) may be proposed for individual subject(s) after the evaluation of safety and tolerability data as well as biomarker and treatment response data after 24 weeks of treatment (13 doses). Dose modifications will not be considered until Part B of the study, except for instances where a dose reduction is required for reasons of safety and tolerability. Subjects who receive doses of 0.3 mg/kg in Part A may be considered for a second dose escalation to 3 mg/kg at any time during Part B provided that they have tolerated at least 2 doses of 1 mg/kg in Part B. Safety, PK, and PD/efficacy assessments will be conducted at regular intervals throughout Part B. Subjects who have received and tolerated at least 4 doses of SBC-103 QOW at 3 mg/kg may be considered for participation in Part C. **Part C (Therapy at 5 and/or 10 mg/kg):** Subjects who meet the eligibility criteria for Part C may begin dosing in Part C at their next scheduled visit once the necessary regulatory and ethics committee review and approval (where required) are obtained and provided that the criteria for dosing (see below) are met. Part C is a randomized, open-label assessment of SBC-103 at doses of 5 or 10 mg/kg administered IV. Subjects will be randomized such that at least 1 subject from each cohort assigned in Part A will receive SBC-103 at 5 mg/kg and at least 1 subject from each cohort assigned in Part A will receive SBC-103 at 10 mg/kg. Thus each of the assigned dose levels from Part A will be represented in each of the 2 dose levels being studied in Part C. Treatment in Part C will continue through Week 156 of the study. **Criteria for Dosing and Dose Escalation in Part C:** Dosing in Part C will begin at the 5 mg/kg dose level. The decision to **continue dosing in the 1st subject** at 5 mg/kg and to **initiate dosing in the remaining 4 subjects** at 5 mg/kg will be made by the Sponsor based on SRC recommendations after review of 24-hour safety data from that subject. The decision to **escalate to the 10 mg/kg dose** will be made by the Sponsor based on SRC recommendations after review of safety data from 1 subject who completes the first 2 doses at 5 mg/kg, and review of available safety data from any other subjects who have received 5 mg/kg. The decision to **continue dosing in the 1st subject at 10 mg/kg and to initiate dosing in the remaining 5 subjects** at 10 mg/kg will be made by the Sponsor based on SRC recommendations after review of 24-hour safety data from that subject. 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. At any time during this 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 SRC and Sponsor.
Study Duration	The 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 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 (Parts B and C), and a 4-week follow-up period after the last dose is administered.
Study Centers	Approximately 4 centers are expected to participate in this study.
Number of Subjects Planned	Approximately 9 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. Has a definitive diagnosis of MPS IIIB, as determined by either of the following: a. Documented deficiency in alpha-N-acetylglucosaminidase (NAGLU) enzyme activity ≤10% of the mean value in normal individuals (Heron, 2011, *Am J Met Genet A*) based on test results from a central laboratory at Screening. *OR* b. Documented functionally-relevant mutations in both alleles of the NAGLU gene based on historical test results from a local laboratory (if available) or results from the central laboratory at Screening. 2. Greater than or equal to 2 years old but less than 12 years old at the time of written informed consent, and has an age equivalent of ≥1 year on the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II). 3. Has documented developmental delay with onset before 6 years of age, as defined by: a. Cognitive delay evaluated by Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) or Kaufman Assessment Battery for Children, Second Edition (KABC-II). *OR* b. Language delay, plateauing or regression of language skills as determined by the Investigator and confirmed by the Vineland-II (communication domain) administered at Screening (eg, subject uses isolated words, associated words such as two-word combination, sentences, poor or reduced language and/or language difficult to understand). 4. Subject or subject's parent or legal guardian (if applicable) consents 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.

5. 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 consent 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. Women may be considered of non-childbearing potential if they have not started their menses or are surgically sterile (ie, total hysterectomy or bilateral salpingo-oophorectomy).
6. Male subjects must consent to 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.
7. 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 utilize magnetic fields, or any other medical condition or circumstance in which magnetic resonance imaging (MRI) is contraindicated according to local institutional policy.
3. Previous hematopoietic stem cell or bone marrow transplant.
4. Known or suspected hypersensitivity to anesthesia 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 co-morbidities (eg, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3x the upper limit of normal [ULN], confirmed by repeat testing, analyzed centrally or locally and based on the standardized reference range provided in the central laboratory manual), or other markers of clinically significant liver dysfunction (eg, elevated bilirubin, [with the exception of patients with confirmed Gilberts Disease] confirmed by repeat testing, or elevated prothrombin time [PT]/International normalized ratio [INR] confirmed

<table>
<tr><td></td><td>by repeat testing analyzed centrally or locally and based on the standardized reference range provided in the central laboratory manual) which in the opinion of the Investigator, in consultation with the Sponsor, would interfere with study compliance, or confound data interpretation.
Qualifications for Part B (Therapy at 1 and/or 3 mg/kg):
Subjects are eligible for continued SBC-103 dosing at 1 and/or 3 mg/kg QOW in Part B if they do not meet any Exclusion criteria listed above and if they meet the following:
1. Completion of Part A with no unmanageable study drug toxicity;
2. Continue to meet Inclusion Criteria items 4-7 above; and
3. SRC and Sponsor have reviewed the subject’s safety data from Part A and have deemed it acceptable for the subject to re-initiate dosing in Part B.
Qualifications for Part C (Therapy at 5 and/or 10 mg/kg):
Subjects are eligible for continued SBC-103 dosing at a higher dose (5 or 10 mg/kg QOW) in Part C if they do not meet any Exclusion criteria listed above and if they:
1. Have completed at least 4 doses of 3 mg/kg in either Part A or Part B with no unmanageable study drug toxicity; and
2. Continue to meet Inclusion Criteria items 4-7 above</td></tr>
<tr><td>Investigational Product, Dose, Route, Regimen</td><td>SBC-103 is rhNAGLU manufactured using transgenic Gallus, which produce rhNAGLU in egg white.
All dose administration is open label.
Part A (Initial Therapy) Dosing Schedule
In Part A, 3 dose levels of SBC-103 (0.3, 1, and 3 mg/kg) administered by IV infusion QOW for 24 consecutive weeks (13 doses) as follows. Infusions must be administered at least 10 days apart.
<table>
<tr><th>Dose Cohort #</th><th>Dose of SBC-103*</th><th>Dosing Regimen</th><th>Sample size**</th></tr>
<tr><td>1</td><td>0.3 mg/kg</td><td>QOW for 24 weeks</td><td>n=3</td></tr>
<tr><td>2</td><td>1 mg/kg</td><td>QOW for 24 weeks</td><td>n=3</td></tr>
<tr><td>3</td><td>3 mg/kg</td><td>QOW for 24 weeks</td><td>n=3</td></tr>
</table>
*Intra-patient dose escalation is not planned during Part A.
**Enrollment of an additional subject in a cohort may occur as described in the Methodology section.

Part B (Therapy at 1 and/or 3 mg/kg) Dosing Schedule
Only subjects who meet eligibility criteria for Part B will re-initiate SBC-103 dosing in Part B. Eligible subjects may re-initiate SBC-103 dosing in Part B no sooner than 4 weeks after the subject’s last dose in Part A.
In Part B, dose or dosing frequency (eg, QOW or QW) modifications may be considered by the Sponsor after consultation with the SRC.
Subjects who received doses of either 0.3 mg/kg or 1 mg/kg during Part A may escalate to the next higher dose of SBC-103 considered to be safe by the</td></tr>
</table>

	Sponsor and SRC with their first dose in Part B or at any time thereafter. Subjects who received doses of 0.3 in Part A may be considered for a second dose escalation to 3 mg/kg at any time during Part B provided that they have tolerated at least 2 doses of 1 mg/kg in Part B. **Part C (Therapy at 5 and/or 10 mg/kg) Dosing Schedule** Only subjects who meet eligibility criteria for Part C will continue SBC-103 therapy in Part C. Subjects will initiate SBC-103 therapy in Part C at either 5 or 10 mg/kg based upon a randomized assignment. SBC-103 will be administered IV QOW (infusions must be administered at least 10 days apart) until Study Week 156. Intra-subject dose escalation from 5 to 10 mg/kg based on all available safety, PK, and PD/efficacy data may not occur without prior written approval from the Sponsor. Dose reductions may be considered for safety and tolerability at any time in Part C.
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 (IAR)s; • Changes from baseline in clinical laboratory tests (hematology, serum chemistry, and urinalysis) and CSF findings (cell counts, glucose, and protein); • Changes from baseline in 12-lead electrocardiograms (ECGs) ; • Changes in vital signs during and post-infusion, relative to pre-infusion values; • Physical examination findings; • Use of concomitant medications/therapies; • Assessment of anti-drug antibodies (ADAs), including seroconversion rate, time to seroconversion, and ADA titer by time point, peak ADA titer, and ADA titer 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 baseline and post-treatment measures of the following assessments: • PK profile of SBC-103 after single and multiple doses: o Maximum observed serum concentration (C_{max}) o Time to reach C_{max} (T_{max}) o Area under the concentration-time-curve from time 0 to the last measurable time point (AUC_{last}) o Area under the concentration-time-curve extrapolated to infinity (AUC_{∞}) o Half-life ($T_{1/2}$)

- Clearance (CL)
- Volume of distribution at terminal phase (V_z)
- Accumulation ratio (R_{ac})

- Effects of SBC-103 treatment on the onset, magnitude, and reversibility of changes in levels of total HS in CSF, serum, and urine.
- Neurocognitive and developmental function as determined by the scores on the Vineland-II and, as appropriate to the subject's age, the BSID-III or 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).
- Brain structure as determined by the relative proportion of grey and white matter volume and indices of microstructural integrity as assessed by MRI of the brain.
- Effect of temporary interruption of SBC-103 therapy (between Parts A and B) on safety, tolerability, and select PD/efficacy markers.

Exploratory Endpoints

Exploratory endpoints in this study include measures to examine the onset, magnitude, and reversibility of changes in exploratory biomarkers, SBC-103 concentration in CSF, MPS IIIB disease characteristics, symptoms, and QOL after IV 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 (HGF), 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/serum albumin index (CSF-AI)
  - Changes in IgG index ([CSF/serum IgG ratio] / [CSF-AI])
  - Changes in inflammatory markers in serum
- Disease characteristics, symptoms, and QOL
  - Assessment of sleep disorders or dysfunction as determined by the Children's Sleep Habits Questionnaire (CSHQ)
  - Assessment of behavior as determined by the Sanfilippo Behavior Rating Scale (SBRS)
  - Assessment of subjective QOL as determined by the Short Form Health Survey for Children (SF-10)
  - Assessment of caregiver QOL as determined by the Zarit Burden Interview (ZBI) 12-item short form
  - Coarsening of features by Facial Dysmorphology Novel Analysis (FDNA)

	• Additional 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). • Assessment of genes that may contribute to and/or modify the disease phenotype via a DNA sample (where local regulations permit and subject to discretionary approval from each center's Institutional Review Board [IRB]/Independent Ethics Committee [IEC] and the consent/assent of the subject [and/or consent of the subject's parent or legal guardian]).
Statistical Methods	**General Considerations** Descriptive summary statistics will be provided for demographics, disposition and dose exposure. Number 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 summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) and, where appropriate, graphic representation and two-sided 95% confidence intervals (CI); categorical data will be summarized by sample size, proportions, and two-sided 95% CIs. The sample size of approximately 9 subjects is based on clinical and not statistical consideration and is considered sufficient to provide PK, safety, and PD/efficacy data to inform dose and regimen selection for additional clinical studies. **Analysis Datasets** The full analysis set (FAS), defined as all subjects who have received any amount of SBC-103 and from whom informed consent has been obtained, will be used to summarize PK, PD, and efficacy data. The safety analysis set, which is the same population as the FAS, will be used to summarize all safety and tolerability data. **Safety Analysis** Descriptive statistics will be computed for safety parameters, as appropriate. Number and percentage of subjects who discontinued from the study because of AEs, will be tabulated across dose cohorts; severity and frequency of AEs and SAEs will also be tabulated across dose cohorts. All other safety data will be provided in listings. Baseline, within study, end-of-study, and change from baseline in physical examination findings, ECG, clinical laboratory values, and vital signs will be summarized by dose cohort. The proportion of subjects with measurable antibodies to SBC-103 will be displayed. In addition, IARs will be tabulated by cohort and overall. Medications to treat IARs, including any medications for pretreatment, will also be presented by cohort and over 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. Further statistical evaluations will be applied for select endpoints, if warranted. All baseline data and safety data collected during the study will be listed for

	each subject. Safety analyses may be performed for Parts A, B, C, and/or all 3 study parts (ie, the entire study). Details for the analyses will be provided in the SAP. **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_{last}, AUC_{∞}, $T_{1/2}$, CL, V_z, and R_{ac}) assessments will be summarized for each subject, as well as for each dose group. SBC-103 concentration in CSF will be summarized at available time points. Additional analysis of PK data, including assessment of the impact of ADA, may be performed as appropriate. Pharmacokinetic analyses may be performed for Parts A, B, C, and/or all 3 study parts (ie, the entire study). Further details will be provided in the PK section of the statistical analysis plan (SAP). **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 quality of life 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. PD, disease characteristics, symptoms, and QOL outcomes analyses will be summarized. Observed measurements and changes or percent changes from baseline in HS and NRE HS derivatives and disease related biomarkers will be summarized overall and by dosing regimen for each time point. Change in relative proportion of grey and white matter volume and microstructural integrity will be summarized. 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. Pharmacodynamic/efficacy analyses will be performed for Parts A and C, and/or all 3 study parts (ie, the entire study). Further details of the pre-specified analyses will be provided in the SAP. **Summaries of Data Prior to Study Completion** Interim data will be summarized for presentation to regulatory authorities or to the scientific community to facilitate discussions and obtain input on late phase study designs. For some of these summaries, CIs may be computed. Additional details of the pre-specified statistical analyses will be provided in a separate SAP.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ADA	Anti-drug antibody(ies)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{last}	Area under the concentration-time-curve from time 0 to the last measureable time point
AUC_{∞}	Area under the concentration-time-curve extrapolated to infinity
BBB	Blood brain barrier
BMI	Body mass index
BOT-2 Brief Form	Bruininks-Oseretsky Test of Motor Proficiency, Second Edition, Brief Form
BP	Blood pressure
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
BUN	Blood urea nitrogen
CCC-2	Children's Communication Checklist, Second Edition
CDC	Centers for Disease Control
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed serum 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
CT	Computed tomography
DNA	Deoxyribonucleic acid
DQ	Developmental quotient
ECG	Electrocardiograms
ERT	Enzyme replacement therapy
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration

Abbreviation	Definition
FDNA	Facial Dysmorphology Novel Analysis
GAG	Glycosaminoglycan(s)
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HED	Human equivalent dose
HFA	Height-for-age
HGF	Hepatocyte growth factor
HS	Heparan sulfate
IAR	Infusion-associated reaction
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IT	Intrathecal(ly)
IV	Intravenous(ly)
KABC-II	Kaufman Assessment Battery for Children, Second Edition
LSDs	Lysosomal storage disorders
M6PR	Mannose-6-phosphate receptor
MCH	Mean corpuscular hemoglobin;
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mL	Milliliter
MMR	Macrophage mannose receptor
MPS	Mucopolysaccharidosis(ses)
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)

Abbreviation	Definition
PDCO	Pediatric Committee
PET	Positron emission tomography
PK	Pharmacokinetic(s)
PT	Prothrombin time
QOL	Quality of life
QOW	Every other week
QW	Every week
R_{ac}	Accumulation ratio
rhNAGLU	Recombinant human alpha-N-acetylglucosaminidase
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBRS	Sanfilippo Behavior Rating Scale
SDTM	Study data tabulation model
SF-10	Short Form Health Survey for Children
sMRI	Structural magnetic resonance imaging
SOA	Schedule of assessments
SRC	Safety Review Committee
$T_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
T_{max}	Time to reach C_{max}
ULN	Upper limit of normal
US	United States
Vineland-II	Vineland Adaptive Behavior Scales, Second Edition
V_z	Volume of distribution at terminal phase
WFA	Weight-for-age
WFH	Weight-for-height
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 Council for 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 catalyzing 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 characterized by severe degeneration of the central nervous system (CNS) which dominates the clinical picture (Heron, 2011, *Am J Med Genet A*; Neufeld, 2012, *The Metabolic and Molecular Bases of Inherited Disease*). The MPS III syndromes are all characterized by the accumulation of heparan sulfate (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.

MPS IIIB, also known as Sanfilippo B syndrome (OMIM #252920), is a very rare LSD associated with significant morbidity and mortality in affected subjects. 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 - 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 Med 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, behavioral 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 are supported by the successful use of ERT with favorable benefit/risk profiles to treat other LSDs; nonclinical data demonstrating the benefit of substrate reduction in the CNS on CNS manifestations in LSDs including the MPS III syndromes; and nonclinical data demonstrating 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.

ERT has been used successfully to treat a number of LSDs with favorable benefit/risk profiles. The successful treatment of Gaucher's disease with placental glucocerebrosidase in the 1990s and, with the follow-on enzyme produced by recombinant deoxyribonucleic acid (DNA) 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 idursulfase 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 idursulfase, his somatic disease was stable or improved; however, he continued to decline cognitively. By comparison, after 32 months of treatment with idursulfase, 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 reduces substrate levels in both systemic tissues (liver/kidney) and in the brain in the MPS IIIB animal model (Leavitt 2013, LDN WORLD Conference).

In summary, this knowledge and the precedent established for other LSDs, provide rationale that ERT with SBC-103 may benefit patients with MPS IIIB. Developing a more complete understanding of the pharmacokinetics (PK), and pharmacodynamics (PD)/efficacy of SBC-103 via this study will further inform the dose and regimen selection for future studies 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 catalyzes 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 IV administration of SBC-103 (4-6 repeated doses), with doses ranging from 0.3 to 27 mg/kg for up to 6 weeks in duration. 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 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 (SBC103-P004, SBC103-P007, SBC103-P009, SBC103-P010) and are consistent with published literature (Hovland 2007, *Toxicol Pathol;* Flaherty 2012, *Toxicological Sciences;* Finkelman 2007, *J Allergy Clin Immunol;* Khodoun 2011, *PNAS*). Pretreatment with diphenhydramine was used to minimize the effects, but did not completely block the reactions. This finding is consistent with the existence of 2 distinct pathways of anaphylaxis in mice; either by Immunoglobulin E (IgE) mediated histamine release from mast cells or by Immunoglobulin G (IgG) mediated PAF 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 0.3, 1, 3, 5 or 10 mg/kg of SBC-103 once every week (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).

Consistent with ICH guidelines (ICH S6 [Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals and Addendum to ICH6, Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1)]), the potential toxicity of SBC-103 was evaluated in 2 species, the Sprague-Dawley rat (4 weeks) and the Cynomolgus monkey (4 weeks and 3 months). Since monkeys of 0.5-3 years of age corresponds to a human child of 2-12 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 ~80% in SBC-103 treated animals (irrespective of the dose), and 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 NOAEL in this study was considered to be 20 mg/kg QW.

The potential toxicity of SBC-103 was also evaluated in juvenile Cynomolgus monkeys following repeated IV doses at QW dose levels of 3 and 10 mg/kg or at an every other week (QOW) dose level of 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; however, 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 behavior.

The presence of anti-SBC-103 IgG antibodies was confirmed in 87%, 60%, and 87% animals in the 3 mg/kg, 10 mg/kg, and 20 mg/kg dose groups, respectively, and no animals in the control group were confirmed positive for anti-SBC-103 antibody. Antibody titers did not increase with dose level administered. Consequently, the NOAELs were considered to be 10 mg/kg QW and 20 mg/kg QOW in this study.

Overall, the findings in 2 different toxicology species and data from a 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 in 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, SBC-103 administered IV at high doses resulted in microscopic findings in both the rat and Cynomolgus monkey in numerous tissues presumably reflecting exaggerated hypersensitivity reaction to a human protein.

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

1.4 Clinical Data

1.4.1 Data for SBC-103

As this is a first-in-human study, no clinical data for SBC-103 were available when this study was planned and initiated.

As described in Section 3.1, subjects in Part A receive IV infusions of SBC-103 at 1 of 3 doses (0.3, 1, or 3 mg/kg) QOW for 24 weeks followed by a 4-week temporary interruption of therapy prior to re-initiating therapy at Week 28 in Part B. Modifications to dose or dosing frequency for individual subject(s) is permitted in Part B with the intent of treating subjects with the lowest potentially efficacious dose that is safe and tolerable.

As of 20 November 2015, preliminary data were available for all subjects enrolled in this study, including approximately 20 to 40 weeks (~11 to 20 QOW doses) of preliminary safety data, and preliminary PK and PD data through Week 12 (~7 QOW doses).

These data are briefly summarized below. *However, it should be noted that these are preliminary data from an ongoing study and an open database, and therefore, are subject to change based on data review, reconciliation, and/or auditing.*

As described in Section 3.1.1, approximately 9 subjects were to be enrolled in this study across 3 dose cohorts (n=3/cohort) with a provision to permit enrollment of additional subjects if more than 3 subjects in a cohort had entered Screening and were eligible to participate in the study. A total of 11 subjects were sequentially enrolled in this study into Cohort 1 (0.3 mg/kg, n=3), Cohort 2 (1 mg/kg, n=4), or Cohort 3 (3 mg/kg, n=4). All subjects had a confirmed diagnosis of MPS IIIB and documented developmental delay with onset before 6 years of age. The majority of subjects enrolled in this study are PPD The age range across all patients at study entry was PPD and the mean (SD) age was 7.5 (2.82) years for subjects in the 0.3 mg/kg dose cohort, 6.6 (4.54) years for subjects in the 1 mg/kg dose cohort, and 4.5 (2.10) years for subjects in the 3 mg/kg dose cohort.

As of 20 November 2015, all 3 subjects in Cohort 1 have completed Part A of the study and have received between 5 and 7 doses of SBC-103 at 1.0 mg/kg QOW in Part B; all 4 subjects in Cohort 2 have completed Part A and 2 of these subjects have received 2 doses at 3.0 mg/kg QOW in Part B; and the 4 subjects in Cohort 3 have completed between 20 and 24 weeks of Part A at 3.0 mg/kg.

1.4.1.1 Preliminary Safety Data

Preliminary safety data as of 20 November 2015, which corresponds to at least 20 and up 40 weeks on study, demonstrate that IV infusions of SBC-103 at 0.3, 1, or 3 mg/kg administered QOW appear overall to be safe and well tolerated.

While 10 subjects (90.9%) experienced a total of 80 treatment-emergent adverse events (TEAEs)[1], the majority of the events were assessed by the investigator as mild in intensity (75/80, 93.8%) and as either unlikely related or unrelated to study drug (71/80, 88.8%). The most common AEs (occurring in ≥2 subjects) were pyrexia, vomiting, diarrhoea, cough, rhinorrhoea, erythema, and dermatitis diaper; with the exception of pyrexia, none of these was considered by the investigator to be related to treatment with SBC-103.

A total of 9 AEs (11.2%) occurring in 5 subjects (45.5%) were considered by the investigator to be related or possibly related to treatment with SBC-103; the majority of these (7/9 events) were infusion associated reactions (IARs), which are commonly observed with other enzyme replacement therapies (Desnick 2012, *Ann Rev Genomics Hum Genet*; Fabrazyme® prescribing information, 2010; Aldurazyme® prescribing information, 2013; Elaprase® prescribing information, 2013; Naglazyme® prescribing information, 2013). The IARs occurred in 3 subjects and included 4 events of pyrexia and 1 event each of tachycardia, hypertension, and chills. These events were all non-serious, mild in intensity, and resolved without sequelae. These IARs were treated with oral anti-pyretics and/or antihistamines and, for some events, infusion rate was slowed as per the protocol specified guidelines for the management of IARs. None of the subjects needed extended pre-medication to continue receiving SBC-103. Anti-drug antibody status is under evaluation.

There have been no deaths or life-threatening events, no discontinuations due to AEs, and no severe AEs. Three (3) treatment-emergent serious adverse events (TESAEs) (staphylococcal bacteraemia, bacteraemia, and pyrexia) were reported in 1 subject (9.1%) PPD all 3 TESAEs were assessed by the investigator as mild or moderate in intensity and unrelated to study drug, and all 3 resolved without sequelae.

One (1) subject PPD met the protocol specified criterion to pause dosing with SBC-103 based on confirmed elevations (≥2 × upper limit of normal [ULN]) in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (see Section 6.2.1); this is briefly described below. No other subjects met any of the criteria requiring that SBC-103 dosing be paused.

1 Any adverse event (AE) that occurred after the first dose of SBC-103 is considered a treatment-emergent adverse event (TEAE).

In addition to AEs, serum chemistry, liver function tests, hematology, coagulation, and urinalysis parameters were assessed at scheduled visits; vital signs were also measured and physical examinations were performed at scheduled visits. As of the data cut-off date, there were no apparent dose-related trends nor any apparent trends over time indicative of potential toxicity of SBC-103.

1.4.1.2 Preliminary Pharmacokinetic and Pharmacodynamic Data

Preliminary Pharmacokinetic Results

Preliminary PK data through a data cut-off date of 09 October 2015 are available, and summary statistics for select PK parameters are presented in Table 1.

Exposure to SBC-103 increased in a dose proportional manner across the doses tested (0.3, 1, and 3 mg/kg) based on the maximum observed serum concentration (C_{max}) and the area under the concentration-time-curve from time 0 to the last measureable time point (AUC_{last}) on Day 0 and at Week 12. Power analyses, in which the Ln AUC_{last} PK exposure was regressed against Ln Dose (0.3 to 3 mg/kg) across all subjects yielded a β value of 1.075 (95% CI: 0.865-1.29) at Day 0 following single dose (first dose) administration and 0.804 (95% CI: 0.537-1.07) at Week 12 following multiple dose administration QOW. These values were 1.12 (95% CI: 0.893-1.35) at Day 0 and 0.855 (95% CI: 0.617-1.10) at Week 12 for C_{max}.

The mean half-life ($T_{1/2}$) for SBC-103 increased from 0.14 to 0.29 hours and was independent of dose and time (Table 1). As shown in Table 1, accumulation (C_{max} and AUC_{last}) was observed at Weeks 12 and 24 in the 0.3 and 1 mg/kg dose cohorts. In contrast, no accumulation was observed at Week 12 in the 3 mg/kg dose group (R_{ac}=0.95 to 0.99).

Table 1: Preliminary Serum Pharmacokinetic Results (Study NGLU-CL02)

Parameter[a]		0.3 mg/kg (N=3)			1 mg/kg (N=4)			3 mg/kg (N=4)		
		n	Mean (SD)	CV%	n	Mean (SD)	CV%	n	Mean (SD)	CV%
AUC_{last} (ng•h/mL)	Day 0	3	440 (94)	22%	4	1862 (374)	20%	4	5538 (2448)	44%
	Week 12	3	782 (58)	7.4%	4[b]	2789 (725)	26%	3[b]	5299 (2659)	50%
	Week 24	3	630 (149)	24%	1	2703	NA	ND	ND	ND
C_{max} (ng/mL)	Day 0	3	250 (38)	16%	4	1073 (199)	19%	4	3617 (1960)	54%
	Week 12	3	433 (29)	6.6%	4[b]	1571 (493)	31%	3[b]	3231 (1315)	41%
	Week 24	3	333 (30)	9%	1	1424	NA	ND	ND	ND
$T_{1/2}$ (h)	Day 0	1	0.29	NA	3	0.22 (0.04)	19%	3	0.14 (0.04)	28%
	Week 12	2	0.21 (0.05)	22%	4[b]	0.27 (0.13)	48%	2[b]	0.28 (0.16)	59%
	Week 24	1	0.19	NA	1	0.28	NA	ND	ND	ND
R_{ac} for C_{max}	Week 12	3	1.77 (0.39)	22%	3[b]	1.53 (0.29)	18.8%	3[b]	0.95 (0.61)	63.5%
	Week 24	3	1.34 (0.13)	9.5%	1	1.53	NA	ND	ND	ND
R_{ac} for AUC_{last}	Week 12	3	1.81 (0.25)	14%	3[b]	1.59 (0.11)	7.0%	3[b]	0.99 (0.68)	68%
	Week 24	3	1.44 (0.17)	12.0%	1	1.64	NA	ND	ND	ND
			Mean	Range		Mean	Range		Mean	Range
T_{max} (h)	Day 0	3	1.08	0.5-2.25	4	1.63	1.5-2.0	4	1.25	0.5-1.5
	Week 12	3	1.67	1.5-2.00	4[b]	1.25	1.5-1.5	3[b]	2.00	0.5-2.5
	Week 24	3	1.75	1.5-2.25	1	2.00	NA	ND	ND	ND

Key: NA = not applicable for CV% because N<3; ND = not determined (due to ongoing sample analysis, serum levels of SBC-103 were not available as of the data cut-off [09 October 2015] for the PK analysis).

[a] PK parameters were estimated using Phoenix™ WinNonlin® (Version 6.4).Nominal time was used for computation.

[b] Subject PPD was enrolled in Cohort 3 and received 3 mg/kg on Day 0. However, due an unrelated SAE (see Section 1.4.1.1), PPD was not dosed at Weeks 2, 4, or 6, and PPD resumed dosing at 1 mg/kg and received 1 mg/kg at Weeks 8 and 12. This subject was, therefore, included in the 1 mg/kg group at Week 12.

Preliminary Pharmacodynamic Results

Preliminary PD data through a data cut-off date of 30 October 2015 are available. At doses up to 3 mg/kg QOW, decreases in heparan sulfate in cerebrospinal fluid (CSF) were directionally consistent and moderately correlated with increased serum SBC-103 exposure (Pearson correlation coefficient R=0.5831 for C_{max} and 0. 5968 for AUC_{last}). Across all 3 dose levels, the maximum observed HS reduction from baseline was 16.5% in CSF and 68.8% in serum.

1.4.2 Assessment of Neurodegeneration by Structural and Diffusion MRI

Neurodegenerative diseases such as Alzheimer's disease, multiple sclerosis, and multiple system atrophy are characterized 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 evaluating the pathophysiology of the diseased brain. The aim is to quantify the single or

combined weight of magnetic resonance imaging (MRI) parameters to describe neurodegenerative processes. Measurement of MRI parameters sensitive to complementary tissue characteristics (eg, 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 analyzed 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 (eg, tumors, 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 (eg, 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.

In addition, blood brain barrier (BBB) integrity will be assessed by calculating the CSF/serum albumin index (CSF-AI). 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 synthesized 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, *Scan J Clin Lab Invest*).

The Sponsor has conducted a non-interventional/observational study in patients with 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.

1.5 Dose Rationale and Risk/Benefits

1.5.1 Study Dose Rationale

1.5.1.1 Defining a Pharmacologically Active Dose

Extended treatment with an ERT is generally required to offer any benefit for a chronic disease such as MPS IIIB, and in a pediatric population such as this, it is important to provide some prospect for benefit with the investigational treatment. Therefore, this study was designed to support chronic dosing for an extended period of time and to allow for intra-patient dose escalation based on evidence of biological activity. Because of the profound neurocognitive abnormalities that dominate the clinical presentation of patients with MPS IIIB, HS reduction in CSF is considered to be an important predictor of potential clinical efficacy in these patients, and therefore, an important PD endpoint representative of biological activity.

However, there is no precedence in MPS IIIB for the magnitude of reduction of HS in the CNS that will be required for efficacy. Based on a combination of data including: the size of systemic substrate reduction with other IV enzyme replacement therapies in MPS I (Clarke 2009, *Pediatrics*) and MPS II (Muenzer 2006, *Genet Med*), reduction of CSF substrate from intrathecally (IT) administered ERT in a related disease, MPS IIIA (Breen 2013, *www.ashg.org*), and the degree of reduction of HS in the brain in the NAGLU mouse model experiments (SBC-103 IB), an estimated substrate reduction of ~40% in the CSF in humans is considered to be a reasonable target to identify a pharmacologically active and potentially efficacious clinical dose of SBC-103.

1.5.1.2 Part A (Initial Therapy): Dose Selection Rationale

Part A of this study is an open label, dose escalation study of 3 dose levels of SBC-103 (0.3, 1, and 3 mg/kg) administered by IV infusion QOW for 24 weeks. For a 7-year-old MPS IIIB patient weighing approximately 30 kg, the 3 dose levels of SBC-103 (0.3, 1, and 3 mg/kg) would equate to total doses of 9 mg, 30 mg, and 90 mg, respectively (Centers for Disease Control [CDC] Clinical Growth Charts, NGLU-CL01 Data on File).

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

The selection of 0.3 mg/kg as the starting dose of SBC-103 in Part A was based on: the NOAELs in the 3-month juvenile Cynomolgus monkey study and in the 4-week Sprague-Dawley rat study when SBC-103 was administered as an IV infusion, along with the pharmacologic effects observed in the NAGLU-deficient nonclinical mouse model of MPS IIIB and PK/PD modeling of nonclinical data.

In the Sprague-Dawley rat, the NOAEL was defined as 3 mg/kg based on the observed vascular/perivascular inflammation in the heart and lungs; this represents a 10-fold margin over the proposed starting dose (0.3 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 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 monkey study, which is considered the most relevant study to support studying SBC-103 in the MPS IIIB pediatric population, the NOAEL was defined as 10 mg/kg QW and 20 mg/kg QOW. This represents a 33- and 66-fold margin over the proposed starting dose (0.3 mg/kg) on a mg/kg body weight basis.

Pharmacological effects were seen in a highly relevant nonclinical mouse model of MPS IIIB (NAGLU-deficient) with IV bolus doses of SBC-103. These mice were administered 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, thus 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 the 0.3 mg/kg establishing the PAD in the liver at 0.3 mg/kg (HED = 0.3 mg/kg based on body weight). 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 and soluble GAG (microgram/mg dry tissue) levels are several fold higher in the liver than in the brain (Li, 1999, *Proc Natl Acad Sci USA*).

The above data from the NGLU-deficient mouse model, PK modeling, and toxicology data as well as affinity data for SBC-103 binding to the macrophage mannose receptor (MMR) and mannose-6-phosphate receptor (M6PR) support the 0.3 mg/kg starting dose and the QOW dosing frequency in this study. Based on these data, the planned starting dose of 0.3 mg/kg was expected to provide possible therapeutic effect in this Phase 1/2 study. The increment between doses in this study is approximately 3-fold, allowing for the assessment of initial safety, tolerability, PK and PD/efficacy in MPS IIIB patients across a 10-fold range of doses on a mg/kg basis (0.3, 1 and 3 mg/kg).

1.5.1.3 Part B (Therapy at 1 and/or 3 mg/kg): Dose Selection Rationale

As described in Section 3.1.2, after review of safety, tolerability, and treatment response data in Part A, dose modification for individual subjects is permitted in Part B; this allows for either dose escalation to 1 and/or 3 mg/kg or reductions to 1 or 0.3 mg/kg based on safety and tolerability and the greatest potential for benefit.

1.5.1.4 Part C (Therapy at 5 and/or 10 mg/kg): Dose Selection Rationale

Preliminary PD data through Week 12 showed that while decreases in heparan sulfate in CSF were moderately correlated with increased serum PK exposure (AUC_{last} and C_{max}), the maximum HS reduction in CSF across all 3 doses was 16.5%, which did not reach the target reduction of ~40% (see Section 1.5.1.1). Greater systemic reduction in substrate was observed following administration of SBC-103; the maximum HS reduction in serum observed across all 3 doses was 68.8%, which is consistent with systemic reductions observed for other ERTs. In addition, the initial safety profile of SBC-103 indicates that it appears to be safe and well tolerated in patients with MPS IIIB (see Section 1.4.1.1).

In the NAGLU-deficient mouse model, SBC-103 administered QW as IV bolus doses of 0.3, 1, 3, 5, or 10 mg/kg for 4 weeks resulted in decreases in HS in the liver and brain, and while near maximal HS decreases were observed in the liver at doses ≥1 mg/kg, HS levels in the brain continued to decrease with each increasing dose (SBC103-P010). Furthermore, similar reductions in HS (brain and liver) were observed in the NAGLU-deficient mouse model regardless of administration regimen (ie, IV bolus QW, IV bolus QOW, or IV infusion QOW)

(SBC103-P010; SBC103-P013). Therefore, it is reasonable to expect that greater reductions of HS in CSF may be expected at increased dose levels in this clinical study. Dose escalation above 3 mg/kg in Part C will explore whether substrate reduction in the CNS can be increased with higher doses (5 and 10 mg/kg) or whether maximal clearance from the CNS has been achieved, thus allowing for identification of doses for extended therapy in this study and for future clinical development that will ensure the greatest potential for clinical benefit.

Therefore, based on the availability of the initial clinical data as well as existing toxicokinetic and toxicology data from the 3-month juvenile Cynomolgus monkey study, new human PK and PK/PD modelling were performed to predict exposure-based safety margins at doses of 5 and 10 mg/kg QOW. As shown in Table 2, scenarios were modelled using 2 sets of assumptions: (1) that exposure remains dose proportional; and (2) that exposure is dose disproportional as was observed in the juvenile monkey toxicology study. A starting dose of 5 mg/kg QOW in Part C has a projected exposure safety margin of ~6-fold (based on PK exposure) and a dose safety margin of 4. This dose level should provide information on whether or not additional HS reduction in CSF can be achieved with greater doses. If the initial doses at 5 mg/kg are tolerated, the 10 mg/kg dose, which has a projected exposure-based safety margin of ~2- to 3-fold (based on PK exposure) and a dose safety margin of 2, will also be evaluated (see Section 3.1.3 for a summary of the Part C study design).

Table 2: Predicted Safety Margins at Clinical Doses of 5 and 10 mg/kg QOW

Dose (mg/kg, QOW)	AUC_{last} (ng•h/mL)		Exposure-Based Safety Margin[a]		Dose Safety Margin[b]
	Dose Proportional[c]	Dose Disproportional[d]	Dose Proportional[c]	Dose Disproportional[d]	
5	9,515		6.1		4.0
10	19,030	31,742	3.0	1.8	2.0

[a] Calculated as SBC-103 exposure (AUC_{last} = 58,000 ng•h/mL) on Day 85 in the 3-month juvenile monkey toxicology study (SBC103-T009) at the NOAEL dose (20 mg/kg QOW) / predicted SBC-103 exposure (AUC_{last}) at Week 12 in humans

[b] Dose margin = NOAEL dose (20 mg/kg) in the 3-month juvenile monkey toxicology study (SBC103-T09) / SBC-103 proposed human dose

[c] Predicted based on the dose proportionality as observed from 0.3 to 3 mg/kg QOW up to Week 12 in this clinical study.

[d] Predicted based on a greater than dose proportional increase (5.56-fold) from 3 to 10 mg/kg and a less than dose proportional increase (1.6-fold) from 10 to 20 mg/kg in AUC_{last} observed at Day 85 in the3-month juvenile monkey toxicology (SBC103-T009)

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 subjects. Currently, there are no safe or effective therapies for MPS IIIB.

Part A (Initial Therapy)

The initial benefit/risk assessment of SBC-103 for this study was based on data from nonclinical studies. Data from safety and toxicity studies conducted in the Sprague-Dawley rat and Cynomolgus monkey (including a 3-month study in juvenile monkeys) demonstrated that SBC-103 administered IV was generally well tolerated at the doses planned in Parts A and B of 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 behavior were noted generally after the third or fourth dose of SBC-103. These observations were transient and not correlated with any other parameters evaluated. 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.

Extensive clinical experience with approved ERTs for other LSD indications is also 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 anti-pyretics and anti-histamines. While severe infusion reactions, including anaphylaxis and 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 (eg, diphenhydramine, parenteral and oral), corticosteroids, epinephrine (adrenaline), and cardiopulmonary resuscitation devices. Anti-drug antibodies (ADA) 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 IV infusion 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 first-in-human study is based on *in vivo* pharmacology data from a relevant disease model supporting the potential for CNS activity following IV administration (SBC103-P004, SBC103-P007, SBC103-P009, SBC103-P010), with supportive information from *in vivo* pharmacology data in a relevant disease model supporting the potential for CNS activity following IV/IT administration (SBC-103 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 (CT) investigations of the PK of radiolabeled SBC-103 in non-human primates (IV administration and IT administration) indicating access to the CNS following IV administration (SBC103-K004), and PK modeling 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 stabilized 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.

Part B (Therapy at 1 and/or 3 mg/kg) and Part C (Therapy at 5 and/or 10 mg/kg)

It is anticipated that extended dosing of SBC-103 may have beneficial effects on disease activity, including the neurologic manifestations of MPS IIIB, and it is important to provide the pediatric patient population with this disease the greatest prospect of direct benefit in this clinical study by evaluating extended therapy at doses that are both safe and have the potential to reach the identified target for pharmacologic activity and potential efficacy (see Section 1.5.1.1). Thus, Parts B and C provide for subjects to receive extended therapy and also permit periodic review of ongoing safety, PK, and PD data. Periodic data review permits continued assessment of potential benefit and risk based on clinical data and may be used to guide dose modification accordingly (escalation or de-escalation, as appropriate).

Furthermore, the data provided from the study will guide and inform the design of future clinical studies.

1.5.2.1 Risk Assessment for Selected Study Procedures

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.

Anesthesia

Disease progression in subjects with MPS IIIB is associated with cognitive decline and behavioral 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 anesthesia prior to, and during the MRI procedure (and lumbar puncture, as appropriate). Sedation of children is associated with risks of hypoxemia, inadequate sedation, and failed sedation. General anesthesia 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 anesthesia prior to the lumbar puncture, if clinically appropriate. See above regarding risks associated with anesthesia.

Magnetic Resonance Imaging

The primary risks of MRI in patients with MPS IIIB are those associated with the administration of anesthesia 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 anesthesia.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the safety and tolerability of IV administration of SBC-103 in subjects with mucopolysaccharidosis III, type B (MPS IIIB, Sanfilippo B) with evaluable signs or symptoms of developmental delay.

2.2 Secondary Objectives

- To characterize the PK profile of SBC-103 administered IV.
- To determine the effects of SBC-103 administered IV on the levels, onset and magnitude of changes in total HS in CSF, serum, and urine.
- To evaluate the PD/efficacy of doses of SBC-103 administered IV as measured by neurocognitive and developmental function and change in brain structures.
- To evaluate the impact of temporary interruption of SBC-103 therapy (between Parts A and B) on safety, tolerability, and select PD/efficacy markers, including the reversibility of changes in levels of total HS in CSF, serum, and urine.

2.3 Exploratory Objectives

- To examine the onset, magnitude, and reversibility of changes in exploratory biomarkers, SBC-103 concentration in CSF, MPS IIIB disease characteristics, symptoms, and quality of life (QOL) after IV administration of SBC-103.

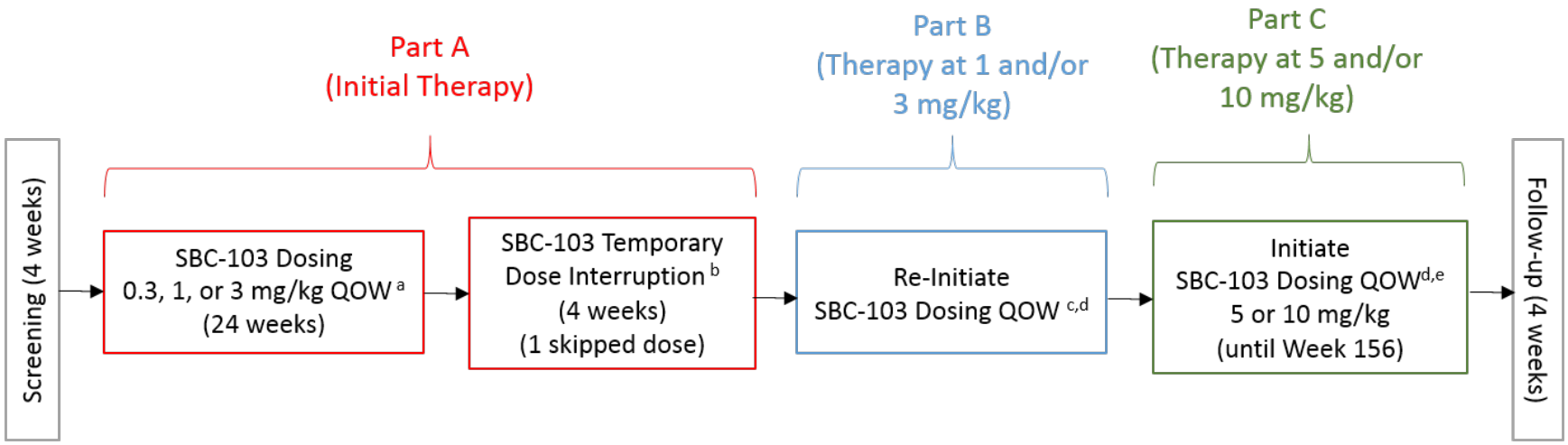
3 INVESTIGATIONAL PLAN

3.1 Overall Design and Plan of the Study

This study is designed to evaluate the safety and tolerability of IV administration of SBC-103 for the treatment of MPS IIIB. Approximately 9 subjects at approximately 4 centers are expected to participate in this study. As illustrated in Figure 1, this study will be conducted in 3 parts: Part A (Initial therapy), Part B (Therapy at 1 and/or 3 mg/kg), and Part C (Therapy at 5 and/or 10 mg/kg). All subjects who participate in Part A may continue SBC-103 dosing in Part B if they qualify for continued dosing (see Section 4.3.3), and all subjects participating in Part B are eligible for dose escalation in Part C providing that the criteria in Section 4.3.4 are met.

As indicated in Figure 1, the total duration of the study is approximately 164 weeks. This includes a Screening period that will last up to 4 weeks, 156 weeks of therapy with SBC-103, 4 weeks of time off therapy (between Weeks 24 - 28) , and a 4-week follow-up period after the last dose is administered.

Figure 1: Study Schematic for Part A (Initial Therapy), Part B (Therapy at 1 and/or 3 mg/kg), and Part C (Therapy at 5 and/or 10 mg/kg)



[a] In Part A, the SRC will review data as described in Section 3.1.1.1.
[b] Subjects will have 4 weeks in between their last dose in Part A and their first dose in Part B instead of the 2 weeks that occurs with QOW dosing.
[c] Subjects who meet qualifying criteria may re-initiate therapy in Part B (see Section 4.3.3); dosing in Part B will continue until necessary regulatory and ethics committee review and approval (where required) are obtained for each site to dose escalate in Part C and the subject meets the qualifying criteria to begin dosing in Part C.
[d] In Parts B and C, the SRC will review aggregate safety data as described in Section 7.5.
[e] Subjects who meet qualifying criteria may dose escalate in Part C (see Section 4.3.4); in Part C, the SRC will also review data as described in Section 3.1.3.1.

3.1.1 Part A (Initial Therapy)

In Part A, following completion of the screening assessments to confirm study eligibility, approximately 9 subjects will be treated in 1 of 3 different dosing cohorts (0.3, 1, or 3 mg/kg). In the event that more than 3 subjects in a cohort have entered Screening and are determined to be eligible to participate in the study, an additional subject may be dosed with SBC-103 within the intended dose cohort. This will be acceptable provided the following conditions are met: 1) the SRC has met and approved the continued dosing of the 1st subject in the cohort and the first dose of the 2nd subject and 2) the Sponsor has reviewed safety information of the 2nd subject in the cohort and has approved the 3rd patient to be dosed.

Each subject in each cohort will be dosed sequentially with SBC-103 administered by IV infusion QOW for 24 consecutive weeks. See Table 3 and Figure 1.

Table 3: Part A (Initial Therapy) Dose Cohorts

Dose Cohort #	Dose of SBC-103[a]	Dosing Regimen	Sample Size[b]
1	0.3 mg/kg	QOW for 24 weeks	n=3
2	1 mg/kg	QOW for 24 weeks	n=3
3	3 mg/kg	QOW for 24 weeks	n=3

[a] Intra-patient dose escalation is not planned during Part A.

[b] Enrollment of an additional subject in a cohort may occur as described above.

Details regarding the maximum planned dose, dose adjustments, and stopping rules in the event of poor tolerability are provided in Section 6.1 and Section 6.2.

Safety, PK and PD/efficacy assessments will be performed in all subjects as noted in the Schedule of Assessments (SOA) for Part A, detailed in Section 14.1 (Appendix A). All subjects will be monitored in an in-patient setting for safety and tolerability for at least 24 hours following the first dose of SBC-103. To evaluate safety, follow-up phone calls will be made to each subject (or the subject's parent or caregiver) within 24 hours after the subject's second, third, and fourth doses in Part A (Weeks 2, 4 and 6, respectively).

After receiving SBC-103 QOW for 24 consecutive weeks, subjects will have a 4-week temporary interruption of therapy prior to being considered for participation in Part B.

If a subject will not participate in Part B of the study, an additional follow-up phone call will be made 4 weeks after the subject's last administered dose in Part A unless the subject has a scheduled follow-up visit.

3.1.1.1 Criteria for Dosing and Cohort Dose Escalation in Part A

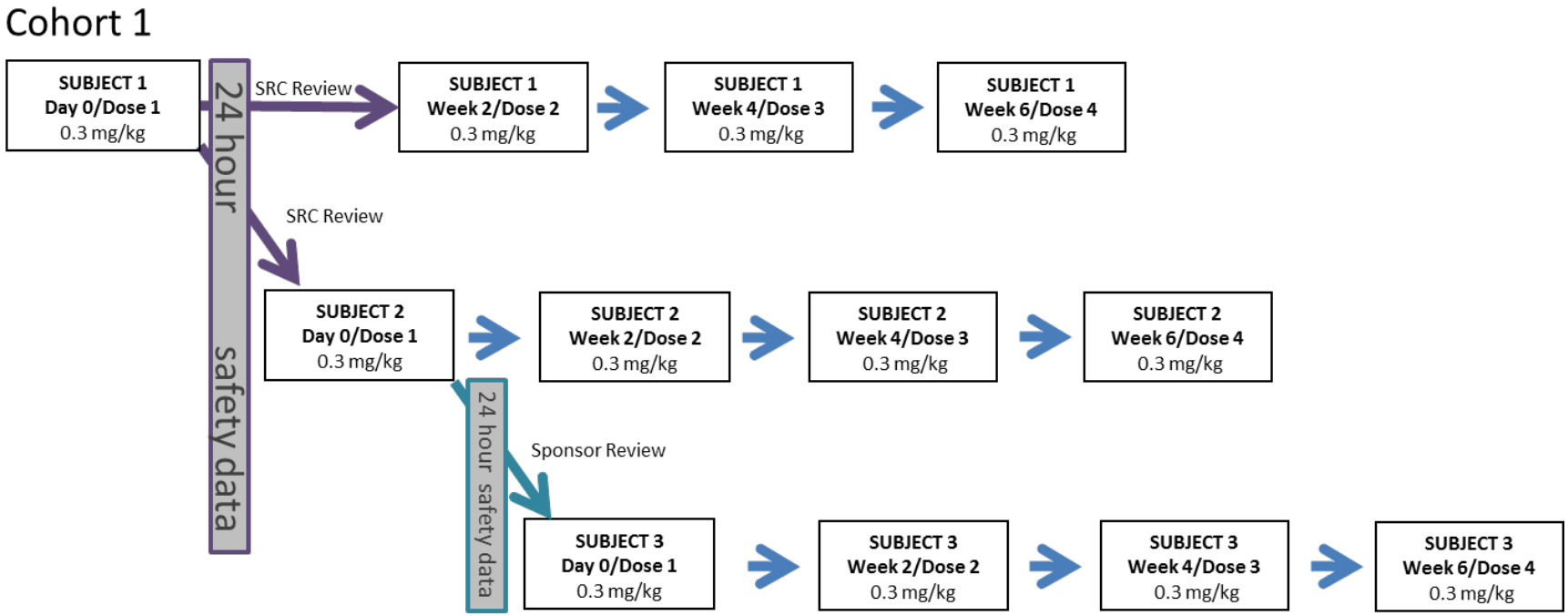
As illustrated in Figure 2, the decision to **continue dosing in the 1st subject** in the 1st, 2nd, and 3rd cohorts will be made by the Sponsor based on SRC recommendations after review of 24-hour safety data from that subject and available safety data from all other subjects.

The decision to **initiate dosing in the 2nd subject** of each cohort will be made by the Sponsor based on SRC recommendations after review of 24-hour safety data from Subject 1 in the same cohort and available safety data from all other subjects.

The decision to **initiate dosing in the 3rd subject** of each cohort will be made by the Sponsor based on 24-hour safety data from Subject 2 in the same cohort and available safety data from all other subjects.

As described in Figure 2, the decision to **escalate into the next dose cohort** will be made by the Sponsor based on SRC recommendations after review of safety data from the 1st subject who completes the first 4 doses in the dose cohort, 24-hour safety data after the first dose from the 3rd subject of the same cohort, and available safety data from all other subjects.

Figure 2: Planned Staggered Subject Treatment and Dose Escalation Schedule for the First Four Doses of SBC-103 in Part A (Initial Therapy)



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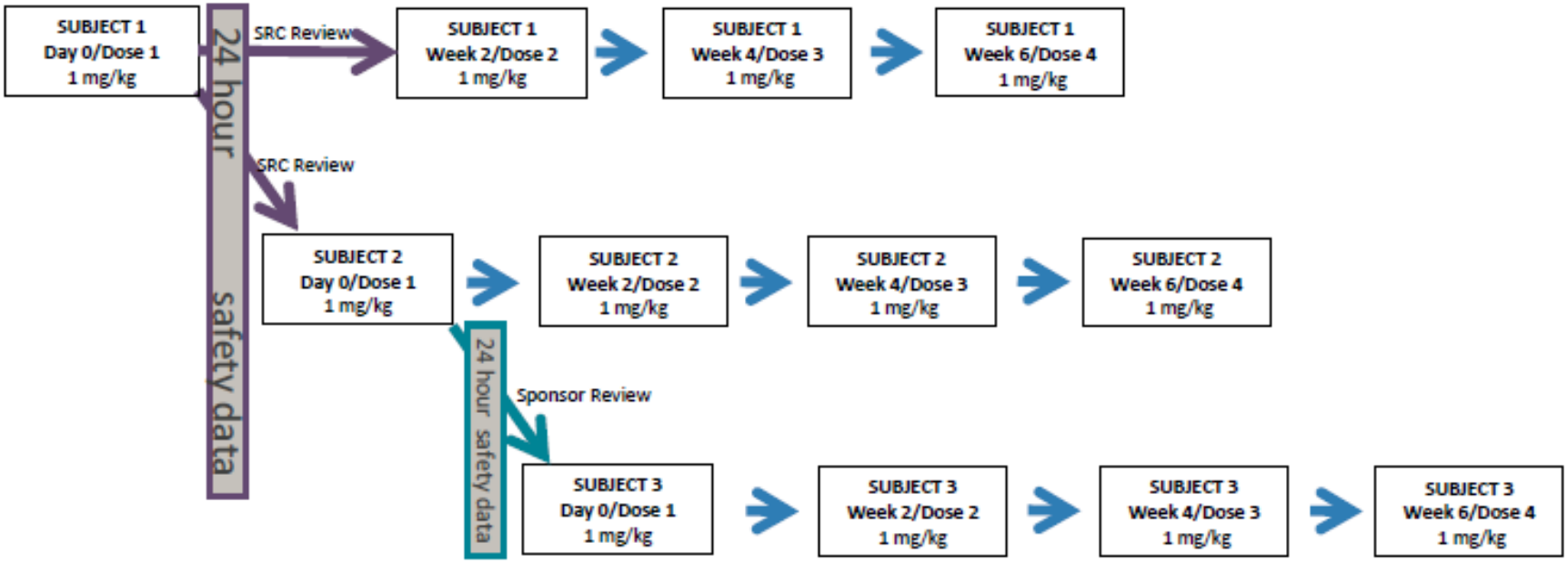
Escalation to Cohort 2 is based on SRC review of safety data after 4 doses from 1 Subject and 24 hour safety data from Subject 3

Cohort 2



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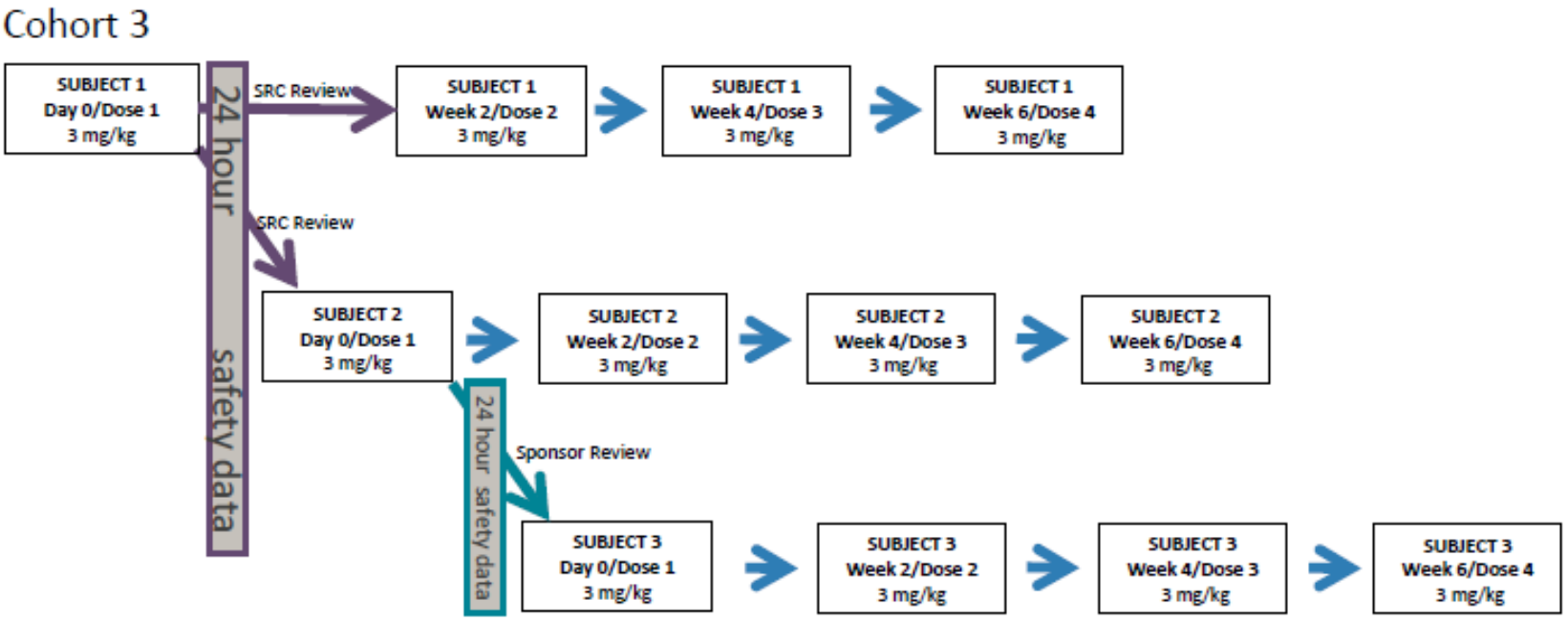
Escalation to Cohort 3 is based on SRC review of safety data after 4 doses from 1 Subject and 24 hour safety data from Subject 3



3.1.2 Part B (Therapy at 1 and/or 3 mg/kg)

Subjects who meet qualifying criteria may commence Part B (Therapy at 1 and/or 3 mg/kg) after completing Part A, and after the SRC and Sponsor have evaluated an individual subject's available safety data and has deemed it acceptable for that subject to initiate continued therapy in Part B. Only subjects who meet eligibility criteria for Part B will re-initiate SBC-103 dosing in Part B. Refer to Section 4.3.3. Eligible subjects may re-initiate SBC-103 dosing in Part B no sooner than 4 weeks after the subject's last dose in Part A.

In Part B, dose or dosing frequency (eg, QOW or QW) modifications may be considered by the Sponsor after consultation with the SRC, based on a review of safety, tolerability and treatment response data. With the intent of treating patients with the lowest dose that is safe and tolerable and which has potential for efficacy, dose modification (either an increase to 1 or 3 mg/kg, or a decrease to 0.3 or 1 mg/kg) may be proposed for individual subject(s) after evaluation of the safety and tolerability data as well as biomarker and treatment response data after 24 weeks of study participation.

Dose modifications will not be considered until Part B of the study, except for instances where a dose reduction is required for reasons of safety and tolerability. Subjects who receive doses of 0.3 mg/kg in Part A may be considered for a second dose escalation to 3 mg/kg at any time during Part B provided that they have tolerated at least 2 doses of 1 mg/kg in Part B.

Details regarding the maximum planned dose to be evaluated, dose adjustments, and stopping rules in the event of poor tolerability are provided in Section 6.1 and Section 6.2.

Safety, PK, and PD/efficacy assessments will be conducted at regular intervals throughout Part B as specified in the SOA for Part B. See Sections 14.2 and 14.3 (Appendix B and Appendix C).

Subjects who have received and tolerated at least 4 doses of SBC-103 QOW at 3 mg/kg may be considered for participation in Part C (see Section 3.1.3 and Section 4.3.4). Subjects will continue to be dosed in Part B of the study until necessary regulatory and ethics committee review and approval (where required) are obtained for each site to dose escalate in Part C. Subjects who are unable to tolerate at least 4 doses of SBC-103 at 3 mg/kg will continue to be dosed at the highest tolerable dose in Part B until study completion.

If a subject prematurely discontinues, a follow-up call will be made 4 weeks after the subject's last administered dose in Part B unless the subject has a scheduled follow-up visit.

3.1.3 Part C (Therapy at 5 and/or 10 mg/kg)

Subjects who meet eligibility criteria for Part C (see Section 4.3.4) may begin Part C at their next scheduled visit provided that regulatory and ethics committee review and approval (where required) have been obtained for at their study site and the criteria for dosing in Section 3.1.3.1 are met. Part C is a randomized, open-label assessment of SBC-103 at doses of 5 or 10 mg/kg administered IV. Subjects will be randomized such that at least 1 subject from each cohort assigned in Part A will receive SBC-103 at 5 mg/kg and at least 1 subject from each cohort assigned in Part A will receive SBC-103 at 10 mg/kg. Thus each of the assigned dose levels from Part A will be represented in each of the 2 dose levels being studied in Part C. Treatment in Part C will continue through Week 156 of the study.

Details regarding the maximum planned dose, dose adjustments, and stopping rules in the event of poor tolerability are provided in Section 6.1 and Section 6.2.

Safety, PK and PD/efficacy assessments will be performed in all subjects as noted in the SOA for Part C, detailed in Section 14.4 (Appendix D). To minimize unnecessary risk and burden to subjects, the following study assessments in Part B may be used as baseline assessments for Part C in lieu of repeating the assessment prior to the first dose in Part C:

- An MRI performed within 8 weeks prior to Day 0 in Part C (Day 0C) may be used as the baseline assessment for Part C in lieu of performing an MRI on Day 0C.
- Neurocognition testing performed within 8 weeks prior to Day 0C may be used as the baseline assessment for Part C in lieu of performing neurocognition testing on Day 0C.
- A lumbar puncture performed within 4 weeks prior to Day 0C may be used as the baseline assessment for Part C in lieu of performing a lumbar puncture on Day 0C.

In addition, because individual subjects may reach Week 156 of the study at unique study visits in Part C, the following assessments in Part C may be used as the end-of-treatment assessment in lieu of repeating the assessment at Study Week 156:

- An MRI performed within 8 weeks prior to Study Week 156 may be used as the final assessment for Part C in lieu of performing an MRI at Study Week 156.
- Neurocognition testing performed within 8 weeks prior to Study Week 156 may be used as the final assessment for Part C in lieu of performing neurocognition testing at Study Week 156.
- A lumbar puncture performed within 4 weeks prior to Study Week 156 may be used as the final assessment for Part C in lieu of performing a lumbar puncture at Study Week 156.

These assessments are also noted on the SOA for Part C.

To provide complete safety data for SRC review (described in Section 3.1.3.1 below), the following subjects will be monitored in an in-patient setting for safety and tolerability as follows:

- The first subject to receive SBC-103 at 5 mg/kg will be monitored for at least 24 hours after administration of the first 5 mg/kg dose.
- The first subject to receive SBC-103 at 10 mg/kg will be monitored for at least 24 hours after administration of the first 10 mg/kg dose.

If a subject discontinues participation from Part C of the study, an additional follow-up phone call will be made 4 weeks after the subject's last administered dose in Part C unless the subject has a scheduled follow-up visit.

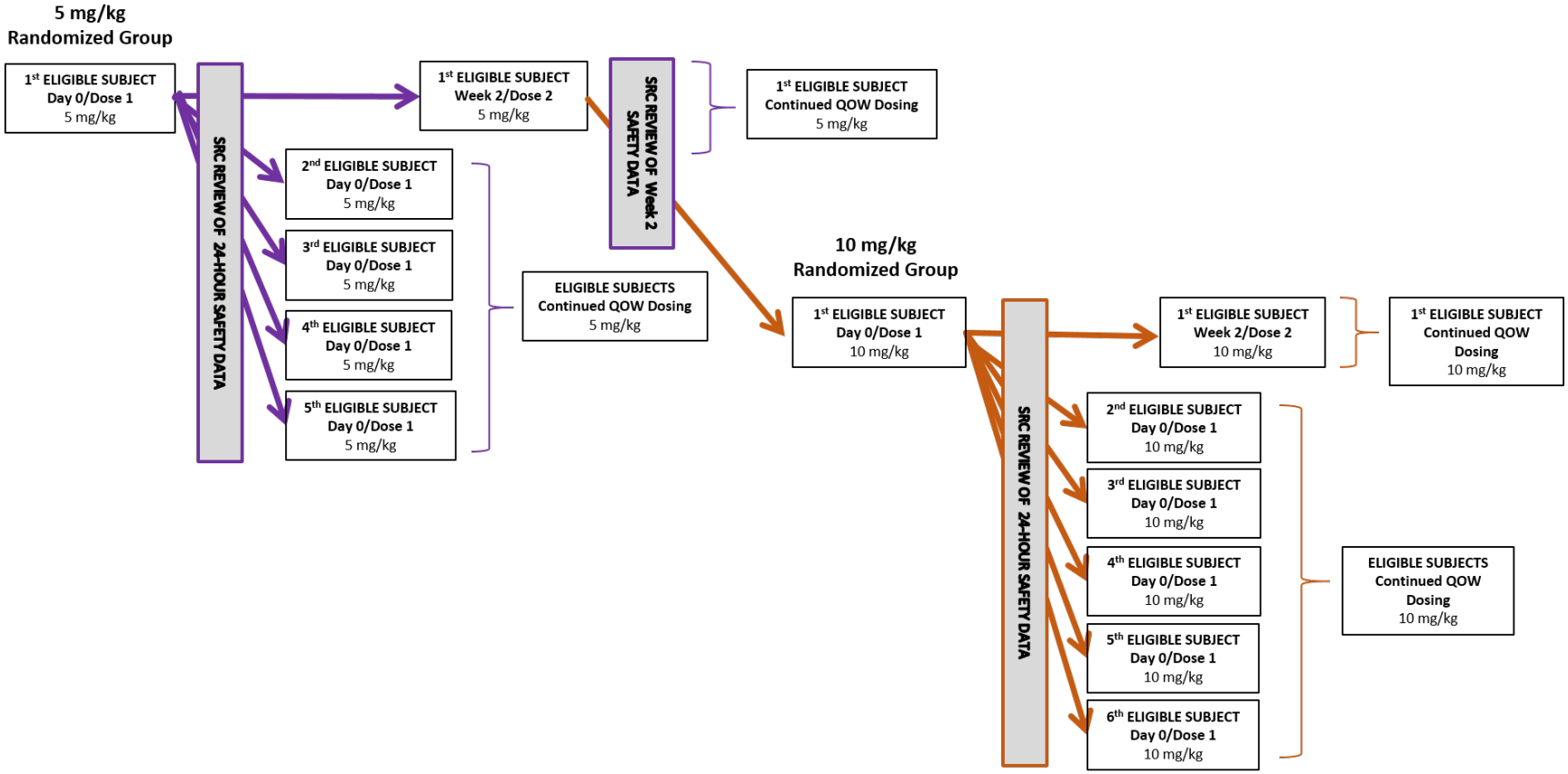
3.1.3.1 Criteria for Dosing in Part C

The first subject who is eligible to dose escalate in Part C (see Section 4.3.4) and who is randomized to receive 5 mg/kg in Part C will be the first subject dosed in Part C; in the event that >1 subject is eligible at the same time, subjects will be dosed sequentially based on subject identification number (eg, Subject [Site #]-003 would be dosed before Subject [Site #]-005). As shown in Figure 3, the decision to continue dosing this subject and to start dosing the remaining 4 subjects at 5 mg/kg will be made by the Sponsor based on SRC recommendations after review of 24-hour safety data from the first subject dosed at 5 mg/kg. The remaining subjects randomized to the 5 mg/kg dose group may be dosed in parallel providing they meet all eligibility criteria to participate in Part C.

The decision to dose the first subject at 10 mg/kg will be made by the Sponsor based on SRC recommendations after review of safety data from 1 subject who completes the first 2 doses at 5 mg/kg, and review of all available safety data from any other subjects who have received at least 1 dose of SBC-103 at 5 mg/kg (Figure 3). Similar to initiation of dosing at the 5 mg/kg dose level, the first subject to receive the 10 mg/kg dose will be the first eligible subject to dose escalate in Part C who is randomized to the 10 mg/kg group; in the event that >1 subject is eligible at the same time, subjects will be dosed sequentially based on subject identification number. The decision to dose the remaining 5 subjects at 10 mg/kg will be made by the Sponsor based on SRC recommendations after review of 24-hour safety data from the first subject dosed at 10 mg/kg. The remaining subjects randomized to the 10 mg/kg dose group may be dosed in parallel providing they meet all eligibility criteria to dose escalate in Part C.

Intra-subject dose escalation from 5 to 10 mg/kg based on all available safety, PK, and PD/efficacy data may not occur without prior written approval from the Sponsor. Dose reductions may be considered for safety and tolerability at any time in Part C.

Figure 3: Planned Subject Treatment and Dose Escalation Schedule in Part C (Therapy at 5 and/or 10 mg/kg)



3.2 Rationale for Study Design

This study will be conducted in 3 parts: Part A (Initial therapy), Part B (Therapy at 1 and/or 3 mg/kg), and Part C (Therapy at 5 and/or 10 mg/kg). Part A is designed to assess the safety, tolerability, PK, and PD/efficacy of 3 escalating doses of SBC-103 dosed QOW over 24 weeks. As this is the first-in-human study, 24-hour in-patient safety monitoring following the first dose for each subject and SRC and/or Sponsor review of safety data have been incorporated into Part A to minimize risk and to monitor subject safety (see Section 3.1.1.1). Following Part A and prior to entering Part B, subjects will have a 4-week period of time off therapy (instead of the usual 2 weeks between doses that occurs with QOW dosing) in order to assess the impact of treatment interruption on safety, tolerability, and select PD markers, including the assessment of reversibility of any observed on-therapy changes in HS.

In light of the pediatric patient population intended for enrollment, it is important (and often required by regulation) to provide some prospect for benefit with the investigational treatment. For an enzyme replacement therapy for a chronic disease such as MPS IIIB, extended treatment is generally required to offer any prospect of benefit. Therefore, Part B is designed to assess the safety, tolerability, PK, and PD/efficacy of chronic dosing for an extended period of time and to allow for intra-patient dose modification based on available data. Prior to commencing Part B, the SRC will review all available safety data from a specific cohort and any safety data available from other cohorts to determine the demonstration of an acceptable safety and tolerability profile to support extended therapy (see Section 7.5). Additionally, in Part B, the SRC will continue to provide oversight of subject safety through periodic reviews of safety data. Ad-hoc reviews of safety data will be performed by the SRC on an as-needed basis in the event of emerging safety signals of clinical concern in one or more subjects, including subjects who meet pre-defined stopping rules (see Section 6.2).

Part C (added with Amendment 6 based on preliminary safety and PK/PD data from Parts A and B) is designed to assess the safety, tolerability, PK, and PD/efficacy of SBC-103 at 5 and 10 mg/kg over at least 24 weeks as well as to assess the effects on chronic dosing. Intrasubject dose modification is permitted in Part C (based on data review and Sponsor agreement) with the intent to treat subjects with the lowest potentially efficacious dose that is safe and tolerable. Because dose escalation occurs in Part C, 24-hour in-patient safety monitoring following the first dose for each subject and SRC and/or Sponsor review of safety data have been incorporated into Part C to minimize risk and to monitor subject safety (see Section 3.1.3.1). Additionally, in Part C, the SRC will continue to provide oversight of subject safety through periodic reviews of safety data. Ad-hoc reviews of safety data will be performed by the SRC on an as-needed basis in the event of emerging safety signals of clinical concern in one or more subjects, including subjects who meet pre-defined stopping rules (see Section 6.2).

To provide the greatest likelihood of benefit, subjects are permitted to enter Part C as soon as necessary regulatory and ethics committee review and approval (where required) has been obtained and the subject meets the qualifying criteria to begin dosing in Part C (see Section 4.3.4). Therefore, each subject's duration of treatment and assessments in Part B may vary. Once a subject enters Part C, the study visit schedule is reset to Day 0 Part C (Day 0C) to ensure that the visit days/assessments correspond to the same number of infusions of SBC-103 for each subject. All study visits in Part C will be scheduled relative to Day 0C to allow for a more meaningful assessment of the PK and PD/efficacy profile of the 5 and 10 mg/kg doses. In addition, subjects will be randomized such that at least 1 subject from each cohort assigned in Part A will receive SBC-103 at 5 mg/kg and at least 1 subject from each cohort assigned in

Part A will receive SBC-103 at 10 mg/kg. Thus each of the assigned dose levels from Part A will be represented in each of the 2 dose levels being studied in Part C.

There are emerging compelling 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, pediatric 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 will provide important insights into the utility of SBC-103 therapy administered IV.

Important manifestations of MPS IIIB disease include developmental and cognitive delay and regression as well as sleep and behavior 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 1.4.2, 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. Blood-brain-barrier integrity will also be evaluated by measuring CSF-AI.

Information regarding the safety and tolerability of each dosing cohort, along with PK/PD data, will be used to guide any additional dose escalation in this study as well as to support the selection of doses and dose scheduling for subsequent studies.

3.3 Rationale for Dose and Escalation Timing

3.3.1 Rationale for Dose Escalation in Part A (Initial Therapy)

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. Most clinical observations in nonclinical studies occurred by the fourth dose (see Section 1.3). Therefore, In Part A, the decision to escalate into the next dosing cohort (from Cohort 1 to Cohort 2 and from Cohort 2 to Cohort 3) will be made by the Sponsor, based on SRC recommendations after review of safety data from the first subject who completes the first 4 QOW doses in the dose cohort and 24-hour safety data from Subject 3 in the same dose cohort. Intra-patient dose escalation is not planned for Part A.

3.3.2 Rationale for Intra-Patient Dose Escalation in Part B (Therapy at 1 and/or 3 mg/kg)

Based on the experience with neurodegenerative diseases, it is anticipated that clinical response to treatment may not be observed sooner than 6 months after initiating treatment with SBC-103. Therefore, evaluation of safety and tolerability data as well as biomarker and response to treatment data will take place after 24 weeks of treatment in Part A. With the intent of treating patients with the lowest dose that is safe and tolerable and which has potential for efficacy, dose escalation may be proposed for individual subject(s) at any time in Part B as described in Section 3.1.2 and Section 6.1.

3.3.3 Rationale for Additional Dose Escalation in Part C (Therapy at 5 and/or 10 mg/kg)

Preliminary available clinical safety, PK, and PD data (see Section 1.4.1) from this study together with existing toxicokinetic and toxicology data from the juvenile Cynomolgus monkey study provide a safety margin (see Section 1.5.1.4) that supports dose escalation to 5 and 10 mg/kg in Part C. Given the available safety data from Parts A and B and the prior SBC-103 exposure in these patients, 24-hour safety data from 1 subject at each dose are considered appropriate to permit the expansion of each dose cohort, and data from 1 subject who completes the first 2 doses at 5 mg/kg is considered appropriate to initiate dosing at 10 mg/kg.

In addition, ongoing safety and PD data from Part C will be reviewed on an ongoing basis to guide further dose selection (ie, escalation from 5 to 10 mg/kg or reduction from 10 to 5 mg/kg) in this study with the goal of treating patients at the lowest dose that is likely to demonstrate clinical benefit while also being safe and tolerable.

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 (hematology, serum chemistry, and urinalysis) and CSF findings (cell counts, glucose, and protein);
- Changes from baseline in 12-lead electrocardiograms (ECGs);
- Changes in vital signs during and post-infusion, relative to pre-infusion values;
- Physical examination findings;
- Use of concomitant medications/therapies;
- Assessment of ADAs, including seroconversion rate, time to seroconversion, and ADA titer by time point, peak ADA titer, and ADA titer 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 baseline and post-treatment measures of the following assessments:

- PK profile of SBC-103 after single and multiple doses:
  - Maximum observed serum concentration (C_{max})
  - Time to reach C_{max} (T_{max})
  - Area under the concentration-time-curve from time 0 to the last measurable time point (AUC_{last})
  - Area under the concentration-time-curve extrapolated to infinity (AUC_{∞})
  - Half-life ($T_{1/2}$)

  - Clearance (CL)
  - Volume of distribution at terminal phase (V_z)
  - Accumulation ratio (R_{ac})
- Effects of SBC-103 treatment on the onset, magnitude, and reversibility of changes in levels of total HS in CSF, serum, and urine.
- Neurocognitive and developmental function as determined by the scores on Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) and, as appropriate to the subject's age, 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).
- Brain structure as determined by the relative proportion of grey and white matter volume and indices of microstructural integrity as assessed by MRI of the brain.
- Effect of temporary interruption of SBC-103 therapy (between Parts A and B) on safety, tolerability, and select PD/efficacy markers.

3.4.3 Exploratory Endpoints

Exploratory endpoints in this study include measures to examine the onset, magnitude, and reversibility of changes in exploratory biomarkers, SBC-103 concentration in CSF, MPS IIIB disease characteristics, symptoms, and QOL after IV 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 (HGF), 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/serum albumin index (CSF-AI).
  - Changes in IgG index ([CSF/serum IgG ratio] / [CSF-AI])
  - Changes in inflammatory markers in serum
- Disease characteristics, symptoms, and QOL
  - Assessment of sleep disorders or dysfunction as determined by the Children's Sleep Habits Questionnaire (CSHQ)
  - Assessment of behavior as determined by the Sanfilippo Behavior Rating Scale (SBRS)
  - Assessment of subjective QOL as determined by the Short Form Health Survey for Children (SF-10)
  - Assessment of caregiver QOL as determined by the Zarit Burden Interview (ZBI) 12-item short form

- Coarsening of features by Facial Dysmorphology Novel Analysis (FDNA)
- Additional 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).
- Assessment of genes that may contribute to and/or modify the disease phenotype via a DNA sample (where local regulations permit and subject to discretionary approval from each center's Institutional Review Board [IRB]/Independent Ethics Committee [IEC] and the consent/assent of the subject [and/or consent of the subject's parent or legal guardian]).

4 STUDY POPULATION

4.1 Target Population

The target population for this study is male and female subjects with documented MPS IIIB who are greater than or equal to 2 years old but less than 12 years old.

4.2 Number of Subjects

Approximately 9 subjects with MPS IIIB are planned to be treated in this study. All subjects may enter Part B if they meet eligibility criteria described in Section 4.3.3, and once the site has received approval to escalate to doses of 5 and 10 mg/kg, subjects may enter Part C if they meet eligibility criteria described in Section 4.3.4.

4.3 Eligibility Criteria

4.3.1 Inclusion Criteria

A subject who meets all of the following inclusion criteria will be eligible to participate in this study:

1. Has a definitive diagnosis of MPS IIIB, as determined by either of the following:
   a. Documented deficiency in NAGLU enzyme activity ≤10% of the mean value in normal individuals (Heron, 2011, *Am J Med Genet A*) based on test results from a central laboratory at Screening.

      OR

   b. Documented functionally-relevant mutations in both alleles of the NAGLU gene based on historical test results from a local laboratory (if available) or results from the central laboratory at Screening.

1. Greater than or equal to 2 years old and less than 12 years old at the time of written informed consent, and has an age equivalent of ≥1 year on the Vineland-II.
2. Has documented developmental delay with onset before 6 years of age, as defined by:
   a. Cognitive delay evaluated by BSID-III or KABC-II.

      OR

   b. Language delay, plateauing or regression of language skills as determined by the Investigator and confirmed by the Vineland-II (communication domain) administered at Screening (eg, subject uses isolated words, associated words such as two-word combination, sentences, poor or reduced language and/or language difficult to understand).
3. Subject or subject's parent or legal guardian (if applicable) consents 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.
4. 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 consent 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 last dose of SBC-103. Women may be considered of non-childbearing potential if they have not started their menses or are surgically sterile (ie, total hysterectomy or bilateral salpingo-oophorectomy).

5. Male subjects must consent to 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.
6. 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

A subject who meets any 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 utilize 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 anesthesia 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 co-morbidities (eg, ALT or AST > 3x ULN, confirmed by repeat testing, analyzed centrally or locally and based on the standardized reference range provided in the central laboratory manual), or other markers of clinically significant liver dysfunction (eg, elevated bilirubin, [with the exception of patients with confirmed Gilberts Disease] confirmed by repeat testing, or elevated prothrombin time [PT]/International normalized ratio [INR] confirmed by repeat testing analyzed centrally or locally and based on the standardized reference range provided in the central laboratory manual) which in the opinion of the Investigator, in consultation with the Sponsor, would interfere with study compliance, or confound data interpretation.

4.3.3 Qualifications for Participation in Part B (Therapy at 1 and/or 3 mg/kg)

Subjects are eligible for continued SBC-103 dosing in Part B if they do not meet any Exclusion criteria listed above and if they meet the following:

1. Completion of Part A with no unmanageable study drug toxicity;
2. Continue to meet Section 4.3.1 Inclusion Criteria items 4-7; and

3. SRC and Sponsor have reviewed the subject's safety data from Part A and have deemed it acceptable for the subject to re-initiate dosing in Part B.

4.3.4 Qualifications for Participation in Part C (Therapy at 5 and/or 10 mg/kg)

Subjects are eligible for continued SBC-103 dosing at a higher dose (5 or 10 mg/kg QOW) in Part C if they do not meet any Exclusion criteria listed above and if they:

1. Have completed at least 4 doses of 3 mg/kg in either Part A or Part B with no unmanageable study drug toxicity; and
2. Continue to meet Section 4.3.1 Inclusion Criteria items 4-7.

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 (eg, 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
- Adverse events, including severe infusion reactions
- Pregnancy
- 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 (excluding ineligibility for Part B), all efforts should be made to have the subject complete follow-up visit procedures, including End of Study/Early Withdrawal Visit per SOA (refer to Section 14). 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: three 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 who discontinue prior to administration of SBC-103 will be replaced. Subjects who discontinue for reasons other than medically important adverse event(s) considered related to the administration of SBC-103 may be replaced after discussion between the Sponsor and the SRC.

4.7 Subject Re-screening

Subjects who were unable to complete all Screening procedures within the 28-day screening window may be re-screened. 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 (SOA) is presented in Section 14.1 (Appendix A) for Part A (Initial Therapy), in Sections 14.2 and 14.3 (Appendices B and C) for Part B (Therapy at 1 and/or 3 mg/kg), and in Section 14.4 (Appendix D) for Part C (Therapy at 5 and/or 10 mg/kg). Unless otherwise specified, all study assessments described in the following sections are applicable to Parts A, B, and C of this study. 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 IRB/IEC before screening procedures are initiated, and will be given a copy of the signed and dated informed consent form. 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. All eligibility assessments are to be completed prior to the commencement of any Day 0 procedure (ie, any invasive procedures, including general anesthesia or sedation, lumbar puncture and MRI). Sites are requested to provide documentation/confirmation of eligibility to the Sponsor, which is subject to Sponsor review and agreement.

In Part B, all subjects will also be assessed to determine whether they qualify for re-initiation of SBC-103 dosing as described in Section 4.3.3, and subjects will be permitted to enter Part C (expanded dose escalation) if they meet the criteria in Section 4.3.4.

5.1.3 Medical History

A complete medical history will be obtained for each subject at Screening, including (but 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 behaviors (hyperactivity, aggressiveness, irritability, endangering behaviors)
    - 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 apnea)
- Ear-nose-throat problems (recurrent ear infections, adenoidectomy or tonsillectomy, grommets, documented history of hearing loss)

In addition, a family medical history will be obtained, documenting the number of siblings and the medical status of each sibling, including the presence of abnormalities suggestive of MPS IIIB. Where NAGLU enzyme activity or genetic testing has confirmed the presence of MPS IIIB in additional family members, data will be collected on relationship, age of diagnosis, medical complications, and, if applicable, cause of death.

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

5.1.4 Demographic Information

The following demographic information will be collected at Screening: date of birth, gender, race, and ethnicity. If local regulations do not allow a full date of birth to be collected, the birth date will be reported to the extent allowed (eg, month and year or year only).

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 (WFA), weight-for-height (WFH), height-for-age (HFA), and body mass index (BMI)-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 CDC growth charts.

5.1.7 Vital Signs and Electrocardiogram

Vital signs, including pulse rate, respiratory rate, systolic and diastolic blood pressure (BP), and body temperature will be taken at the time points specified in the SOA. In addition, a baseline blood pressure measurement should be taken in triplicate prior to administration of SBC-103 at screening or prior to SBC-103 administration on either Day 0 in Part A or the subject's the next scheduled infusion. The baseline BP measurement should be done as follows:

- Ensure the subject is relaxed or distracted.
- Obtain 3 separate BP measurements.
  - The same arm should be used for each reading.
  - The right arm is preferred for these repeat BP measurements for consistency and comparison with standard tables and, because of the possibility of coarctation of the aorta, which might lead to false (low) readings in the left arm.

  - Each reading should be taken on the same day >15 minutes apart.
  - The same suitable equipment should be used for each reading.
- Each measurement should be recorded in the subject's source records and in the CRF

On Day 1 in Part A, vital signs will be taken prior to hospital discharge. During dosing visits vital signs will be taken pre-dose (within approximately 30 minutes), 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. In Part B, 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. In Part C, the duration of post-infusion vital signs monitoring may be shortened to 1 hour starting with Week 26 of Part C, 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; 12-lead ECGs will be collected in triplicate during Part A of the study only. ECGs will be reviewed by the Investigator, or designee, and any abnormalities will be specified as clinically significant or not clinically significant.

Due to the behavioral 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 14.5 (Appendix E) and will be performed at time points specified in the SOA. BSID-III and/or 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 and/or based on evaluation during Screening physical exam.

Assessments to be performed will include the Vineland-II, BSID-III and/or KABC-II, BOT-2 Brief Form, CCC-2, CSHQ, SBRS, ZBI 12-item, 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 Sections 5.1.8.2 and 5.1.8.3 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 behaviors. In this study, all sections except for the critical items in the Maladaptive Behavior domain will be used. Standardized scores, percentile ranks, and adaptive levels are provided for each domain, as well as for an adaptive behavior 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 behavior domains. Administration of the Vineland-II Survey Interview Form with the parent/caregiver takes approximately 20 to 60 minutes.

The Vineland overall adaptive behavior composite (mean domain age equivalent) will be calculated based on all age equivalent scores for the sub-domains under communication, daily living skills and socialization, both including and excluding motor skills. Maladaptive behavior is not included in this calculation. A developmental quotient (DQ) will also be calculated as: (age equivalent / calendar age) × 100; DQ will also be calculated both including and excluding the motor domain.

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 development 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 behavior.

In this study, cognition, language, and motor functioning will be assessed. The social, emotional, and adaptive behavior domains are not being used due to overlap with the Vineland scale. The mean domain age equivalent will be calculated based on all age equivalent scores for the sub-tests, and mean overall age equivalent will be calculated based on all domain age equivalent scores. A DQ will also be calculated as: (age equivalent / calendar age) × 100.

Switching from BSID-III to the 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 and CCC-2.

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.

5.1.8.3 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 sub-tests by MPS IIIB Subjects

Children with MPS IIIB may not be able to complete all subtests, due to a limited attention span and behavioral problems. Therefore, only completion of the non-verbal index (NVI) battery, as appropriate for the developmental age of the child, is required to be completed. 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 required NVI tests 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 7-18 years), and Knowledge/Gc.

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 3-5 years. The first tests for the NVI are Conceptual thinking and Face recognition. If the raw scores for both these first two 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 two tasks, the motor scales of the BSID-II 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 two domains of language and pragmatics, the following sub-domains are evaluated: speech, syntax, semantics, coherence, initiation, scripted language, context, nonverbal 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.

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 pediatric 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 behavior 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 that will be completed in Parts B and C include a specific follow-up version of Section 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 subjects with Alzheimer's 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 4; the time points for sample collection are specified in the SOA. Central lab reference ranges will be used throughout the study, including in the event that labs are analyzed locally. All attempts should be made to draw lab samples for central lab analysis when samples are needed for local analysis.

Blood will be collected for standard hematology and serum chemistry (including coagulation parameters).

During Screening, if a subject's ALT or AST is greater than 3 × ULN; or a subject has elevated bilirubin or PT/INR, confirmatory testing will be completed. Confirmatory testing may be completed locally or by the central lab, however results will be based on the standardized reference ranges provided in the central laboratory manual for this study. Abnormal safety labs at Screening can be repeated within 1 to 2 weeks. The difference between these two pre-treatment values for each abnormal lab should differ by <20% in 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 Criteria #8.

During the study, after treatment with SBC-103, in the event that a subject's ALT or AST are 2× ULN (when baseline ALT or AST were within normal limits) or 3× ULN (when baseline ALT or AST was greater than 1.5× 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 lab sampling at the discretion of the investigator, using the same lab for analysis of each sample), or normalized if the baseline level was within normal limits. See Section 6.2.1 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 for females of child-bearing potential. If a urine sample is not able to be provided, a serum pregnancy test will be performed.

Blood will also be collected for determination of NAGLU enzyme activity and NAGLU gene mutation analysis. A sample will be obtained at Screening for measurement of NAGLU enzyme activity by a central laboratory, irrespective of whether historical enzyme activity results are available from a local laboratory. A sample will be collected for determination of NAGLU genotype, only if a historical result is not available from the study central laboratory. If available, historical NAGLU enzyme activity and genotyping data from the local laboratory will also be recorded in the CRF.

Serum, and where possible, urine, will be collected for analysis of MPS IIIB substrate (total HS) and other disease-related exploratory biomarkers including NRE HS derivatives. CSF will be collected via lumbar puncture for analysis of total HS and other disease-related exploratory 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 5.2.1.4 for details regarding the lumbar puncture.

A specific sample for exploratory biomarker analysis is being collected in this study; however, remaining blood and urine samples collected in this study may also be used to analyze 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 (CHMP) and Pediatric Committee (PDCO) 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 four 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.

Only Tier 1 assessments (see Table 4) 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 central laboratory with the exception of the urine pregnancy test (or serum pregnancy test if the urine cannot be collected), CSF routine findings, and (as of 23 March 2015) all coagulation panels, which will be done locally.

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 4: Clinical Laboratory Tests

Lab Panel	Tier	Matrix	Tests
Hematology	1	Whole Blood	White blood cell count; red blood cell count; hemoglobin; hematocrit; MCV, MCH, MCHC; platelet count; neutrophil; lymphocytes; monocytes; eosinophils; basophils;
Serum Chemistry	1	Serum	ALT, AST, alkaline phosphatase, GGT, albumin, total bilirubin, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus), glucose, creatinine, bicarbonate, total protein, BUN
Coagulation	1	Plasma [c]	PT, INR [c]
Urinalysis	N/A	Urine	pH, clarity, color, 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	Urine	
MPS IIIB Diagnostics	1	Dried blood spot	NAGLU enzyme activity
	1	Dried blood spot	NAGLU gene mutation analysis
PK	1	Serum	PK profile
PK	3	CSF	SBC-103 concentration
ADA	1	Serum	Anti-SBC-103 Antibody (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	Serum	HS (total and NRE)
	2	Serum	Ferritin and chitotriosidase
	2	Plasma	Glutamic acid and glycine
	2	Serum	IgG, inflammatory markers, and exploratory biomarkers
	N/A	Urine	HS (total and NRE)
	1	CSF	HS (total and NRE)
	2	CSF	HGF, calbindin D, Tau, pTau, amyloid β, albumin, IgG, glutamic acid and glycine
	1	CSF/Serum[b]	CSF/Serum Albumin Index (CSF-AI) and IgG index ([CSF/serum IgG ratio] / [CSF-AI])
	2	CSF [c]	Routine findings (cell counts, glucose, protein)[c]
DNA Sample[d]	2	Whole blood	
Serum Tryptase	*If clinically indicated*	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; BUN = blood urea nitrogen; CSF = cerebrospinal fluid; DNA = deoxyribonucleic acid; GGT = gamma-glutamyl transpeptidase; HGF = hepatocyte growth factor; HS = heparan sulfate; IAR = infusion-associated reaction; IgE = immunoglobulin E; IgG = immunoglobulin G; IgG index = immunoglobulin G index; IgM = immunoglobulin M; INR= international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; N/A = not applicable; NRE = non-reducing end; NAGLU = alpha-N-acetylglucosaminidase; PK = pharmacokinetics; PT = prothrombin time.

Unless specified in the SOA, the laboratory tests apply to Part A (Initial Therapy), Part B (Therapy at 1 and/or 3 mg/kg), and Part C (Therapy at 5 and/or 10 mg/kg).

[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.

[c] Test performed by a local laboratory.

[d] Performed only where local regulations permit and consent is received from the subject or the subject's parent or legal guardian.

5.2.1.1 DNA Sample

Where local regulations permit and subject to discretionary approval from each center's IRB/IEC and the consent of the subject (and/or consent of the subject's parent or legal guardian), a whole blood sample will be collected from each subject for DNA extraction.

DNA sequences, including both the protein-coding sequences and the noncoding sequences involved in transcriptional and translational regulation and other biological functions, will be analyzed by the Sponsor for genetic modifications that may contribute to and/or modify the disease phenotype or rate of progression of MPS IIIB. Such DNA sequences, that may be investigated include:

- NAGLU;
- Genes coding for other proteins involved in HS biology that may contribute to and/or modify the disease phenotype of MPS IIIB.

DNA samples will be stored by the Sponsor, or designee, in a secure and controlled environment until analysis, and will be destroyed by the Sponsor 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 these samples.

5.2.1.2 Exploratory 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 exploratory biomarker analysis is being collected in this study; however, remaining blood and/or urine samples collected in this study may also be used to analyze 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 exploratory biomarker analysis will be subject to discretionary approval from each center'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.

5.2.1.3 Pharmacokinetic Assessments

As described in Table 5 (Part A), Table 6 (Part B), and Table 7 (Part C) 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 5: PK Sampling in Part A (Initial Therapy)

	Day 0	Week 12	Week 24
Pre-infusion (within 30 minutes)	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			
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 6: PK Sampling in Part B (Therapy at 1 and/or 3 mg/kg)

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

[a]Time point may be omitted, if necessary, to avoid exceeding blood volume limitations.
[b]After the infusion bag has been emptied, but prior to the flush.
[c]Time is relative to the end of the infusion, not the end of the flush.
Note: Subjects may enter Part C at any time point during Part B, therefore not all weeks in Part B may be applicable.

Table 7: PK Sampling in Part C (Therapy at 5 and/or 10 mg/kg)

	Day 0	Wk 12	Wk 24	Wk 52	Wk 78	Wk 104	Wk 130 or End-of-Tx Visit[a]
Pre-infusion (within 30 min.)	X	X	X	X	X	X	X
During Infusion							
30 minutes (±5 minutes)	X	X	X	X	X	X	X
90 minutes (±5 minutes)[b]	X	X	X	X	X	X	X
120 minutes/End of Infusion[c] (±5 minutes)	X	X	X	X	X	X	X
After Completion of Infusion[d]							
15 minutes (±2 minutes)	X	X	X	X	X	X	X
30 minutes (±5 minutes)	X	X	X	X	X	X	X
60 minutes (±5 minutes)	X	X	X	X	X	X	X
90 minutes (±5 minutes)	X	X	X	X	X	X	X
120 minutes (±5 minutes)	X	X	X	X	X	X	X
4 hours (±5 minutes)	X	X	X	X	X	X	X
6 hours (±15 minutes)	X	X	X	X	X	X	X

Key: min. = minutes; Tx = treatment; Wk = Week
[a]Week 130 in Part C or the subject's end-of-therapy visit (ie, Week 156 of the study or early termination visit)
[b]Time point may be omitted, if necessary, to avoid exceeding blood volume limitations.
[c]After the infusion bag has been emptied, but prior to the flush.
[d]Time is relative to the end of the infusion, not the end of the flush.

5.2.1.4 Lumbar Puncture (Cerebrospinal Fluid)

Lumbar punctures will be performed for the collection of CSF at the time points specified in the SOA. The coagulation laboratory panel should be collected within 48 hours prior to performing the lumbar puncture, and the results should be available prior to sedating/anesthetizing the subject or performing the lumbar puncture. At Day 0, the lumbar puncture (including the initiation of sedation/anesthesia) shall not commence until the site receives the coagulation results, confirms that a subject continues to meet eligibility, and provides such documentation to the Sponsor for review and agreement. For all other lumbar punctures during the study, the procedure (including the initiation of sedation/anesthesia) will not commence until the site receives these results and confirms that it is safe for the subject to receive anesthesia/sedation and the lumbar puncture. This documentation should be filed as part of the subject's file and does not need to be reviewed by the Sponsor before the procedure. To facilitate this process, all coagulation panels (as of 23 March 2015) will be drawn and analyzed locally rather than sent to the central laboratory for analysis.

The lumbar puncture may be performed under general anesthesia, 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 prioritized as noted in Table 4.

Routine CSF findings will also be documented (eg, cell counts, glucose, and protein levels), and MPS IIIB substrate (HS) and other exploratory CSF biomarkers will be analyzed (see Table 4 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 Facial Dysmorphology Novel Analysis (FDNA) at the time points specified in the SOA. This technology enables automatic detection and evaluation of subtle cranio-facial dysmorphology associated with multiple rare diseases, by processing and analyzing standard 2-dimensional (2D) facial photos. The FDNA system uses proprietary computer algorithms to recognize 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 Anesthesia/Sedation

Subject compliance and maintenance of appropriate and stable positioning in the MRI is complicated due to the anticipated behavior disturbances characteristic of MPS IIIB subjects. A key advantage of general anesthesia is that it minimizes 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 immobilized.

Thus, subjects will receive general anesthesia prior to the MRI procedure. In principle all types of general anesthesia 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 anesthetic for subjects undergoing imaging assessments. An IV anesthetic without endotracheal intubation allows for careful titration of sedation to achieve a clinical effect. Propofol provides the ability to titrate an anesthetic 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 anesthetic 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 utilized under supervision of a pediatric anesthesiologist, however, in subjects aged 2 - 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 2-10 mg/kg (depending on age) can be given initially, followed by a continuous infusion of propofol. If no IV is in place, then anesthesia can be induced with an inhalative narcotic such as halothane or sevoflurane (with N20 and oxygen), and IV can be inserted, and then continuous infusion of propofol started (Schulte-Uentrop 2010, *Curr Opin Anaesthesiol*).

As indicated in Section 5.2.1.4, if clinically appropriate, lumbar punctures may also be performed under general anesthesia in accordance with local institutional procedures. When applicable, the lumbar puncture should be performed just prior to or after the MRI. Lumbar puncture, when not performed alongside the MRI, may also be performed under light sedation.

If clinically indicated, subjects may also receive general anesthesia 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 anesthetized or sedated for another study procedure.

5.2.4 Structural and Diffusion MRI

MRI will be performed at 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 ≥ 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 5-10 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 (Week 2, Week 4, and Week 6, respectively) in Part A to assess AEs.

If the subject does not participate in Part B or in Part C of the study, an additional follow up telephone call will be made to the subject (or the subject's parent or caregiver) to assess AEs and concomitant medications at least 4 weeks after the subject's last administered dose in either Part A or Part B unless the subject has a scheduled follow-up visit.

If the subject participates in Part C of the study, a follow-up telephone call will be made to the subject (or the subject's parent or caregiver) to assess AEs and concomitant medications at least 4 weeks after the subject's last dose of SBC-103 administered under this protocol unless the subject has a scheduled follow-up visit.

6 STUDY TREATMENTS

6.1 Treatments Administered

Part A (Initial Therapy)

In Part A, all subjects in each dosing cohort (0.3 mg/kg, 1 mg/kg, 3 mg/kg) will receive SBC-103 administered by IV infusion QOW for 24 consecutive weeks. Infusions must be administered at least 10 days apart. All study visits will be scheduled relative to Day 0.

Part B (Therapy at 1 and/or 3 mg/kg)

For eligible subjects, dosing in Part B may not be re-initiated sooner than 4 weeks and no greater than 4 weeks and 3 days after the last dose administered in Part A (See SOA). Subjects who received doses of either 0.3 mg/kg or 1 mg/kg during Part A may escalate to the next higher dose of SBC-103 considered to be safe by the Sponsor and SRC with their first dose in Part B or at any time thereafter. Subjects who received doses of 0.3 mg/kg in Part A may be considered for a second dose escalation to 3 mg/kg at any time during Part B provided that they have tolerated at least 2 doses of 1 mg/kg in Part B (see Section 3.1.2).

In Part B, if a subject misses ≥ 3 consecutive infusions, additional assessments will be required prior to resuming dosing, including safety labs (hematology, 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.

Part C (Therapy at 5 and/or 10 mg/kg)

Dosing in Part C may start as soon as a subject is eligible (Section 4.3.4) and according to the schema outlined in Section 3.1.3. Therefore, each subject's duration of treatment and assessments in Part B may vary. Once a patient is dose escalated in Part C, the study visit schedule is reset to Day 0 Part C (Day 0C). In Part C, subjects will be randomized such that at least 1 subject from each cohort assigned in Part A will receive SBC-103 at 5 mg/kg and at least 1 subject from each cohort assigned in Part A will receive SBC-103 at 10 mg/kg. Thus each of the assigned dose levels from Part A will be represented in each of the 2 dose levels being studied in Part C. Infusions must be administered at least 10 days apart. All study visits in Part C will be scheduled relative to Day 0C.

6.1.1 Dose Adjustments

The maximum planned dose to be evaluated in this study is 10 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 patients.

6.2 Stopping Rules

6.2.1 Stopping Rules in Individual Subjects

During Part A (Initial Therapy), Part B (Therapy at 1 and/or 3 mg/kg), and Part C (Therapy at 5 and/or 10 mg/kg), subjects who experience a severe IAR, a serious or severe AE that is

considered related to SBC-103, or a 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 SRC. Dosing with alterations to the infusion regimen (eg, pretreatment or slowing the rate of infusion) may resume once the SRC and the Sponsor approve.
- Subjects with mild or moderate IARs can continue receiving SBC-103 in the study. The SRC or Sponsor may recommend alterations to the infusion regimen (eg, pretreatment or slowing the rate of infusion).

For all other AEs (ie, AEs that are not characterized 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 SRC and the Sponsor 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 AST or ALT under the following circumstances:
  - In the event that a subject's AST or ALT is greater than or equal to 2 times the ULN (when baseline ALT or AST was within normal limits)
  - In the event that a subject's AST or ALT is greater than or equal to 3 times the ULN (if baseline ALT or AST greater than 1.5 ULN).

  Dosing will only resume after AST or ALT 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 normalized if the baseline level was within normal limits.

  The subject should be restarted at a reduced dose. For example, if a subject was receiving a dose of 10 mg/kg, he/she would be restarted at 5 mg/kg; subjects receiving 5 mg/kg would be restarted at 3 mg/kg; etc. In the event that the subject was receiving a dose of 0.3mg/kg, he/she may resume at the 0.3 mg/kg dose only after AST or ALT 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 normalized 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 times the 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 be paused based on confirmed elevations in AST or ALT with accompanying elevations in the following
    - Confirmed bilirubin greater than 1.5 times ULN

- Confirmed INR increase of 0.2
- Eosinophilia (more than 5%), rash or fever

If these bilirubin and INR values normalize (and the independent SRC believes that it is safe to do so), the subject may resume dosing on a lower dose of the study drug (eg, those on a 3 mg/kg would resume dosing at 1 mg/kg, those on a 0.3 mg/kg dose would resume the 0.3 mg/kg dose). However, in this scenario, if a subject develops recurrent elevations in AST or ALT (with or without elevations in total bilirubin or INR), the drug should be stopped and not resumed.

Subjects whose rise in LFTs is accompanied by eosinophilia (more than 5%), rash or fever should not be restarted on the study drug.

6.2.2 Stopping Rules for Multiple Subjects

At any time during this study, if 2 or more subjects experience the same (or similar) event considered related to SBC-103 which is either serious or severe, or any 1 subject experiences a life-threatening AE considered to be related to SBC-103, **dosing will be paused for all subjects treated at that dose or higher**. The SRC and the Sponsor will review the subject(s) data and dosing will resume only after review and agreement. 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.

At any time during this study, the SRC or Sponsor may request a pause in dosing of all subjects based on review of reported events and all available data. 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/mL. The study drug contains no preservatives and vials are single use only.

6.4 Method for Assigning Subjects to Treatment Groups

In Part A, subjects will be treated sequentially as described in Section 3.1.1. In Part B, if they qualify, subjects will re-initiate treatment with SBC-103 as described in Section 6.1. In Part C, subjects will be randomized such that at least 1 subject from each cohort assigned in Part A will receive SBC-103 at 5 mg/kg and at least 1 subject from each cohort assigned in Part A will receive SBC-103 at 10 mg/kg. Thus each of the assigned dose levels from Part A will be represented in each of the 2 dose levels being studied in Part C.

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 2-8°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 (eg, 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 authorization 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 discolored. 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 instructions 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 micron filter.

The recommended duration of the infusion is 2 hours at a constant rate. The protocol allows for a change in rate should the patient 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 patient 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 instructions on the administration of SBC-103.

6.7 Randomization and Blinding of SBC-103

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

In Part C, subjects will be randomized such that at least 1 subject from each cohort assigned in Part A will receive SBC-103 at 5 mg/kg and at least 1 subject from each cohort assigned in Part A will receive SBC-103 at 10 mg/kg. Thus each of the assigned dose levels from Part A will be represented in each of the 2 dose levels being studied in Part C. As noted in Section 1.4.1, a total of 11 subjects are enrolled in this study; 5 of these will be randomized to receive 5 mg/kg QOW and 6 will be randomized to receive 10 mg/kg QOW.

Details of the randomization will be provided in a randomization specification document, which will be maintained by the Sponsor.

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 unfavorable 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 (CDISC) Study Data Tabulation Model (SDTM) 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 8 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 8: 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 adverse event 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 hospitalization 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 jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

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 central 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 for this study. 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 adverse event 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, acetaminophen, antihistamines (eg, diphenhydramine, parenteral and oral), corticosteroids, epinephrine, 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, diarrhea, abdominal cramping), cardiopulmonary reactions, including chest pain, cardiac arrhythmias, dyspnea, wheezing, stridor, hypotension or hypertension.

General guidelines for the diagnosis and management of IARs are provided in Table 9. These guidelines are not intended to be comprehensive. 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 9: Guidelines for the Management of IARs

Symptoms	Action
Mild Reaction Common • Hyperemia (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% • Increase infusion time in accordance with institutional standard of care • Administer oral anti-pyretic and/or antihistamine • Once the event has resolved, the infusion should continue at reduced rate for a minimum of 30 minutes before infusion is increased to 75% of original rate • Decrease infusion rate by a further 25% if symptoms persist • If symptoms continue despite rate reduction, stop infusion • Pre-treat with oral antihistamine and antipyretic prior (approx. 1.5 hours) to next infusion • eg, diphenhydramine 25-50 mg by mouth and acetaminophen 650 mg by mouth
Moderate Reaction • Hyperemia (flushing) • Chest discomfort • Itching and/or raised urticarial rash • Severe headache • Gastrointestinal symptoms, vomiting, diarrhea, abdominal cramping	• Stop infusion • Give antihistamine intravenously and consider IV steroids in accordance with institutional standard of care • Give any prescribed inhaler treatment if appropriate • 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. • Pre-treat with oral antihistamine and antipyretic prior to next infusion • Skin testing may be considered
Severe Reaction • Clinically significant cardiovascular effects (hypotension defined as a decline approaching 20-30% of their preinfusion value without alternative etiology (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 intramuscular injection of epinephrine (adrenaline) • Give antihistamines intravenously and steroids intravenously • 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. • Skin testing may be considered • Dosing of the subject will be suspended until the SRC has completed review of the IAR, and any other relevant safety data (Section 6.2)

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. Adverse events 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 stabilized 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 subject 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 be using 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.

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 fetus. 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 counseled 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 one diagnosis.

Adverse events will be recorded from the time of signing of the informed consent until completion of the last scheduled visit, ie, the follow-up visit. Adverse events 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 related or 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 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 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	PPD
US	PPD

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 (FDA), the European Medicine 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)

Part A (Initial Therapy), Part B (Therapy at 1 and/or 3 mg/kg), and Part C (Therapy at 5 and/or 10 mg/kg)

It will be the responsibility of the Principal Investigator 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 minimize the chance that clinical study participants are exposed to unreasonable or unnecessary risks. The SRC will provide additional oversight for safety through periodic and ad-hoc reviews of safety data. The specific activities and composition of the SRC 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. 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.

Part B (Therapy at 1 and/or 3 mg/kg) and Part C (Therapy at 5 and/or 10 mg/kg)

The SRC will perform a review of each subject's available safety data prior to the start of Part B for each subject. The SRC will also conduct periodic reviews (at least every 6 months during the first year and annually thereafter) of aggregate safety data as indicated in the SRC Charter.

Ad-hoc reviews of safety data will be performed on an as-needed basis in the event of emerging safety signals of clinical concern in one or more subjects, including subjects who meet the pre-defined stopping rules for study treatment (see Section 6.2). Additionally the Sponsor will review the PD/efficacy every 6 months during the first year and at least annually thereafter to confirm the appropriateness of continued dosing.

8 STATISTICAL PLAN

8.1 General Considerations

Descriptive summary statistics will be provided for demographics, disposition and dose exposure. Number 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 summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) and, where appropriate, graphic representation and two-sided 95% confidence intervals (CI); categorical data will be summarized by sample size, proportions, and two-sided 95% CIs.

8.2 Determination of Sample Size

The sample size of approximately 9 subjects is based on clinical and not statistical consideration and is considered sufficient to provide PK, safety, and PD/efficacy data to inform dose and regimen selection for additional clinical studies.

8.3 Analysis Sets

8.3.1 Full Analysis Set

The full analysis set (FAS), defined as all subjects who have received any amount of SBC-103 and from whom informed consent has been obtained, will be used to summarize PK, PD, and efficacy data.

8.3.2 Safety Analysis Set

The safety analysis set, which is the same population as the FAS, will be used to summarize all safety and tolerability data.

8.4 Safety Analysis

Safety analyses may be performed for Parts A, B, C, and/or all 3 study parts (ie, the entire study). Descriptive summaries of data will be presented overall for all treated subjects and by dose group, as appropriate. Details of these analyses, including how baseline values are defined, will be specified in the statistical analysis plan (SAP).

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

The proportion of subjects with measurable antibodies to SBC-103 will be displayed. In addition, IARs will be tabulated by cohort and overall. Medications to treat IARs, including any medications for pretreatment, will also be presented by cohort and over 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.

Further statistical evaluations will be applied for select endpoints, if warranted. All baseline data and safety data collected during the study will be listed for each subject.

8.5 Pharmacokinetic Analysis

PK analysis will be performed using non-compartmental analysis. 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_{last}, AUC_{∞}, $T_{1/2}$, CL, V_z, and R_{ac}) assessments will be summarized for each subject, as well as for each dose group. SBC-103 concentration in CSF will be summarized at available time points. Additional analysis of PK data, including assessment of the impact of ADA, may be performed as appropriate.

Pharmacokinetic analyses may be performed for Parts A, B, C, and/or all 3 study parts (ie, the entire study). Further details will be provided in the PK section of the SAP.

8.6 Pharmacodynamic/Efficacy Analyses

Pharmacodynamic/efficacy analyses will be performed for Parts A and C, and/or all 3 study parts (ie, the entire study). Descriptive summaries of data will be presented overall for all treated subjects and by dose group, as appropriate. Details of these analyses, including how baseline values are defined, will be specified in the SAP.

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, CSHQ, CCC-2, SBRS, 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 summarized. Observed measurements and changes or percent changes from baseline in HS and NRE HS derivatives and disease related biomarkers will be summarized overall and by dosing regimen for each time point. Change in relative proportion of grey and white matter volume and microstructural integrity will be summarized.

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.

8.7 Summaries of Data Prior to Study Completion

Interim data will be summarized for presentation to regulatory authorities or to the scientific community to facilitate discussions and obtain input on late phase study designs.

For some of these summaries, CIs may be computed. Additional 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 indicate 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 authorized 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 (eg, 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 (eg, source documents, regulatory documents, data collection instruments, study data). The Investigator will ensure the capability for inspections of applicable study-related facilities (eg, 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 21CFR50 and 21CFR312), 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 (Part A, Initial Therapy)

Schedule of Study Assessments																
	Part A: Initial Therapy															Time Off
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****	**-4 to 0**		**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
Informed Consent/Assent	X															
Inclusion/Exclusion Criteria	X															
Medical History/ Demography	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[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG (Triplicate[2])	X	X[P]							X[P]						X[P]	
FDNA	X														X	
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI 12-item, SF-10[3]	X[3]														X[P]	
NAGLU Enzyme Activity[4]	X															
NAGLU Genotype[5]	X															
DNA Sample[6]	X															
Hematology, Serum Chemistry (including Coagulation[7]), Urinalysis[8]	X	X[P]	X		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	
Pregnancy Test (Urine)[9]	X	X[P]			X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	
Serum and Urine Heparan Sulfate (Total and NRE)[10]	X	X[P]			X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	
Serum Ferritin and Chitotriosidase[11]	X	X[P]			X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	
Plasma Glutamic Acid and Glycine[11]	X	X[P]			X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	
Serum Biomarkers (Exploratory, including IgG and Inflammatory Markers)		X[P]			X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	
Blood Pharmacokinetic Profile[12]		X							X						X	
SBC-103 ADA[13]		X[P]			X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	

Schedule of Study Assessments																
	Part A: Initial Therapy															Time Off
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****	**-4 to 0**		**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
General Anesthesia/Sedation[14]		X^P							X^P						X^P	
Lumbar Puncture[7,14,15]		X^P							X^P						X^P	
Heparan Sulfate (Total and NRE) in CSF		X^P							X^P						X^P	
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF[14]		X^P							X^P						X^P	
Glutamic Acids and Glycine in CSF		X^P							X^P						X^P	
Routine Findings (Cell Counts, Glucose, Protein) in CSF		X^P							X^P						X^P	
SBC-103 in CSF		X^P							X^P						X^P	
Structural and Diffusion MRI[14]		X^P													X^P	
SBC-103 Dosing		X		X	X	X	X	X	X	X	X	X	X	X	X	
Telephone call[16]				X	X	X									X	
Part B Eligibility Assessment																X
Adverse Events[17]	CONTINUOUS															
Concomitant Medications[18]	CONTINUOUS															

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; ECG = electrocardiogram; FDNA = Facial Dysmorphology Novel Analysis; HGF = hepatocyte growth factor; IgG = immunoglobulin G; KABC-II = Kaufman Assessment Battery for Children, Second Edition; MRI = magnetic resonance imaging; NAGLU = alpha-N-acetylglucosaminidase; NRE = non-reducing end; SBRS = Sanfilippo Behavior Rating Scale; SF-10 = 10-item Short Form Health Survey for Children; Vineland-II = Vineland Adaptive Behavior Scales, Second Edition; ZBI = Zarit Burden Interview, 12-item.

* All study visits will be scheduled relative to Day 0; infusions must be administered at least 10 days apart.

** Subjects who are unable to complete all Screening procedures within 28-day window may be re-screened. See Section 4.7.

*** Day 0 assessments may be completed over 5 days (starting on Day -4) provided that all eligibility assessments are completed prior to the commencement of any Day 0 procedure (ie, any invasive procedures, including general anesthesia or sedation, lumbar puncture, and MRI). Subjects will be monitored for at least 24 hours in an in-patient setting at the Day 0 visit. Documentation/confirmation of eligibility must be provided to the Sponsor and is subject to Sponsor review and agreement. At Day 0, the lumbar puncture (including the initiation of sedation/anesthesia) shall not commence until the site receives the coagulation results, confirms that a subject continues to meet eligibility, and provides such documentation to the Sponsor for review and agreement.

X^P Assessments to be performed pre-dose.

1. Vital signs will be taken pre-dose (within approximately 30 minutes), approximately every 15 minutes during infusion and approximately every 15 minutes for 2 hours after completion of the infusion. On Day 1, vital signs will be obtained prior to discharge. Vital signs will be obtained after any lumbar puncture as per site standard of care. In addition, a baseline blood pressure measurement should be taken in triplicate at screening or prior to SBC-103 administration on either Day 0 in Part A or the subject's next scheduled infusion (see Section 5.1.7).

2. 12-lead ECGs should be collected in triplicate (within 5 minutes), when possible during Part A of the study only.
3. If the identical assessment(s) were previously administered, historical results should be recorded. 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.
4. NAGLU enzyme activity will be assessed by a central laboratory at Screening, irrespective of whether historical enzyme activity results are available from a local laboratory.
5. DNA sample for NAGLU genotype is required to confirm Diagnosis of MPS IIIB when a historical result is not available from the study central lab.
6. Performed where local regulations permit and subject to discretionary approval from each center's IRB/IEC and the consent/assent of the subject (and/or consent of the subject's parent or legal guardian).
7. The coagulation laboratory panel should be collected within 48 hours prior to performing the lumbar puncture, and the results should be available prior to sedating/anesthetizing the subject or performing the lumbar puncture. The procedure (including the initiation of sedation/anesthesia) will not commence until the site receives these results and confirms that it is safe for the subject to receive anesthesia/sedation and the lumbar puncture. To facilitate this process, all coagulation panels (as of 23 March 2015) will be drawn and analyzed locally rather than sent to the central laboratory for analysis.
8. 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 lab reference ranges will be used throughout the study, including in the event that labs are analyzed locally. All attempts should be made to draw lab samples for central lab analysis when samples are needed for local analysis.
9. If a urine sample is not able to be provided, a serum pregnancy test will be performed by a local laboratory.
10. If serum or urine heparan sulfate is collected within 7 days of Day 0, it does not need to be repeated at Day 0. All attempts should be made to collect a urine sample for heparan sulfate.
11. If serum ferritin, chitotriosidase and amino acid panel is collected within 7 days of Day 0, it does not need to be repeated at Day 0.
12. Refer to Section 5.2.1.3 for directions and timing of PK sampling.
13. In addition to time points indicated, obtain a sample for ADA determination anytime subject experiences a moderate or severe IAR during the next study visit (≥ 4 days after the IAR) and prior to the infusion.
14. 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 anesthesia 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 anesthetized or sedated for another study procedure. During study visits where CSF is collected that do not coincide with a serum chemistry sample per the SOA, a serum albumin should be collected in order to assess CSF-AI Index. After the lumbar puncture is completed, the subject should be observed as per institution standard practice.
15. Subjects should be observed following the lumbar puncture as per institution standard practice. Vital signs, adverse events and concomitant medications should be assessed before the subject is discharged from the site.
16. A follow-up telephone call will be made to the subject (or the subject's parent or caregiver) within 24 hours of the 2nd, 3rd , and 4th doses in Part A, and after the last dose of SBC-103 administered in the study (Week 24 or Early Termination) unless the subject has a scheduled follow-up visit.
17. All AEs should be followed until they have returned to baseline values or stabilized or until the Investigator and Sponsor or designee agree that follow-up is no longer necessary.
18. 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.

14.2 Appendix B: Schedule of Study Assessments (Part B, Therapy at 1 and/or 3 mg/kg – Year 1)

Schedule of Study Assessments													
	Part B: Therapy at 1 and/or 3 mg/kg (Weeks 28 through 52)												
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)*	**+3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
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[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG					X								X
FDNA													X
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI 12-item, SF-10[2]													X
Hematology, Serum Chemistry (including Coagulation[3]), Urinalysis[4]	X^P				X^P				X^P				X^P
Pregnancy Test (Urine)[5]	X^P		X^P		X^P		X^P		X^P		X^P		X^P
Serum and Urine Heparan Sulfate (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
Exploratory Serum Biomarkers, including IgG, Inflammatory markers	X^P				X^P				X^P				X^P
Serum Pharmacokinetic Profile[6]													X
SBC-103 ADA[7]	X^P		X^P		X^P		X^P		X^P		X^P		X^P
General Anesthesia/Sedation[8]	X^P						X^P						X^P
Lumbar Puncture[3,8,9]	X^P						X^P						X^P
Heparan Sulfate (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
Routine Findings (Cell Counts, Glucose, Protein) in CSF	X^P						X^P						X^P
SBC-103 in CSF	X^P						X^P						X^P
Structural and Diffusion MRI[8]													X^P

Schedule of Study Assessments													
	Part B: Therapy at 1 and/or 3 mg/kg (Weeks 28 through 52)												
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)*	**+3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
SBC-103 Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[10]	CONTINUOUS												
Concomitant Medications[11]	CONTINUOUS												

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; 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; NRE = non-reducing end; SBRS = Sanfilippo Behavior Rating Scale; SF-10 = 10-item Short Form Health Survey for Children; Vineland-II = Vineland Adaptive Behavior Scales, Second Edition; ZBI = Zarit Burden Interview, 12-item.

* All study visits will be scheduled relative to Day 0; infusions must be administered at least 10 days apart.

X^p Assessments to be performed pre-dose.

1. Vital signs will be taken pre-dose (within approximately 30 minutes), approximately every 15 minutes during infusion and approximately every 15 minutes for 2 hours after completion of the infusion. Vital signs will be obtained after any lumbar puncture as per site standard of care.
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. The coagulation laboratory panel should be collected within 48 hours prior to performing the lumbar puncture, and the results should be available prior to sedating/anesthetizing the subject or performing the lumbar puncture. The procedure (including the initiation of sedation/anesthesia) will not commence until the site receives these results and confirms that it is safe for the subject to receive anesthesia/sedation and the lumbar puncture. To facilitate this process, all coagulation panels (as of 23 March 2015) will be drawn and analyzed locally rather than sent to the central laboratory for analysis.
4. Central lab reference ranges will be used throughout the study, including in the event that labs are analyzed locally. All attempts should be made to draw lab samples for central lab analysis when samples are needed for local analysis.
5. If a urine sample is not able to be provided, a serum pregnancy test will be performed by a local laboratory.
6. Refer to Section 5.2.1.3 for directions and timing of PK sampling.
7. In addition to time points indicated, obtain a sample for ADA determination anytime subject experiences a moderate or severe IAR during the next study visit (≥ 4 days after the IAR) and prior to the infusion.
8. 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 anesthesia 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 anesthetized 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.
9. During study visits where CSF is collected that do not coincide with a serum chemistry sample per the SOA, a serum albumin should be collected in order to assess CSF-AI Index. After the lumbar puncture is completed, the subject should be observed as per institution standard practice.
10. All AEs should be followed until they have returned to baseline values or stabilized 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.

14.3 Appendix C: Schedule of Study Assessments (Part B, Therapy at 1 and/or 3 mg/kg – Years 2-3, as applicable)

Schedule of Study Assessments													
Part B: Therapy at 1 and/or 3 mg/kg (Years 2 and 3, as applicable prior to Part C)													
Assessments	**Wk 54 / Wk 106**	**Wk 56 / Wk 108**	**Wk 58 / Wk110**	**Wk 60 / Wk 112**	**Wk 62 / Wk 114**	**Wk 64/ Wk 116**	**Wk 66/ Wk 118**	**Wk 68/ Wk 120**	**Wk 70/ Wk 122**	**Wk 72/ Wk 124**	**Wk 74/ Wk 126**	**Wk 76/ Wk 128**	**Wk 78/ Wk 130**
Visit Window (Days)*	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
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[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG													X
FDNA													X
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI 12-item, SF-10[2]													X
Hematology, Serum Chemistry (including Coagulation[3]), Urinalysis[4]				X^P				X^P					X^P
Pregnancy Test (Urine)[5]		X^P		X^P		X^P		X^P		X^P		X^P	
Serum and Urine Heparan Sulfate (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
Exploratory Serum Biomarkers, including IgG, Inflammatory markers				X^P				X^P					X^P
Serum Pharmacokinetic Profile[6]													X
SBC-103 ADA[7]		X^P		X^P		X^P		X^P		X^P		X^P	
General Anesthesia/Sedation[8]							X^P						X^P
Lumbar Puncture[3,8,9]							X^P						X^P
Heparan Sulfate (Total and NRE) in CSF							X^P						X^P
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF							X^P						X^P

Schedule of Study Assessments													
Part B: Therapy at 1 and/or 3 mg/kg (Years 2 and 3, as applicable prior to Part C)													
Assessments	**Wk 54 / Wk 106**	**Wk 56 / Wk 108**	**Wk 58 / Wk110**	**Wk 60 / Wk 112**	**Wk 62 / Wk 114**	**Wk 64/ Wk 116**	**Wk 66/ Wk 118**	**Wk 68/ Wk 120**	**Wk 70/ Wk 122**	**Wk 72/ Wk 124**	**Wk 74/ Wk 126**	**Wk 76/ Wk 128**	**Wk 78/ Wk 130**
Visit Window (Days)*	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Glutamic Acids and Glycine in CSF							X^P						X^P
Routine Findings (Cell Counts, Glucose, Protein) in CSF							X^P						X^P
SBC-103 in CSF							X^P						X^P
Structural and Diffusion MRI[7]													
Telephone call[10]													
SBC-103 Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[11]	CONTINUOUS												
Concomitant Medications[12]	CONTINUOUS												

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; NRE = non-reducing end; SBRS = Sanfilippo Behavior Rating Scale; SF-10 = 10-item 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 must be administered at least 10 days apart.

X^P Assessments to be performed pre-dose.

1. Vital signs will be taken pre-dose (within approximately 30 minutes), approximately every 15 minutes during infusion and approximately every 15 minutes for 2 hours after completion of the infusion. Vital signs will be obtained after any lumbar puncture as per site standard of care.
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. The coagulation laboratory panel should be collected within 48 hours prior to performing the lumbar puncture, and the results should be available prior to sedating/anesthetizing the subject or performing the lumbar puncture. The procedure (including the initiation of sedation/anesthesia) will not commence until the site receives these results and confirms that it is safe for the subject to receive anesthesia/sedation and the lumbar puncture. To facilitate this process, all coagulation panels (as of 23 March 2015) will be drawn and analyzed locally rather than sent to the central laboratory for analysis.
4. Central lab reference ranges will be used throughout the study, including in the event that labs are analyzed locally. All attempts should be made to draw lab samples for central lab analysis when samples are needed for local analysis.
5. If a urine sample is not able to be provided, a serum pregnancy test will be performed by a local laboratory.
6. Refer to Section 5.2.1.3 for directions and timing of PK sampling.
7. 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.
8. 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 anesthesia 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 anesthetized 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.
9. During study visits where CSF is will be collected that do not coincide with a serum chemistry sample per the SOA, a serum albumin should be collected in order to assess CSF-AI Index. After the lumbar puncture is completed, the subject should be observed as per institution standard practice.
10. A telephone 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.
11. All AEs should be followed until they have returned to baseline values or stabilized or until the Investigator and Sponsor or designee agree that follow-up is no longer necessary.

12. 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.

Schedule of Study Assessments														
Part B: Therapy at 1 and/or 3 mg/kg (Years 2 and 3, as applicable prior to Part C)														
Assessments	**Wk 80/ Wk 132**	**Wk 82/ Wk 134**	**Wk 84/ Wk 136**	**Wk 86/ Wk 138**	**Wk 88/ Wk 140**	**Wk 90/ Wk 142**	**Wk 92/ Wk 144**	**Wk 94/ Wk 146**	**Wk 96/ Wk 148**	**Wk 98/ Wk 150**	**Wk 100/ Wk 152**	**Wk 102/ Wk 154**	**Wk 104/ Wk 156 (End of Tx/ Early Term)**	**Week 160**
Visit Window (Days)*	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
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[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG													X	
FDNA													X	
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI 12-item, SF-10[2]													X	
Hematology, Serum Chemistry (including Coagulation[3]), Urinalysis[4]				X^P				X^P					X^P	
Pregnancy Test (Urine)[5]	X^P		X^P		X^P		X^P		X^P		X^P		X^P	
Serum and Urine Heparan Sulfate (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	
Exploratory Serum Biomarkers, including IgG, Inflammatory markers				X^P				X^P					X^P	
Serum Pharmacokinetic Profile[6]													X	
SBC-103 ADA[7]	X^P		X^P		X^P		X^P		X^P		X^P		X^P	
General Anesthesia/Sedation[8]						X^P							X^P	
Lumbar Puncture[3,8,9]						X^P							X^P	
Heparan Sulfate (Total and NRE) in CSF						X^P							X^P	
Calbindin D, HGF, Tau,						X^P							X^P	

Schedule of Study Assessments														
Part B: Therapy at 1 and/or 3 mg/kg (Years 2 and 3, as applicable prior to Part C)														
Assessments	**Wk 80/ Wk 132**	**Wk 82/ Wk 134**	**Wk 84/ Wk 136**	**Wk 86/ Wk 138**	**Wk 88/ Wk 140**	**Wk 90/ Wk 142**	**Wk 92/ Wk 144**	**Wk 94/ Wk 146**	**Wk 96/ Wk 148**	**Wk 98/ Wk 150**	**Wk 100/ Wk 152**	**Wk 102/ Wk 154**	**Wk 104/ Wk 156 (End of Tx/ Early Term)**	**Week 160**
Visit Window (Days)*	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
pTau, Amyloid β, Albumin, IgG in CSF														
Glutamic Acids and Glycine in CSF						X^P							X^P	
Routine Findings (Cell Counts, Glucose, Protein) in CSF						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	
Telephone call[10]														X^{19}
Adverse Events[11]	CONTINUOUS													
Concomitant Medications[12]	CONTINUOUS													

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; 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; NRE = non-reducing end; SBRS = Sanfilippo Behavior Rating Scale; SF-10 = 10-item Short Form Health Survey for Children; term = termination; Tx = treatment; 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 must be administered at least 10 days apart.

X^P Assessments to be performed pre-dose.

1. Starting at Week 54, vital signs will 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.
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. The coagulation laboratory panel should be collected within 48 hours prior to performing the lumbar puncture, and the results should be available prior to sedating/anesthetizing the subject or performing the lumbar puncture. The procedure (including the initiation of sedation/anesthesia) will not commence until the site receives these results and confirms that it is safe for the subject to receive anesthesia/sedation and the lumbar puncture. To facilitate this process, all coagulation panels (as of 23 March 2015) will be drawn and analyzed locally rather than sent to the central laboratory for analysis.
4. Central lab reference ranges will be used throughout the study, including in the event that labs are analyzed locally. All attempts should be made to draw lab samples for central lab analysis when samples are needed for local analysis.
5. If a urine sample is not able to be provided, a serum pregnancy test will be performed by a local laboratory.
6. Refer to Section 5.2.1.3 for directions and timing of PK sampling.
7. In addition to time points indicated, obtain a sample for ADA determination anytime subject experiences a moderate or severe IAR during the next study visit (≥ 4 days after the IAR) and prior to the infusion.
8. 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 anesthesia 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 anesthetized 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.

9. During study visits where CSF is will be collected that do not coincide with a serum chemistry sample per the SOA, a serum albumin should be collected in order to assess CSF-AI Index. After the lumbar puncture is completed, the subject should be observed as per institution standard practice.
10. A telephone 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.
11. All AEs should be followed until they have returned to baseline values or stabilized or until the Investigator and Sponsor or designee agree that follow-up is no longer necessary.
12. 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.

14.4 Appendix D: Schedule of Study Assessments (Part C, Therapy at 5 and/or 10 mg/kg)

Schedule of Study Assessments															
Part C: Therapy at 5 and/or 10 mg/kg (Weeks 1 through 26)															
Assessments	**Wk 1C D0C**	**Wk 1C D1C***	**Wk 2C**	**Wk 4C**	**Wk 6C**	**Wk 8C**	**Wk 10C**	**Wk 12C**	**Wk 14C**	**Wk 16C**	**Wk 18C**	**Wk 20C**	**Wk 22C**	**Wk 24C**	**Wk 26C**
Visit Window (Days)**	**±5**		**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Part C Informed Consent/Assent	X^{P}														
Part C Eligibility Assessment	X^{P}														
Physical Examination	X^{P}	X		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[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X^{P}		X^{P}					X^{P}						X^{P}	
FDNA	X													X	
Vineland-II, BSID-III, KABC-II, BOT-2 BF, CSHQ, CCC-2, SBRS, ZBI 12-item, SF-10[2,3]	$X^{P,3}$													X	
Hematology, Serum Chemistry (including Coagulation[4]), Urinalysis[5]	X^{P}	X		X^{P}		X^{P}		X^{P}		X^{P}		X^{P}		X^{P}	
Pregnancy Test (Urine)[6]	X^{P}			X^{P}		X^{P}		X^{P}		X^{P}		X^{P}		X^{P}	
Serum and Urine Heparan Sulfate (Total and NRE)	X^{P}			X^{P}		X^{P}		X^{P}		X^{P}		X^{P}		X^{P}	
Serum Ferritin and Chitotriosidase	X^{P}			X^{P}		X^{P}		X^{P}		X^{P}		X^{P}		X^{P}	
Plasma Glutamic Acid and Glycine	X^{P}			X^{P}		X^{P}		X^{P}		X^{P}		X^{P}		X^{P}	
Exploratory Serum Biomarkers including IgG and Inflammatory Markers	X^{P}			X^{P}		X^{P}		X^{P}		X^{P}		X^{P}		X^{P}	
Serum Pharmacokinetic Profile[7]	X							X						X	
SBC-103 ADA[8]	X^{P}			X^{P}		X^{P}		X^{P}		X^{P}		X^{P}		X^{P}	
General Anesthesia/Sedation[9]	X^{P}							X^{P}						X^{P}	
Lumbar Puncture[4,9,10,11]	$X^{P,11}$							X^{P}						X^{P}	
Heparan Sulfate (Total and NRE) in CSF	$X^{P,11}$							X^{P}						X^{P}	
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF	$X^{P,11}$							X^{P}						X^{P}	
Glutamic Acids and Glycine in CSF	$X^{P,11}$							X^{P}						X^{P}	
Routine Findings in CSF (Cell Counts, Glucose, Protein)	$X^{P,11}$							X^{P}						X^{P}	
SBC-103 in CSF	$X^{P,11}$							X^{P}						X^{P}	
Structural and Diffusion MRI[9,12]	$X^{P,12}$													X^{P}	
SBC-103 Dosing	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[13]	CONTINUOUS														

Schedule of Study Assessments															
Part C: Therapy at 5 and/or 10 mg/kg (Weeks 1 through 26)															
Assessments	**Wk 1C D0C**	**Wk 1C D1C***	**Wk 2C**	**Wk 4C**	**Wk 6C**	**Wk 8C**	**Wk 10C**	**Wk 12C**	**Wk 14C**	**Wk 16C**	**Wk 18C**	**Wk 20C**	**Wk 22C**	**Wk 24C**	**Wk 26C**
Visit Window (Days)**	**±5**		**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Concomitant Medications[14]	CONTINUOUS														

Key: ADA = anti-drug antibodies; BOT-2 BF = 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; 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; NRE = non-reducing end; SBRS = Sanfilippo Behavior Rating Scale; SF-10 = 10-item Short Form Health Survey for Children; Vineland-II = Vineland Adaptive Behavior Scales, Second Edition; Wk = week; ZBI = Zarit Burden Interview, 12-item.

* The Week 1C Day 1C visit applies only to the first subject at each dose level.

** All study visits will be scheduled relative to Week 1 Day 0 in Part C; infusions must be administered at least 10 days apart.

X^p Assessments to be performed pre-dose.

1. Starting at Week 26C, vital signs will 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.
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; where possible, the test should be administered prior to dosing.
3. Neurocognition testing performed within 8 weeks prior to Day 0 in Part C may be used as the Day 0C baseline in lieu of repeating the assessments on Day 0C.
4. The coagulation laboratory panel should be collected within 48 hours prior to performing the lumbar puncture, and the results should be available prior to sedating/anesthetizing the subject or performing the lumbar puncture. The procedure (including the initiation of sedation/anesthesia) will not commence until the site receives these results and confirms that it is safe for the subject to receive anesthesia/sedation and the lumbar puncture. To facilitate this process, all coagulation panels (as of 23 March 2015) will be drawn and analyzed locally rather than sent to the central laboratory for analysis.
5. Central lab reference ranges will be used throughout the study, including in the event that labs are analyzed locally. All attempts should be made to draw lab samples for central lab analysis when samples are needed for local analysis.
6. If a urine sample is not able to be provided, a serum pregnancy test will be performed by a local laboratory.
7. Refer to Section 5.2.1.3 for directions and timing of PK sampling.
8. In addition to time points indicated, obtain a sample for ADA determination anytime subject experiences a moderate or severe IAR during the next study visit (≥ 4 days after the IAR) and prior to the infusion.
9. 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 anesthesia 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 anesthetized 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.
10. During study visits where CSF is collected that do not coincide with a serum chemistry sample per the SOA, a serum albumin should be collected in order to assess CSF-AI Index. After the lumbar puncture is completed, the subject should be observed as per institution standard practice.
11. A lumbar picture performed within 4 weeks prior to Day 0 in Part C may be used as the Day 0C baseline in lieu of repeating the assessment on Day 0C.
12. An MRI obtained within 8 weeks prior to Day 0 in Part C may be used as the Day 0C baseline in lieu of repeating the assessment on Day 0C.
13. All AEs should be followed until they have returned to baseline values or stabilized or until the Investigator and Sponsor or designee agree that follow-up is no longer necessary.
14. 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.

Schedule of Study Assessments															
Part C: Therapy at 5 and/or 10 mg/kg (Weeks 28 through 52)															
STUDY WEEK from Part A Day 0														**Wk 156**	**Wk 160**
Part C Visit	**Wk 28C**	**Wk 30C**	**Wk 32C**	**Wk 34C**	**Wk 36C**	**Wk 38C**	**Wk 40C**	**Wk 42C**	**Wk 44C**	**Wk 46C**	**Wk 48C**	**Wk 50C**	**Wk 52C**	**End of Tx**	**Follow -up**
Visit Window (Days)*	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
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[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG													X^P	X^P	
FDNA													X	X	
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI 12-item, SF-10[2,3]													X	X^3	
Hematology, Serum Chemistry (including Coagulation[4]), Urinalysis[5]				X^P				X^P					X^P	X^P	
Pregnancy Test (Urine)[6]		X^P		X^P		X^P		X^P		X^P		X^P		X^P	
Serum and Urine Heparan Sulfate (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	
Exploratory Serum Biomarkers including IgG and Inflammatory Markers				X^P				X^P					X^P	X^P	
Serum Pharmacokinetic Profile[7]													X	X	
SBC-103 ADA[8]		X^P		X^P		X^P		X^P		X^P		X^P		X^P	
General Anesthesia/Sedation[9]							X^P						X^P	X^P	
Lumbar Puncture[4,9,10,11]							X^P						X^P	$X^{P,11}$	
Heparan Sulfate (Total and NRE) in CSF							X^P						X^P	$X^{P,11}$	
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF							X^P						X^P	$X^{P,11}$	
Glutamic Acids and Glycine in CSF							X^P						X^P	$X^{P,11}$	
Routine Findings in CSF (Cell Counts, Glucose, Protein)							X^P						X^P	$X^{P,11}$	
SBC-103 in CSF							X^P						X^P	$X^{P,11}$	
Structural and Diffusion MRI[9,12]													X^P	$X^{P,12}$	
SBC-103 Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Telephone call[13]															X
Adverse Events[14]	CONTINUOUS														
Concomitant Medications[15]	CONTINUOUS														

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; 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; NRE = non-reducing end; SBRS = Sanfilippo Behavior Rating Scale; SF-10 = 10-item Short Form Health Survey for Children; Tx = treatment; 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 in Part C; infusions must be administered at least 10 days apart.

X^P Assessments to be performed pre-dose

1. Starting at Week 26, vital signs will 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.
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; where possible, the test should be administered prior to dosing.
3. Neurocognition testing performed within 8 weeks prior to the Study Week 156 Visit may be used as the last visit assessment in lieu of repeating the assessments at the Study Week 156 Visit.
4. The coagulation laboratory panel should be collected within 48 hours prior to performing the lumbar puncture, and the results should be available prior to sedating/anesthetizing the subject or performing the lumbar puncture. The procedure (including the initiation of sedation/anesthesia) will not commence until the site receives these results and confirms that it is safe for the subject to receive anesthesia/sedation and the lumbar puncture. To facilitate this process, all coagulation panels (as of 23 March 2015) will be drawn and analyzed locally rather than sent to the central laboratory for analysis.
5. Central lab reference ranges will be used throughout the study, including in the event that labs are analyzed locally. All attempts should be made to draw lab samples for central lab analysis when samples are needed for local analysis.
6. If a urine sample is not able to be provided, a serum pregnancy test will be performed by a local laboratory.
7. Refer to Section 5.2.1.3 for directions and timing of PK sampling.
8. In addition to time points indicated, obtain a sample for ADA determination anytime subject experiences a moderate or severe IAR during the next study visit (≥ 4 days after the IAR) and prior to the infusion.
9. 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 anesthesia 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 anesthetized 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.
10. During study visits where CSF is collected that do not coincide with a serum chemistry sample per the SOA, a serum albumin should be collected in order to assess CSF-AI Index. After the lumbar puncture is completed, the subject should be observed as per institution standard practice.
11. A lumbar puncture performed within 4 weeks prior to the Study Week 156 Visit may be used as the last assessment in lieu of repeating the assessment at the Study Week 156 Visit.
12. An MRI performed within 8 weeks prior to the Study Week 156 Visit may be used as the last visit assessment in lieu of repeating the assessment at the Study Week 156 Visit.
13. A telephone 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.
14. All AEs should be followed until they have returned to baseline values or stabilized or until the Investigator and Sponsor or designee agree that follow-up is no longer necessary.
15. 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.

Schedule of Study Assessments															
Part C: Therapy at 5 and/or 10 mg/kg (Weeks 54 through 78 and Weeks 106 through 130)															
STUDY WEEK from Part A Day 0														**Wk 156**	**Wk 160**
Part C Visit	**Wks 54C**	**Wks 56C**	**Wks 58C**	**Wks 60C**	**Wks 62C**	**Wks 64C**	**Wks 66C**	**Wks 68C**	**Wks 70C**	**Wks 72C**	**Wks 74C**	**Wks 76C**	**Wks 78C**	**End of Tx**	**Follow -up**
Visit Window (Days)*	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
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[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG													X^P	X^P	
FDNA													X	X	
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI 12-item, SF-10[2,3]													X	X^3	
Hematology, Serum Chemistry (including Coagulation[4]), Urinalysis[5]				X^P				X^P					X^P	X^P	
Pregnancy Test (Urine)[6]		X^P		X^P		X^P		X^P		X^P		X^P		X^P	
Serum and Urine Heparan Sulfate (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	
Exploratory Serum Biomarkers including IgG and Inflammatory Markers				X^P				X^P					X^P	X^P	
Serum Pharmacokinetic Profile[7]													X	X	
SBC-103 ADA[8]		X^P		X^P		X^P		X^P		X^P		X^P		X^P	
General Anesthesia/Sedation[9]							X^P						X^P	X^P	
Lumbar Puncture[4,9,10,11]							X^P						X^P	$X^{P,11}$	
Heparan Sulfate (Total and NRE) in CSF							X^P						X^P	$X^{P,11}$	
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF							X^P						X^P	$X^{P,11}$	
Glutamic Acids and Glycine in CSF							X^P						X^P	$X^{P,11}$	
Routine Findings in CSF (Cell Counts, Glucose, Protein)							X^P						X^P	$X^{P,11}$	
SBC-103 in CSF							X^P						X^P	$X^{P,11}$	
Structural and Diffusion MRI[9,12]														$X^{P,12}$	
SBC-103 Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Telephone call[13]															X
Adverse Events[14]	CONTINUOUS														
Concomitant Medications[15]	CONTINUOUS														

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; 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; NRE = non-reducing end; SBRS = Sanfilippo Behavior Rating Scale; SF-10 = 10-item Short Form Health Survey for Children; Tx = treatment; 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 in Part C; infusions must be administered at least 10 days apart.

X^P Assessments to be performed pre-dose.

1. Starting at Week 26, vital signs will 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.
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; where possible, the test should be administered prior to dosing.
3. Neurocognition testing performed within 8 weeks prior to the Study Week 156 Visit may be used as the last visit assessment in lieu of repeating the assessments at the Study Week 156 Visit.
4. The coagulation laboratory panel should be collected within 48 hours prior to performing the lumbar puncture, and the results should be available prior to sedating/anesthetizing the subject or performing the lumbar puncture. The procedure (including the initiation of sedation/anesthesia) will not commence until the site receives these results and confirms that it is safe for the subject to receive anesthesia/sedation and the lumbar puncture. To facilitate this process, all coagulation panels (as of 23 March 2015) will be drawn and analyzed locally rather than sent to the central laboratory for analysis.
5. Central lab reference ranges will be used throughout the study, including in the event that labs are analyzed locally. All attempts should be made to draw lab samples for central lab analysis when samples are needed for local analysis.
6. If a urine sample is not able to be provided, a serum pregnancy test will be performed by a local laboratory.
7. Refer to Section 5.2.1.3 for directions and timing of PK sampling.
8. In addition to time points indicated, obtain a sample for ADA determination anytime subject experiences a moderate or severe IAR during the next study visit (≥ 4 days after the IAR) and prior to the infusion.
9. 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 anesthesia 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 anesthetized 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.
10. During study visits where CSF is collected that do not coincide with a serum chemistry sample per the SOA, a serum albumin should be collected in order to assess CSF-AI Index. After the lumbar puncture is completed, the subject should be observed as per institution standard practice.
11. A lumbar puncture performed within 4 weeks prior to the Study Week 156 Visit may be used as the last assessment in lieu of repeating the assessment at the Study Week 156 Visit
12. An MRI performed within 8 weeks prior to the Study Week 156 Visit may be used as the last visit assessment in lieu of repeating the assessment at the Study Week 156 Visit.
13. A telephone 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.
14. All AEs should be followed until they have returned to baseline values or stabilized or until the Investigator and Sponsor or designee agree that follow-up is no longer necessary.
15. 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.

Schedule of Study Assessments															
Part C: Therapy at 5 and/or 10 mg/kg (Weeks 80 through 104)															
STUDY WEEK from Part A Day 0														**Wk 156**	**Wk 160**
Assessments Part C Visit	**Week 80C**	**Week 82C**	**Week 84C**	**Week 86C**	**Week 88C**	**Week 90C**	**Week 92C**	**Week 94C**	**Week 96C**	**Week 98C**	**Week 100C**	**Week 102C**	**Week 104C**	**End of Tx**	**Follow -up**
Visit Window (Days)*	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
Physical Examination	X[P]		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]	X[P]	
Vital Signs[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG													X[P]	X[P]	
FDNA													X	X	
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI 12-item, SF-10[2,3]													X	X[3]	
Hematology, Serum Chemistry (including Coagulation[4]), Urinalysis[5]				X[P]				X[P]					X[P]	X[P]	
Pregnancy Test (Urine)[6]	X[P]		X[P]		X[P]		X[P]		X[P]		X[P]		X[P]	X[P]	
Serum and Urine Heparan Sulfate (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]	
Exploratory Serum Biomarkers including IgG and Inflammatory Markers				X[P]				X[P]					X[P]	X[P]	
Serum Pharmacokinetic Profile[7]													X	X	
SBC-103 ADA[8]	X[P]		X[P]		X[P]		X[P]		X[P]		X[P]			X[P]	
General Anesthesia/Sedation[9]						X[P]							X[P]	X[P]	
Lumbar Puncture[4,9,10,11]						X[P]							X[P]	X[P,11]	
Heparan Sulfate (Total and NRE) in CSF						X[P]							X[P]	X[P,11]	
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF						X[P]							X[P]	X[P,11]	
Glutamic Acids and Glycine in CSF						X[P]							X[P]	X[P,11]	
Routine Findings in CSF (Cell Counts, Glucose, Protein)						X[P]							X[P]	X[P,11]	
SBC-103 in CSF						X[P]							X[P]	X[P,11]	
Structural and Diffusion MRI[9, 12]													X[P]	X[P,12]	
SBC-103 Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Telephone call[13]															X
Adverse Events[14]	CONTINUOUS														
Concomitant Medications[15]	CONTINUOUS														

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; 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; NRE = non-reducing end; SBRS = Sanfilippo Behavior Rating Scale; SF-10 = 10-item Short Form Health Survey for Children; Tx = treatment; 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 in Part C; infusions must be administered at least 10 days apart.

X^p Assessments to be performed pre-dose.

1. Starting at Week 26, vital signs will 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.
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; where possible, the test should be administered prior to dosing.
3. Neurocognition testing performed within 8 weeks prior to the Study Week 156 Visit may be used as the last visit assessment in lieu of repeating the assessments at the Study Week 156 Visit.
4. The coagulation laboratory panel should be collected within 48 hours prior to performing the lumbar puncture, and the results should be available prior to sedating/anesthetizing the subject or performing the lumbar puncture. The procedure (including the initiation of sedation/anesthesia) will not commence until the site receives these results and confirms that it is safe for the subject to receive anesthesia/sedation and the lumbar puncture. To facilitate this process, all coagulation panels (as of 23 March 2015) will be drawn and analyzed locally rather than sent to the central laboratory for analysis.
5. Central lab reference ranges will be used throughout the study, including in the event that labs are analyzed locally. All attempts should be made to draw lab samples for central lab analysis when samples are needed for local analysis.
6. If a urine sample is not able to be provided, a serum pregnancy test will be performed by a local laboratory.
7. Refer to Section 5.2.1.3 for directions and timing of PK sampling.
8. In addition to time points indicated, obtain a sample for ADA determination anytime subject experiences a moderate or severe IAR during the next study visit (≥ 4 days after the IAR) and prior to the infusion.
9. 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 anesthesia 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 anesthetized 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.
10. During study visits where CSF is collected that do not coincide with a serum chemistry sample per the SOA, a serum albumin should be collected in order to assess CSF-AI Index. After the lumbar puncture is completed, the subject should be observed as per institution standard practice.
11. A lumbar puncture performed within 4 weeks prior to the Study Week 156 Visit may be used as the last assessment in lieu of repeating the assessment at the Study Week 156 Visit.
12. An MRI performed within 8 weeks prior to the Study Week 156 Visit may be used as the last visit assessment in lieu of repeating the assessment at the Study Week 156 Visit.
13. A telephone 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.
14. All AEs should be followed until they have returned to baseline values or stabilized or until the Investigator and Sponsor or designee agree that follow-up is no longer necessary.
15. 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.

Schedule of Study Assessments															
Part C: Therapy at 5 and/or 10 mg/kg (Weeks 54 through 78 and Weeks 106 through 130)															
STUDY WEEK from Part A Day 0														**Wk 156**	**Wk 160**
Part C Visit	**Wks 106C**	**Wks 108C**	**Wks 110C**	**Wks 112C**	**Wks 114C**	**Wks 116C**	**Wks 118C**	**Wks 120C**	**Wks 122C**	**Wks 124C**	**Wks 126C**	**Wks 128C**	**Wks 130C**	**End of Tx**	**Follow -up**
Visit Window (Days)*	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
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[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG													X^P	X^P	
FDNA													X	X	
Vineland-II , BSID-III, KABC-II, BOT-2 Brief Form, CSHQ, CCC-2, SBRS, ZBI 12-item, SF-10[2,3]													X	X^3	
Hematology, Serum Chemistry (including Coagulation[4]), Urinalysis[5]				X^P				X^P					X^P	X^P	
Pregnancy Test (Urine)[6]		X^P		X^P		X^P		X^P		X^P		X^P		X^P	
Serum and Urine Heparan Sulfate (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	
Exploratory Serum Biomarkers including IgG and Inflammatory Markers				X^P				X^P					X^P	X^P	
Serum Pharmacokinetic Profile[7]													X	X	
SBC-103 ADA[8]		X^P		X^P		X^P		X^P		X^P		X^P		X^P	
General Anesthesia/Sedation[9]							X^P						X^P	X^P	
Lumbar Puncture[4,9,10,11]							X^P						X^P	$X^{P,11}$	
Heparan Sulfate (Total and NRE) in CSF							X^P						X^P	$X^{P,11}$	
Calbindin D, HGF, Tau, pTau, Amyloid β, Albumin, IgG in CSF							X^P						X^P	$X^{P,11}$	
Glutamic Acids and Glycine in CSF							X^P						X^P	$X^{P,11}$	
Routine Findings in CSF (Cell Counts, Glucose, Protein)							X^P						X^P	$X^{P,11}$	
SBC-103 in CSF							X^P						X^P	$X^{P,11}$	
Structural and Diffusion MRI[9,12]														$X^{P,12}$	
SBC-103 Dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Telephone call[13]															X
Adverse Events[14]	CONTINUOUS														
Concomitant Medications[15]	CONTINUOUS														

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; 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; NRE = non-reducing end; SBRS = Sanfilippo Behavior Rating Scale; SF-10 = 10-item Short Form Health Survey for Children; Tx = treatment; Vineland-II = Vineland Adaptive Behavior Scales, Second Edition; Wk = week; ZBI = Zarit Burden Interview, 12-item.

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4. The coagulation laboratory panel should be collected within 48 hours prior to performing the lumbar puncture, and the results should be available prior to sedating/anesthetizing the subject or performing the lumbar puncture. The procedure (including the initiation of sedation/anesthesia) will not commence until the site receives these results and confirms that it is safe for the subject to receive anesthesia/sedation and the lumbar puncture. To facilitate this process, all coagulation panels (as of 23 March 2015) will be drawn and analyzed locally rather than sent to the central laboratory for analysis.
5. Central lab reference ranges will be used throughout the study, including in the event that labs are analyzed locally. All attempts should be made to draw lab samples for central lab analysis when samples are needed for local analysis.
6. If a urine sample is not able to be provided, a serum pregnancy test will be performed by a local laboratory.
7. Refer to Section 5.2.1.3 for directions and timing of PK sampling.
8. In addition to time points indicated, obtain a sample for ADA determination anytime subject experiences a moderate or severe IAR during the next study visit (≥ 4 days after the IAR) and prior to the infusion.
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11. A lumbar puncture performed within 4 weeks prior to the Study Week 156 Visit may be used as the last assessment in lieu of repeating the assessment at the Study Week 156 Visit
12. An MRI performed within 8 weeks prior to the Study Week 156 Visit may be used as the last visit assessment in lieu of repeating the assessment at the Study Week 156 Visit.
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14.5 Appendix E: NGLU-CL02 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 (ie, BSID-III, KABC-II, BOT-2, 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. Refer to supplemental instructions provided to each site regarding when to switch the BSID-III or KABC-II.

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