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
NCT Number:	NCT02324049
EudraCT Number:	2013-003400-39
Date of Statistical Analysis Plan:	01 September 2017

Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT (CSR)

PROTOCOL NUMBER: NGLU-CL02

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Author: PPD

Date: 01 Sep 2017

Version: 1.0

1. APPROVAL SIGNATURES

PPD		Date dd Mmm yyyy 05 SEP 2017
		Date dd Mmm yyyy 05 Sep 2017
		Date dd Mmm yyyy
	Medical Monitor	Date dd Mmm yyyy

1. APPROVAL SIGNATURES

PPD

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2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this SAP.

Table 1: Abbreviations and acronyms

Abbreviation or acronym	Explanation
ADA	Anti-drug antibodies
AE	Adverse event(s)
AESI	Adverse events of special interest
ATC	Anatomical therapeutic chemical
BBB	Blood brain barrier
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency, Second Edition
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
CCC-2	Children's Communication Checklist, Second Edition
CSF	Cerebrospinal fluid
CSF-AI	Cerebrospinal fluid/serum albumin index
CSHQ	Children's Sleep Habits Questionnaire
CSP	Clinical study protocol
CSR	Clinical study report
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full Analysis Set
FDNA	Facial Dysmorphology Novel Analysis
HGF	Hepatocyte growth factor
HS	Heparan sulfate
IAR	Infusion-associated reaction
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
IV	Intravenous(ly)
KABC-II	Kaufman Assessment Battery for Children, Second Edition
MedDRA	Medical Dictionary for Regulatory Activities
MPS IIIB	Mucopolysaccharidosis III, type B
MRI	Magnetic resonance imaging
NAGLU	Alpha-N-acetylglucosaminidase
NRE	Non-reducing end
NVI	Non-verbal index
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
QOW	Once every other week
Rel Day	Relative study day
SAE	Serious adverse event
SAP	Statistical analysis plan
SBRS	Sanfilippo Behavior Rating Scale
SD	Standard deviation
SDTM	Study Data Tabulation Model
SF-10	10-item Short Form Health Survey for Children
SI	International system of units
MRI	Magnetic resonance imaging
SOA	Schedule of Assessments

Abbreviation or acronym	Explanation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
US	United States (of America)
Vineland-II	Vineland Adaptive Behavior Scales, Second Edition
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
ZBI	Zarit Burden Interview 12-item short form

4. DESCRIPTION OF THE PROTOCOL

Study NGLU-CL02, *A Phase I/II Open Label Study in MPS IIIB Subjects to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics/Efficacy of SBC-103 Administered Intravenously,* is an open label, 3-part Phase I/II study designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics/efficacy 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.

Study NGLU-CL02 is conducted in 3 parts: Part A (Initial therapy at 0.3, 1, or 3 mg/kg), Part B (Extended Therapy at 1 and/or 3 mg/kg), and Part C (Extended Therapy at 5 and/or 10 mg/kg).

Part A is designed to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD)/efficacy of 3 escalating doses of SBC-103 dosed once every other week (QOW) over 24 weeks.

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-subject dose modification based on available data.

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/efficacy markers, including the assessment of reversibility of any observed on-therapy changes in heparan sulfate (HS).

Part C (added with Amendment 6 and 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 QOW, as well as to assess the effects on chronic dosing. Subjects will be followed on Part C until the end of the treatment period at 156 weeks (a period of between 90 and 110 weeks). Intra-subject 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.

The protocol can be referenced for additional details. The Part C Schedule of Assessments (SOA) is attached in Appendix 9.1.4 of this Statistical Analysis Plan (SAP).

On 11 Jul 2017, Alexion decided to stop the clinical development program with SBC-103. A clinical study report (CSR) will detail the final demographic, disposition, exposure, and safety data of each study.

4.1. Changes from Analyses Specified in the Protocol

The data analyses, data summaries and data presentations specified for the NGLU-CL02 CSR represent a reduced subset of the overall total data analyses, data summaries, and data presentations described in the NGLU-CL02 final approved Clinical Study Protocol (CSP) version (Amendment 7, 21 January 2016) for the full study. Only demographic, disposition, safety and exposure data will be used to create data summaries and listings for the reduced subset of the CSP specified full study parameters presented by Part C dose assignment (5 or 10 mg/kg

QOW) and overall (5 and 10 mg/kg QOW combined). Only the assessments/parameters specified in Section 4.1.4 will be included.

4.1.1. Primary Objective

The primary objective of this CSR SAP is 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 and symptoms.

4.1.2. Secondary Objectives

No secondary objectives will be addressed in this SAP.

4.1.3. Exploratory Objectives

No exploratory objectives will be addressed in this SAP.

4.1.4. Assessments / Parameters Included in Analysis

- Demographics
- Disposition
- Use of Prior and Concomitant Medications (Listing only)
- Treatment Exposure, Dosing Administration and Infusion Summary (Listings only)
- Treatment Emergent Adverse Events (TEAEs)
- Treatment Emergent Serious Adverse Events (TESAEs)
- Infusion Associated Reactions (IAR)
- Anti-drug Antibody (ADA) Assay and Titer Results
- Laboratory Parameters: Hematology, Chemistry, Urinalysis, including Coagulation, Renal Function, and Liver Function (Listings only).
- Lumbar Puncture: CSF Findings and CSF-AI Ratio (listings only)
- Vital Signs (listing only)

4.2. Changes from Analyses Specified in the Previous Version of the SAP

Not applicable.

5. DEFINITIONS

5.1. Efficacy

5.1.1. Primary Endpoint(s)

The primary objective is to evaluate the safety and tolerability of IV administration of SBC-103, and as such, there is no primary efficacy endpoint.

5.1.2. Secondary Endpoints

Analyses of secondary efficacy endpoints will not be included in the CSR.

5.1.2.1. Pharmacokinetic (PK) Parameters

Analyses of PK data will not be included in the CSR.

5.1.2.2. Pharmacodynamic (PD) Parameters

Analyses of PD or PK/PD data, including HS, will not be included in the CSR.

5.1.3. Tertiary Endpoints

Not applicable.

5.1.4. Other Efficacy Endpoints

5.1.4.1. Exploratory Endpoints

Analyses of exploratory endpoints will not be included in the CSR.

5.2. Safety

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

- Incidence of treatment emergent adverse events (TEAEs), treatment emergent serious adverse events (TESAEs), and infusion-associated reactions (IARs) which are adverse events of special interest (AESI).
- Incidence of anti-drug antibodies (ADA) including 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.

5.2.1. Adverse Events (AEs)

Adverse events are defined in Protocol Section 7.1. Also refer to Appendix 9.4.3 of this SAP for special handling of AE partial dates. Any AE that occurs after the first dose of SBC-103 in Part A is considered a treatment emergent adverse event (TEAE). AEs will be summarized cumulatively over the entire study and separately for Part C.

5.2.2. Vital Signs

Vital signs will be provided in a listing. The following vital signs were recorded at the times in Parts A, B and C as specified in Appendix 9.1: systolic and diastolic blood pressure (millimeters of mercury (mmHg)), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (degrees Celsius (°C) or degrees Fahrenheit (°F)).

5.2.3. Laboratory Assessments

Serum chemistry, hematology, urinalysis including coagulation, renal function, liver function, CSF, and assessment of ADAs related testing will be performed as per the SOA. Details on specific laboratory assessment timing in Parts A, B and C are provided in Appendix 9.1. All laboratory results will be provided in listings.

5.2.4. Other Safety Assessments of Special Interest

5.2.4.1. Anti-Drug Antibodies (ADA)

Patients will be monitored for the development of antibody production against SBC-103 at the times specified in the Part C SOA (Appendix 9.1.4). Serum will be collected and analyzed for the presence of ADA, and if positive, further analyzed for titer, and characterization of response (e.g., positive/negative).

5.2.4.2. ECG

Analyses of electrocardiogram (ECG) data will not be included in the CSR.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

The following analysis sets will be used for the presentation and analysis of the data for the CSR. For further information on the processing of patient data utilized in creating the following study population analysis dataset(s)/subset(s) and baselines, please see Appendix 9.4.1.

6.1. Full Analysis Set (FAS)

Not applicable.

6.2. Per Protocol (PP) Set

Not applicable.

6.3. Safety Set

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

6.4. Other Sets

Not applicable.

7. STATISTICAL ANALYSIS

All output will be sorted and labeled according to the International Conference on Harmonization (ICH) recommendations, and formatted to the appropriate page size(s).

For the analyses covered by this SAP, data analysis and presentation for this study is primarily descriptive in nature; therefore, no inferential analyses are planned. Selected data will be presented in by-patient data listings and summarized in tables across patients if appropriate.

Descriptive summaries will be presented for treated subjects overall and by dose assignment, as appropriate. Continuous data will be summarized using descriptive statistics including number of patients, mean, standard deviation (SD), median, minimum, maximum, Lower quartile (25^{th} percentile) Q1, and Upper quartile (75^{th} percentile) Q3; categorical data will be summarized by counts and proportions. No formal statistical hypothesis testing will be performed.

For this analysis, information will be displayed by the Part C dose assignment as follows: SBC-103 5 mg/kg – QOW and SBC-103 10 mg/kg – QOW. All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study drug which is designated as Relative Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of study drug is designated with an "L" (e.g., Day 14L).

7.1. Study Patients

7.1.1. Disposition of Patients

Patient enrollment and disposition including number of patients screened, enrolled, dosed, and percentage of patients who discontinued from the study, along with reasons for discontinuations will be tabulated and described in listings.

7.1.2. Protocol Deviations

Analyses of protocol deviations will not be included in the CSR.

7.1.3. Demographics, Disease Characteristics and History

7.1.3.1. Demographics

Demographic and baseline characteristics will be summarized descriptively. Age at study entry (years), gender, race, ethnicity, baseline weight, baseline height and baseline Body Mass Index (BMI) will be summarized. Listings will also be provided.

7.1.3.2. Disease Characteristics

Disease characteristics will not be included in the CSR.

7.1.3.3. Medical / Surgical History and Baseline Physical Examination

Medical/surgical history and physical examination data will not be included in the CSR.

7.1.4. Prior and Concomitant Medications / Therapies

All medications and treatments received by the patient during the study or within the preceding 4 weeks will be collected. Any medication or treatment received after the first dose of SBC-103 will be considered concomitant. Medications will be mapped to a generic term using the current Alexion version of World Health Organization (WHO) Drug Dictionary (WHO-DD). Medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification system. All prior and concomitant medications/therapies will be provided in listings.

7.2. Efficacy Analyses

7.2.1. Primary Analysis

As stated above, the primary objective of this study is to evaluate the safety and tolerability of IV administration of SBC-103, and as such, there is no primary efficacy endpoint or analysis.

7.2.1.1. Handling of Dropouts or Missing Data

Partial dates will be handled as detailed in Appendix 9.4.3 including details for calculating calendar or chronological age, as necessary. Missing data will be handled as detailed below for each measure.

7.2.1.2. Subgroup Analysis

Not applicable.

7.2.1.3. Multicenter Studies

Four centers are participating in this study and the number of subjects at each center by assignment is not large enough to produce meaningful summaries by center; therefore analyses by center will not be performed. Data from all sites will be pooled together.

7.2.1.4. Hypothesis Testing and Significance Level

Data analysis and/or presentation for this study are primarily descriptive in nature; therefore, no inferential analyses are planned and p-values will not be provided.

7.2.1.5. Sensitivity Analyses

Not applicable.

7.2.2. Secondary Analyses

Analyses of secondary endpoints will not be included in the CSR.

7.2.2.1. Neurocognitive and Developmental Assessments

Analyses of neurocognitive and developmental assessments will not be included in the CSR.

7.2.2.2. MRI Findings

Analyses of MRI findings will not be included in the CSR.

7.2.2.3. Blood Brain Barrier (BBB) Integrity Assessments

CSF/serum albumin index (CSF-AI) assessments of BBB integrity will be provided in listings.

7.2.2.4. Pharmacokinetic and Pharmacodynamic Analyses

7.2.2.4.1. Pharmacokinetic Analyses

Analyses of pharmacokinetic (PK) data will not be included in the CSR.

7.2.2.4.2. Pharmacodynamic Analyses

Analyses of pharmacodynamic (PD) data will not be included in the CSR.

7.2.3. Tertiary Analyses

Not applicable.

7.2.4. Other Efficacy Analyses

Not applicable.

7.2.5. Exploratory Analyses

No exploratory analyses will be included in the CSR.

7.3. Safety Analyses

As stated above in Section 5.2, the primary objective of this study is the safety and tolerability of SBC-103 in subjects with MPS IIIB. Descriptive statistics will be computed for specified safety parameters using the Safety Analysis Set, as appropriate, including treatment emergent adverse events (TEAEs), treatment emergent serious adverse events (TESAEs), and infusion-associated reactions (IARs) which are adverse events of special interest (AESI). The incidence of anti-drug antibodies (ADA) including ADA titer by time point, peak ADA titer, ADA titer status (positive/negative), neutralizing antibodies, and the relationship between ADA-positivity and the incidence of IARs will be presented.

7.3.1. Study Duration, Treatment Compliance, and Exposure

Dosing administration information will be listed by patient number, Part C dose assignment, and visit and will present details on confirmation of SBC-103 administration, reasons SBC-103 was not administered, total # of vials used, target dose (mg/kg), and dose concentration (mg/mL). Exposure to study drug (SBC-103) related information will be listed by patient number, Part C dose assignment and visit. The stop/start dates/times, total actual volume of drug infused (mL), infusion rate (mL/hr), type of infusion (dosing or saline flush), rate reduction percentage

compared to previous infusion rate, and information on any modification to the infusion including reason for modification will be presented in the listings.

7.3.2. Adverse Events (AEs)

Information will be summarized on all AEs that began at any time from the date of first study dose in Part A through the last procedure at the last study visit. Adverse events will be classified by the study Investigator into one of the following relations to study drug: not related, unlikely related, possibly related or related to study drug. For reporting purposes, "related" events will include all AEs assessed by the Investigator as: possibly related, or related to study drug.

All AEs captured in the eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system and displayed in tables and data listings using System Organ Class (SOC) and Preferred Term (PT). All AEs will be coded using the MedDRA, version 13.1 or higher.

Severity of AEs will be graded on a 3-point scale (mild, moderate and severe) based on the definitions, developed from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standard terminology v3.1.1 (see Protocol Section 7.1.1).

Adverse event incidence will be reported based on the concept of treatment emergence for the purposes of this analysis. Any AE that occurs after the first dose of SBC-103 in Part A is considered a treatment emergent adverse event (TEAE) for this study.

Adverse events are summarized by patient incidence rates; therefore, in any tabulation, a patient contributes only once to the count for a given AE.

The number of events, as well as the number and percentage of patients with a TEAE, will be summarized by Part C dose assignment and overall, cumulatively over the entire study and separately for Part C.

7.3.2.1. Overall Summary of Adverse Events

An overall summary of TEAEs and treatment-emergent SAEs (TESAEs) will include summaries of events (n) and number of patients with events (n, %).

Within each summary category (TEAEs, TESAEs) the following subcategories will also be summarized, as appropriate:

- At Least 1 TEAE
- At Least 1 Severe TEAE
- At Least 1 Related TEAE (possibly related or related to study drug)
- At Least 1 TEAE Leading to Withdrawal / Discontinuation from the Study
- At Least 1 IAR
- At Least 1 Serious TEAE

Additionally, the number and percentage of patients who died on study will be presented.

7.3.2.2. AEs and SAEs by System Organ Class (SOC) and Preferred Term (PT)

The number of TEAEs and the number and percentage of patients with events will be descriptively summarized and presented by SOC and PT. Patients are counted once in each SOC and PT. Percentages will be based on the total number of treated patients by Part C dose assignment and overall for each visit assessed.

The number of Serious TEAE's and the number and percentage of patients with events will be descriptively summarized and presented by PT. Patients are counted once in each PT. Percentages will be based on the total number of treated patients by Part C dose assignment and overall for each visit assessed.

All AEs will be presented in by-patient listings.

7.3.2.3. AEs and SAEs by SOC, PT, and Relationship

Individual patient AE/SAE data for Relationship to Study Drug and Relationship to Study Procedures is presented in the by-patient AE listings.

7.3.2.4. AEs and SAEs by SOC, PT, and Severity

Individual patient AE/SAE data for severity is presented by-patient AE listings.

7.3.2.5. Deaths, Other SAEs, and Other Significant Adverse Events

Deaths and other SAE's will be identified by the data presented in the by-patient listings of AEs.

7.3.2.5.1 Other Significant Adverse Events

Procedure-related AEs will be identified by the relationship to study procedures data presented in the by-patient listings of AEs.

7.3.2.5.2. Infusion-Associated Reactions

Infusion-associated reactions (IARs) will be considered AEs of special interest (AESIs). An AE will be considered an IAR if it meets either of the following criteria:

- The Investigator checks "Yes" to the question "Is AE an IAR?" on the AE eCRF.
- The AE (diagnosis and/or symptom) occurs between the start of the infusion up to 4 hours after the infusion and is assessed by the Investigator as at least possibly related to Investigational Medicinal Product (IMP).

Note that several AEs may be associated with 1 IAR observed with SBC-103 administration; each AE is captured as a separate event. The number and percentage of patients who experience any IAR and the number of IARs reported over the course of the study will be summarized. Any patient who experiences an IAR is only counted once regardless of the number of associated events. Patients may be counted more than once if IARs occur on more than 1 dosing day.

Summaries of AEs that comprise an IAR will be displayed by MedDRA PT. Each patient will be counted only once within each PT.

A by-patient data listing of all AEs will be presented.

7.3.3. Other Safety

7.3.3.1. Analyses for Laboratory Tests

The clinical laboratory data include hematology, chemistry, urinalysis (including coagulation, renal function and liver function), CSF findings and CSF-AI ratio. All clinical laboratory data will be listed.

Clinical laboratory values by time of assessment will be expressed in International System of units (SI units) in data listings. Unscheduled lab test results will also be presented in the data listings. Abnormal lab values will be flagged with "H"/"L" or "HIGH"/"LOW" for out of range values, and an asterisk for clinical significance in the data listings.

Patient data for clinical laboratory data will be presented in listings by Part C dose assignment, patient number and visit.

7.3.3.2. Vital Signs

Vital signs include systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature. A listing of vital signs will be presented by patient number, vital sign parameter, vital sign value, and visit.

7.3.3.3. Other Safety Parameters of Special Interest

7.3.3.3.1. Antidrug Antibody (ADA)

Assays testing for screening, confirmed, neutralizing ADA will be performed and ADA titers will be measured for neutralizing antibodies. For this analysis, confirmed ADA assay results will be descriptively presented by ADA status (Positive, Negative) as the proportion of patients, n (%), with measurable confirmed antibodies to SBC-103 by Part C dose assignment and overall for each assessed visit. Neutralizing antibodies for confirmed positive cases will also be presented.

ADA titer result statistics will be descriptively presented by ADA status, visit, Part C dose assignment and overall.

The number and percentage of patients with Infusion-Association Reactions (IARs) adverse events by MedDRA System Organ Class, Preferred Term, and ADA positivity will be presented along with the number of IAR events. If a patient experienced more than one event in a given SOC, that patient is counted once for that SOC. If a patient experienced more than one event with a given PT, that patient is counted only once for that PT.

7.3.3.3.2. ECG

Analyses of ECG data will not be included in the CSR.

8. REFERENCES

9. APPENDICES

9.1. Schedule of Study Assessments

9.1.1. 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.

9.1.2. 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.

9.1.3. 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.

9.1.4. Schedule of Study Assessments (Part C, Therapy at 5 and/or10 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.

* 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.

9.2. Changes from Analyses Specified in the Previous Version of the SAP

Not applicable.

9.3. Sample Size, Power, and Randomization

9.3.1. Sample Size and Power

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.

9.3.2. Randomization

Parts A and B were open label and non-randomized with no requirement for blinding.

In Part C, subjects are randomized such that at least 1 subject from each dose assignment in Part A received SBC-103 at 5 mg/kg and at least 1 subject from each dose assignment in Part A received SBC-103 at 10 mg/kg. Thus each of the assigned dose levels from Part A is represented in each of the 2 dose levels being studied in Part C.

As noted in the CSP Section 1.4.1, a total of 11 subjects enrolled in this study; 5 of these randomized to receive 5 mg/kg QOW and 6 randomized to receive 10 mg/kg QOW.

Details of the randomization are provided in a randomization specification document, which is maintained by the Sponsor.

9.4. Technical Specifications for Derived Variables

9.4.1. Baseline Definition

Baseline is defined as the value closest and prior to the first administration of SBC-103 on the first day of dosing. Once a subject enters Part C, the study visit schedule is reset to Week 1 Day 0 Part C (WK1C D0C) 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 WK1C D0C to allow for a more meaningful assessment of the PK and PD/efficacy profile of the 5 and 10 mg/kg doses. The first day of dosing is Day 0 in the SOA and will be considered Relative Study Day 1 in order to construct CDISC compliant datasets. Analyses will use the assessments based on the Day 0 visit per the eCRF. Part C baseline is defined as the value of the last assessment performed at the visit closest and prior to the first administration of SBC-103 on the first day of dosing in Part C at 5 mg/kg or 10 mg/kg.

Subjects will begin Part C at varying time points. For some subjects, the Part C Baseline (WK1C D0C) visit will occur at the same time as, and will be equivalent to the 12 Month (Week 52) On-Study visit. Subjects that escalated into Part C prior to the 12 Month (Week 52) On-Study visit will have a Part C Baseline (WK1C D0C) visit only. Finally, subjects who escalated into Part C after the 12 Month (Week 52) On-Study visit, their Part C Baseline (WK1C D0C) visit will be a separate visit from their 12 Month (Week 52) On-Study visit and will occur at the visit closest and prior to the first administration of SBC-103 at the escalated 5 or 10 mg/kg dose.

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 (WK1C D0C) may be used as the baseline assessment for Part C in lieu of performing an MRI on Day 0C (WK1C D0C).
- Neurocognitive and developmental testing performed within 8 weeks prior to Day 0 in Part C (WK1C D0C) may be used as the baseline assessment for Part C in lieu of performing neurocognitive and developmental testing on Day 0C (WK1C D0C).
- A lumbar puncture performed within 4 weeks prior to Day 0 in Part C (WK1C D0C) may be used as the baseline assessment for Part C in lieu of performing a lumbar puncture on Day 0C (WK1C D0C).

To ensure that all assessments are properly summarized, an analysis flag will be created to indicate each Part C baseline assessment.

9.4.2. Visit Windows

It is expected that all visits will occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. In data listings, the relative day of all visits will also be presented.

9.4.3. Imputation of Partial Dates

For descriptive analysis purposes, partial dates will be imputed for some calculations (e.g. time to, and duration of, etc.). For calculation of time of laboratory test from diagnosis, partial dates will be handled as follows. Date of diagnosis must be imputed from age at diagnosis and date of birth (DOB). Date of diagnosis will be defined as DOB + age at diagnosis. If DOB contains partial dates, date of diagnosis will be defined as imputed DOB + age at diagnosis. Time from diagnosis will be calculated from imputed date of diagnosis.

For other analyses, partial dates will be handled by the following imputation methods:

- Imputations for ages (in months): If birthdate is not missing, Age = (Assessment date - birth date)/30.4375. If only birth year and month are available, Age = (Assessment year- birth year)*12 + (assessment month-birth month). If only birth year is available then a “midpoint date” of July 1 will be used for an imputed birth date; using July 1 of the birth year, Age = (Assessment date – imputed birth date)/30.4375. If the birth date is completely missing, Age = (age in years from eCRF*12) for Baseline (add the appropriate number of months for any follow-up assessments).
- AE Start Date Imputation: The earliest possible date will be imputed for start date of AEs. If the day of the month is missing, the day will be set to the first day of the month. If the day and month are both missing, the day and month will be assumed to be January 1.
- AE End Date Imputation: The latest possible date will be imputed for end date of AEs. If the day of the month is missing, the day will be set to the last day of the month. If the day and month are both missing, the day and month will be assumed to be December 31.

- Midpoint Imputation: For all other partial dates, a "midpoint date" will be imputed. If the day of the month is missing, the day will be set to the fifteenth (15th) day of the month. If the day and month are both missing, the day and month will be assumed to be July 1.
- Should the date created with these imputation rules place it outside the possible range of values established by complete, known dates (such as the birth date, death date, ICF date for study procedures), the closest known date will be used. In the case of date imputations for age calculations, the age as reported on the eCRF will be used as a reference to ensure the calculated age is appropriate.

For reporting purposes, a month will be defined as 30.4375 days (rounded and displayed to 1 decimal place) and a year defined as 365.25 days (rounded and displayed to 2 decimal places).

9.5. Additional details on Statistical Methods

Not applicable.