Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT (CSR)

PROTOCOL NUMBER: NGLU-CL01-T

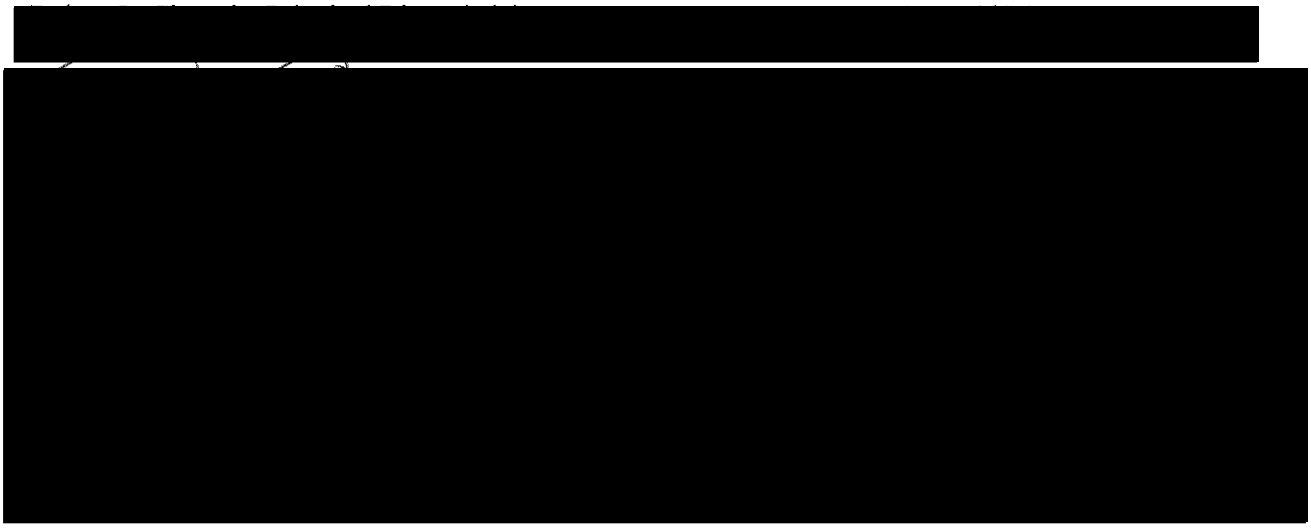
A Phase I/II Open Label Study in Previously Studied, SBC-103 Treatment Naïve MPS IIIB Subjects to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics/Efficacy of SBC-103 Administered Intravenously

Author: [redacted]

Date: 01 Sep 2017

Version: 1.0

1. APPROVAL SIGNATURES



1. APPROVAL SIGNATURES

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

TABLE OF CONTENTS

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 event(s) 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
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
QOW	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
SOA	Schedule of Assessments
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

Abbreviation or acronym	Explanation
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-CL01-T, *A Phase I/II Open Label Study in Previously Studied, SBC-103 Treatment Naïve MPS IIIB Subjects to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics/Efficacy of SBC-103 Administered Intravenously,* is an open label Phase I/II study designed to evaluate the safety and tolerability of intravenous (IV) administration of SBC-103 in previously studied, SBC-103 treatment naïve subjects with mucopolysaccharidosis III, type B (MPS IIIB, Sanfilippo B) who participated in the NGLU-CL01 study. The NGLU-CL01 study was a non-interventional study that evaluated structural brain abnormalities and blood brain barrier (BBB) integrity by magnetic resonance imaging (MRI) and cerebrospinal fluid/serum albumin index (CSF-AI).

The protocol can be referenced for additional details. The schedule of events is attached in Appendix 9.1 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-CL01-T CSR represent a reduced subset of the overall total data analyses, data summaries, and data presentations described in the NGLU-CL01-T final approved Clinical Study Protocol (CSP) version (Amendment 2, 24 February 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. 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 previously studied, SBC-103 treatment naïve subjects with mucopolysaccharidosis III, type B (MPS IIIB, Sanfilippo B) who participated in the NGLU-CL01 study. The NGLU-CL01 study was a non-interventional study that evaluated structural brain abnormalities and blood brain barrier (BBB) integrity by magnetic resonance imaging (MRI) and cerebrospinal fluid/serum albumin index (CSF-AI).

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 is considered a treatment emergent adverse event (TEAE) for this study.

5.2.2. Vital Signs

Vital signs will be provided in a listing. The following vital signs were recorded at the times 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 assessments 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 Appendix 9.1. 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.

SBC-103 1 mg/kg was administered qow for the first 12 weeks of study; the dose was then escalated to 3 mg/kg for all subjects. Descriptive summaries of data will be presented by the SBC-103 3 mg/kg qow dose group without regard to the initial treatment at the 1 mg/kg qow dose or any dose reductions. 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 as the SBC-103 3 mg/kg qow dose only except in treatment exposure and infusion listings. 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

Only 1 center participated in this study and therefore, analyses by center will not be performed.

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 efficacy 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 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 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 procedure performed 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 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 and percentage of patients with a TEAE will be summarized.

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.

The number of Serious TEAEs 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.

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 SAEs 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 to be presented include hematology, chemistry, urinalysis, coagulation, renal function, 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 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 for each visit. Neutralizing antibodies for confirmed positive cases will also be presented.

ADA titer result statistics will be descriptively presented by ADA status and visit.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

X^P Assessments to be performed pre-dose

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

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

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

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

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

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

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

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

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

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

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

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

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 up to 5 subjects was determined by the number of subjects enrolled in the prior NGLU-CL01 study, based on clinical and not statistical considerations and is considered sufficient to provide PK, safety, and PD/efficacy data, which in combination with data from other NGLU studies could be used to inform dose selection, regimen, and study design for future studies.

9.3.2. Randomization

This is an open label, non-randomized study with no requirement for blinding.

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. The first day of dosing is Day 0 in the Schedule of Assessments (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.

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.