Statistical Analysis Plan

Protocol Number:	SB-913-1602, Amendment 7
Title:	A Phase 1/2, Multicenter, Open-Label, Single-Dose, Dose-Ranging Study to Assess the Safety and Tolerability of SB-913, a rAAV2/6-based Gene Transfer in Subjects with Mucopolysaccharidosis II (MPS II)
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STATISTICAL ANALYSIS PLAN

Version 1.0

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STATISTICAL ANALYSIS PLAN

Version 1.0

30 October 2020

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ABBREVIATIONS

AAV	adeno-associated virus
ACTH	adrenocorticotropic hormone
AE	adverse event/experience
AFP	α-fetoprotein
ALT	alanine aminotransferase (SGPT)
ANSI	American National Standards Institute
AQL	acceptable quality level
AST	aspartate aminotransferase (SGOT)
ATC	Anatomical, Therapeutic, and Chemical
BSID-III	Bayley Scales of Infant Development
CDA	clinical data associate
eCRF	electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
CSF	cerebrospinal fluid
DS	dermatan sulfate
ECG	electrocardiogram
ECHO	echocardiogram
EOS	End of Study Visit
ERT	enzyme replacement therapy
FVC	forced vital capacity
GAG	glycosaminoglycan
hIDS	human iduronate-2-sulfatase
HS	heparan sulfate
IDS	iduronate-2-sulfatase
JROM	joint range of motion
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MPS II	Mucopolysaccharidosis II
MRI	magnetic resonance imaging
PFT	pulmonary function test
PT	Preferred Term
QC	quality control
rAAV	recombinant adeno-associated virus
RDC	remote data capture
SAE	serious adverse event
SAP	statistical analysis plan
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	treatment emergent adverse event

VABS-II	Vineland Adaptive Behavior Scales
WASI-II	Wechsler Abbreviated Scale of Intelligence, Second Edition; Shapiro et al. 2015
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence
WHO	World Health Organization
ZFN	zinc finger nuclease
6MWT	6-minute walk test

1. INTRODUCTION

This document details the Statistical Analysis Plan (SAP) for Protocol SB-913-1602, A Phase 1/2, Multicenter, Open-label, Single-dose, Dose-ranging Study to Assess the Safety and Tolerability of SB-913, a rAAV2/6-based Gene Transfer in Subjects with Mucopolysaccharidosis II (MPS II). The SAP summarizes key aspects of the study to provide context for statistical methods and presents details of the planned statistical methods addressing the study aims.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

To evaluate the safety and tolerability of SB-913.

2.1.2 Secondary Objectives

- To evaluate change from baseline over time in the following assessments:
  - Iduronate-2-sulfatase (IDS) activity in blood
  - Glycosaminoglycan (GAG) testing in urine
- Frequency of enzyme replacement therapy (ERT) administration
- Adeno-associated virus (AAV) 2/6 clearance

2.1.3 Exploratory Objectives

To evaluate change from baseline over time in the following assessments:

- Gene modification at the albumin locus in the liver
- Imaging, functional, and neurocognitive testing related to MPS II
- Immune response to AAV2/6, and zinc finger nucleases (ZFNs), and IDS

2.2 Endpoints

2.2.1 Primary Endpoint

The primary endpoint of this study is the incidence of treatment-emergent adverse events (TEAEs) including serious adverse events (SAEs).

Additional safety evaluations will include:

- Routine hematology, chemistry, and liver function laboratory tests, vital signs, physical exam, electrocardiogram (ECG), echocardiogram (ECHO), and concomitant medications.
- Cranial nerve exam and muscle strength testing.
- Serial α–fetoprotein (AFP) testing and magnetic resonance imaging (MRI) of liver to evaluate for liver mass.

Safety assessment will be performed on all subjects. TEAEs will be summarized overall and by treatment cohort. For each subject, the maximum reported severity of each adverse event will be used in the summaries by severity grade. In addition, all SAEs and AEs related to study treatment will be summarized.

2.2.2 Secondary Endpoints

The following are secondary endpoints for this study:

- Change from Baseline in:
  - IDS activity measured in blood.
  - Total GAG, DS GAG, and HS GAG levels (expressed as ratio to creatinine) measured in urine.
- Monthly and annualized frequency and dose of idursulfase (or equivalent ERT).
- AAV2/6 clearance measured by vector genomes in plasma, saliva, urine, stool, and semen by PCR.

2.2.3 Exploratory Endpoints

Change from baseline over time in the following assessments:

- Percentage and durability of gene modification at the albumin locus in liver tissue obtained at biopsy.
- Forced vital capacity (FVC) measured by pulmonary function tests (PFTs).
- Distance walked measured by six-minute walk test (6MWT).
- Joint range of motion (JROM).
- MRI of liver to evaluate liver and spleen volume.
- MRI of brain and cervical spine to evaluate clinical soft tissue and/or bone.
- Neurocognitive abilities by WASI-II (Wechsler Abbreviated Scale of Intelligence, Second Edition; Shapiro et al. 2015), WPPSI-IV (Wechsler Preschool and Primary Scale of Intelligence), or BSID-III (Bayley Scales of Infant Development), and by VABS-II (Vineland Adaptive Behavior Scales).
- Histopathological exam of liver tissue.
- Immune response to AAV 2/6, ZFNs, and IDS measured in serum.

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a Phase 1/2, multicenter, open-label, single-dose, dose-ranging study with sequentially enrolled age cohorts: age ≥18 (adult cohorts 1 through 4), age 12-17 (pediatric cohorts 5 and 6), and age 5-11 (pediatric cohorts 7 and 8).

Subjects who satisfy all eligibility criteria will be enrolled into one of the following treatment

cohorts:

Cohort #	Age Range (years)	Total Dose (vg/kg)	# Subjects
1	≥18	5.00E+12	2
2	≥18	1.00E+13	2
3	≥18	5.00E+13	2
4	≥18	1.20E+14	2
5	12-17	5.00E+13	2
6	12-17	TBD	2
7	5-11	TBD	2
8	5-11	TBD	2

Two subjects will be enrolled in each cohort, and will be dosed at least 4 weeks apart. SMC (Safety Monitoring Committee) review occurs after at least 4 weeks of safety data is available from 2 subjects in each cohort. The pediatric cohorts will be enrolled only after review of cumulative adult safety data by the SMC. The starting dose for pediatric cohorts 6 through 8 will be decided based on SMC review of study data, and must meet pre-defined safety criteria. Approximately 2 additional subjects may be added to any age cohort after SMC review of study data if safety criteria are met, with up to a total of 32 subjects in the study.

For subject inclusion and exclusion criteria, please refer to study protocol SB-913-1602. Subjects that do not complete at least 12 months of the study may be replaced with other subjects. The duration of the study participation will be approximately 39 months for each subject, divided into approximately 3 months for Screening followed by 36 months for treatment and study follow-up. Upon completion of the study, subjects will be asked to participate in a separate Long-term Follow-up Study to monitor the long-term safety of SB-913.

A detailed schedule of events for the study can be found in Appendix A.

3.2 Treatment

3.2.1 Randomization Scheme and Treatment Arm Assignment

This is an open-label study, there is no randomization scheme.

The doses of SB-913 selected for evaluation in this study are:

Cohort	ZFN 1 (SB-47171) (vg/kg)	ZFN 2 (SB-47898) (vg/kg)	hIDS Donor (SB-IDS) (vg/kg)	Total rAAV (vg/kg)
1	5.00E+11	5.00E+11	4.00E+12	5.00E+12
2	1.00E+12	1.00E+12	8.00E+12	1.00E+13
3	5.00E+12	5.00E+12	4.00E+13	5.00E+13

4	1.20E+12	1.20E+13	9.60E+13	1.20E+14
5	5.00E+12	5.00E+12	4.00E+13	5.00E+13
6	TBD	TBD	TBD	TBD
7	TBD	TBD	TBD	TBD
8	TBD	TBD	TBD	TBD

3.2.2 Blinding

This is an open-label study, there is no blinding.

3.2.3 Dosing Schedule

The 3 components of SB-913 (ZFN1, ZFN2, and human iduronate-2-sulfatase (hIDS) Donor) will each be added to 200 mL of diluent and adjusted to 0.25% human serum albumin. Total infusion volumes will depend on subject's cohort assignment and body weight (kg). IV infusions will be administered while the subject is in the hospital or acute care facility. The subject will remain in the hospital or acute care facility for at least 24 hours after SB-913 infusion for observation, and will be discharged when all AEs and vital signs (temperature, heart rate, respiratory rate, and blood pressure) are stable. After being discharged from the hospital or acute care facility, subject will be evaluated at regular clinic visits throughout the study.

3.2.4 Subject Compliance

Subjects who prematurely discontinue the study prior to the 12 months of study follow-up (i.e., subjects who were enrolled but not dosed, lost to follow-up, or discontinued prematurely for another reason) may be replaced at the discretion of Sangamo.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

As a first-in-human and first-in-subject proof-of-concept trial there are no statistical hypotheses regarding treatment effects. Rather, displays and comparisons of study results – regarding dose-related safety profiles among the dose cohorts – will primarily utilize descriptive statistics, as noted below.

Unless otherwise specified, continuous variables will be summarized by presenting the number of non-missing observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by presenting the number of subjects and percentage for each category.

Summary results will be provided for each dose cohort. All tabulations will be based on pooled data across centers.

Analyses will be performed using SAS for Windows statistical software, version 9.2 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

CTI Clinical Trial and Consulting Services (Covington , KY) will perform all safety, primary, secondary, and exploratory endpoint statistical analyses.

Subject data will be listed, sorted by dose cohort and subject number.

4.1 Data Quality Assurance

Sangamo Therapeutics, Inc., or its designated representative, will conduct a pre-study visit for each study site to verify the qualifications of the investigator, inspect study site facilities, become familiarized with site staff assigned to the study, and inform the investigator of responsibilities and procedures for ensuring correct study documentation.

A study coordinator at the investigative site will enter subject data into MediData RAVE EDC by completing electronic case report forms (eCRFs). All information recorded in the eCRFs for this study must be consistent with the investigator's source documentation for the study participants. The investigative site will make available source documents to CTI personnel monitoring the study. The study monitor will verify consent of all subjects to participate in the study and will perform 100% source document verification of the eCRF data.

A CTI Clinical Data Associate (CDA) will review the data for discrepancies via programmed electronic consistency checks, data listings, or manually. Any discrepancies discovered via the data review process will be issued as queries in the EDC system to the investigative site for resolution. Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to CTI Biostatistics for analysis.

Data may be pulled by CTI Biostatistics for SMC analysis at a time when source verification and query resolution is ongoing.

All SAS programs used to create analysis datasets and output will be validated by ensuring that the ".log" files are void of all errors, warnings and notes indicative of problems. Additionally, each program will be checked to ensure that it performs according to the program specification. All programs are developed and validated by separate members of the CTI Biostatistics Department.

When performing a quality control (QC) review of listings and tables output from SAS, it is not always possible to perform a 100% QC review of all fields. If a 100% QC review is not to be performed, the sample size of fields to undergo QC review may be determined by utilizing American National Standards Institute (ANSI) sampling procedures. Sampling procedures are conducted using "normal" inspection criteria (Inspection Level II, Single, and Normal) and an Acceptable Quality Level (AQL) of 0.010%. The following shows the sampling criteria:

Single Normal sampling procedure for Acceptable Quality Level (AQL) 0.010%

Number of Fields	Sample Size	Accept/Reject Criteria
2-8	2	0/1
9-15	3	0/1
16-25	5	0/1
26-50	8	0/1
51-90	13	0/1
91-150	20	0/1
151-280	32	0/1
281-500	50	0/1

Number of Fields	Sample Size	Accept/Reject Criteria
501-1,200	80	0/1
1,201-3,200	125	0/1
3,201-10,000	200	0/1
10,001-35,000	315	0/1
35,001-150,000	500	0/1
150,001-500,000	800	0/1
500,001-up	1,250	0/1

4.2 Analysis Sets

All subjects enrolled in this study who receive any portion of the SB-913 infusion will be included in the Safety Analysis Set . All analyses (i.e., safety, primary, secondary, and exploratory) will be performed using the Safety Analysis Set .

4.3 Assessment Windows

For the purpose of listing and summarizing data, the time-in-study for each subject observation will be defined using study days, weeks and months. Such days will be measured relative to Day 0, the day on which SB-913 is infused. Because protocol-specified visits (e.g., Week 16) will not necessarily occur on the same study day for all subjects, study visits will be defined through the use of windows. Study visits will have windows as per the following schema:

Data will be summarized based on the CRF (Study Visit) in which it was collected.

Baseline will be defined as the last pretreatment value during the screening period except for the GAG/IDS values. For the GAG/IDS test, baseline will be calculated using the mean of all prior dosing values. If more than one assessment exists within a single visit window, the value closest to the protocol study visit will be used for summary and analysis purposes. Data from all assessments will be listed.

4.4 Study Days

For the purpose of the analysis, study day will be calculated relative to first administration of the study drug. Specifically:

If visit date is prior to dosing:

$$\text{Study day} = \text{date of visit} - \text{first dose date}$$

If visit date is on or after dosing:

$$\text{Study day} = \text{date of visit} - \text{first dose date} + 1.$$

Statistical analyses will be performed using study day as defined above.

4.5 Handling of Dropouts or Missing Data

If laboratory result is below detection limit, it will be imputed to half of detection limit in table and figure. The result will be listed as is in listings .

4.6 Multiple Comparisons

No multiple comparisons will be performed.

4.7 Data Derivations and Transformations

No data derivations or transformations will be performed.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

Enrollment, screen failure, major protocol violations, and discontinuations from the study will be summarized by treatment cohort. The number of subjects who were enrolled, dosed, discontinued, and completed the study will be summarized.

5.2 Protocol Deviations

Distribution for the types of major protocol deviations and the number of subjects that deviate from the protocol will be tabulated for the dose cohorts. Also, the number and percent of subjects with a protocol deviation related to COVID-19 will be summarized. A by-subject listing will also be provided. Protocol deviations related to COVID-19 will be flagged in the listing.

5.3 Demographic Characteristics

Demographic characteristics, including age, sex, race, and ethnicity, will be summarized using means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables. All summaries will be presented overall and by treatment cohort for the Safety Analysis Set. A by-subject listing will also be provided.

5.4 Baseline Characteristics

Baseline characteristics including, height, weight, FVC, 6MWT, urine GAG, and IDS, will be summarized using means, standard deviations, medians, and ranges for continuous variables, and proportions for categorical variables. All summaries will be presented overall and by treatment cohort for the Safety Analysis Set. A by-subject listing will also be provided.

5.5 Medical History and Historical Surgeries and Procedures

All past and/or concomitant diseases and past surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA version 23.0). The number and percent of subjects with each medical condition and surgical procedure will be presented for each SOC and PT for the Safety Analysis Set overall and by dose cohorts. A by-subject listing will also be provided.

5.6 Concomitant Medications and Supportive Care

Concomitant medications and supportive care will be coded using World Health Organization (WHO) drug classifications version B2 enhanced September 2017. The number and percent of safety subjects using concomitant medications will be tabulated by default Anatomical, Therapeutic, and Chemical (ATC) classification Level 4 and by preferred name for the Safety Analysis Set overall and by dose cohorts. A by-subject listing will also be provided.

6. ENDPOINT ANALYSIS

Since this is a single-dose study to evaluate safety, analyses will be descriptive and exploratory in nature. Change from the preceding year values may be calculated for selected clinical and laboratory parameters.

If there is a result with a "<" sign, will drop the sign and use half of the number for analysis. If the result is below detection limit, it will be imputed to half of detection limit in table and figure. The result will be listed as is in listings.

6.1 Primary Endpoint and Analysis

The primary endpoint of this study is the safety and tolerability of SB-913. Safety assessments are detailed in Section 7 of this SAP.

6.2 Secondary Endpoints and Analyses

Secondary endpoints will be summarized by presenting descriptive statistics of actual values and changes from baseline at each visit, where applicable. The secondary endpoints consist of the changes from baseline over time in the following assessments:

- IDS activity measured in plasma
- Assessments will be conducted at Screening, Baseline, Weeks 2, 4, 6, 8, 12, 16, 20, 24, 36, 48, Months 15, 18, 21, 24, 27, 30, 33, 36/End of Study (EOS), and at any Early Termination Visit. Total GAG, dermatan sulfate (DS) GAG, and heparin sulfate (HS) GAG levels measured in urine

At each sampling time point, the actual value and the change from baseline for IDS activity and urine GAG levels will be summarized using descriptive statistics and plotted over time by treatment cohort.

For subjects who undergo ERT withdrawal, changes from pre- to post- ERT withdrawal in the frequency and dose of ERT infusions will be evaluated and summarized using monthly, quarterly, and annualized total dose and number of infusions. Duration of ERT withdrawal may also be analyzed. The ERT withdrawal period is defined as the date recorded on the ERT Withdrawal Trigger CRF form to the first date after ERT withdrawal recorded on the ERT administration.

- AAV2/6 clearance measured by vector genomes in plasma, saliva, urine, stool, and semen by PCR

AAV2/6 clearance measured by vector genomes in the different samples will be plotted over time by treatment cohort.

6.3 Exploratory Endpoints and Analyses

Exploratory endpoints will be summarized by presenting descriptive statistics of actual values and changes from baseline at each visit. A by-subject listing will also be provided. The exploratory endpoints consist of the changes from baseline over time in the following assessments:

- Percentage and durability of gene modification at the albumin locus in liver tissue obtained at biopsy

  Assessments will be conducted at Baseline, Week 24, and Week 48

- FVC measured by PFTs

  Assessments will be conducted at Screening, Baseline, Week 24, Week 48, Months 18, 24, 30, 36/EOS, and at any Early Termination Visit.

- Distance walked measured by 6MWT

  Assessments will be conducted at Baseline, Week 24, Week 48, Months 18, 24, 30, 36/EOS, and at any Early Termination Visit.

- Joint ROM (ankle, knee, hip, and shoulder)

  Assessments will be conducted at Baseline, Week 24, Week 48, Months 18, 24, 30, 36/EOS, and at any Early Termination Visit .

- MRI of liver to evaluate liver and spleen volume

  Assessments will be conducted at Screening, Week 24, Week 48, Months 18, 24, 30, 36/EOS, and at any Early Termination Visit.

- MRI of brain and cervical spine to evaluate clinical soft tissue and/or bone

  Assessments will be conducted at Baseline, Week 48, Month 24, Month 36/EOS, and at any Early Termination Visit.

- Neurocognitive abilities by WASI-II, WPPSI-IV, or BSID-III, and by VABS-II

  Assessments will be conducted at Baseline, Week 24, Week 48, Months 18, 24, 30, 36/EOS, and at any Early Termination Visit.

- Histopathological exam of liver tissue

- Immune response to AAV2/6, ZFNs, and IDS measured in plasma

  Assessments will be conducted at Screening, Baseline, Weeks 2, 4, 6, 8, 12, 16, 24, 36, 48, Months 15, 18, 21, 24, 27, 30, 33, 36/EOS, and at any Early Termination Visit.

AAV-related research biomarkers will also be assessed at baseline.

CTI will be analyzing the change from baseline in Plasma IDS Activity, CSF Pressure, Biomarkers, and MRI of Brain and Neck. All other exploratory analyses will be performed by a third party at Sangamo's discretion.

7. SAFETY ANALYSIS

All safety summaries will be conducted using the SAS.

7.1 Extent of Exposure

The expected and actual dose of SB-913, and the reasons for infusion interruption will be summarized and presented in a table.

A listing will also be provided.

7.2 Adverse Events

7.2.1 Treatment-emergent Adverse Events

A TEAE is any AE with an onset from the dateof SB-913 infusion through the last study visit, whether or not it is considered causally related to the study drug.

7.2.2 Adverse Event Severity

Severity will be categorized by toxicity grade according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. AEs not listed in the CTCAE v4.03 will be evaluated by using the following criteria:

- Grade 1, Mild: Symptoms cause no or minimal interference with usual social and functional activities
- Grade 2, Moderate: Symptoms cause greater than minimal interference with usual social and functional activities
- Grade 3, Severe: Symptoms cause inability to perform usual social and functional activities
- Grade 4, Potentially Life-threatening: Symptoms cause inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
- Grade 5: Outcome of AE is death

7.2.3 Adverse Event Relationship to Study Medication

The relationship of the AE to the investigational drug will be categorized by the Principal Investigator as Related or Not Related. Any AE that does not meet the definition of a suspected Adverse Reaction will be categorized as Not Related.

7.2.4 Serious Adverse Events

An AE or Suspected Adverse Reaction is considered serious if, in the view of either the Principal Investigator or Sangamo, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect in the offspring of an exposed subject

7.2.5 Adverse Event Summaries

For TEAEs, the following will be summarized and presented for the Safety Analysis Set overall and by dose cohort:

i. An overall summary of TEAEs, which includes:
   a. the number and percentage of subjects experiencing a TEAE
   b. the number and percentage of subjects experiencing a TEAE equal to or greater than Grade 3 toxicity
   c. the number and percentage of subjects experiencing a related TEAE
   d. the number and percentage of subjects experiencing a TEAE leading to study withdrawal
   e. the number and percentage of subjects experience a TEAE leading to death
   f. the number and percentage of subjects experiencing a treatment emergent SAE (TESAE)

ii. the number and percentage of subjects experiencing a TEAE by SOC and PT

iii. the number and percentage of subjects experiencing a TEAE by SOC, PT and the highest toxicity grade

iv. the number and percentage of subjects experiencing a TEAE by SOC, PT and the strongest relationship to study medication

v. the number and percentage of subjects experiencing a TEAE by PT

vi. the number and percentage of subjects experiencing a TEAE leading to study withdrawal by SOC and PT

vii. the number and percentage of subjects experiencing a TESAE by SOC and PT

In the overall summary of TEAEs table (i), besides tabulating the number and percentage of subjects, the total number of TEAE episodes will also be provided. If a subject has repeated episodes of a particular TEAE, all episodes will be counted in the summary table.

In the remaining summary tables, the incidence of TEAEs will be calculated by dividing the number of subjects who have experienced the event by the total number of subjects in the Safety Analysis set. Thus, the incidence of TEAEs is shown in terms of the total number of subjects and not in terms of the total number of episodes. If a subject has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship to study drug, will be counted in the summary tables.

A subject with more than one type of TEAE in a particular SOC will be counted only once in the total of subjects experiencing TEAEs in that particular SOC. Since a subject could have more than one type of TEAE within a particular SOC, the sum of subjects experiencing different TEAEs within the SOC could appear larger than the total number of subjects experiencing TEAEs in that SOC. Similarly, a subject who has experienced a TEAE in more than one SOC will be counted only once in the total number of subjects experiencing AEs in all SOCs. At each level of summation (relationship, toxicity grade), subjects reporting more than one TEAE are

counted only once using the strongest relationship to study medication and highest toxicity grade.
All AEs (serious and non serious) occurring after completion of the informed consent process and before the end of study, regardless of relationship to study drug, will be included and classified by SOC and PT using MedDRA in a listing by subject, grouped by dose cohort.

The listing will contain the following information: dose cohort, verbatim term, SOC, PT, severity, toxicity grade, relationship to study medication, date and day of onset, date and day of resolution, treatment given to treat the adverse event, the outcome, whether the event was an SAE, whether it led to withdrawal and whether it is a TEAE. Listings will be sorted by subject identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

7.3 Clinical Laboratory Assessments

Change from baseline values and shift tables will be presented for all clinical laboratory assessments except urinalysis. All clinical laboratory assessment data will be listed.

- Chemistry and metabolic assessments will be conducted at Screening, Baseline, Day 1, Weeks 2, 4, 6, 8, 12, 16, 20, 24, 36, 48, Months 15, 18, 21, 24, 27, 30, 33, and 36/EOS and at any Early Termination Visit.

  The serum chemistry panel includes Na, K, Ca, HCO_3, Cl, and P. The metabolic panel includes BUN, creatinine, glucose, and uric acid.

- Hematology assessments will be conducted at Screening, Baseline, Day 1, Weeks 2, 4, 6, 8, 12, 16, 20, 24, 36, 48, Months 15, 18, 21, 24, 27, 30, 33, and 36/EOS and at any Early Termination Visit.

  The hematology panel includes a complete blood count with differential and platelets.

- Urinalysis assessments with microscopic examination include glucose, protein, bilirubin, blood, pH, and specific gravity.

  Urinalysis assessments will be conducted at Screening, Baseline, Day 1, Weeks 2, 4, 6, 8, 12, 16, 20, 24, 36, 48, Months 15, 18, 21, 24, 27, 30, 33, and 36/EOS and at any Early Termination Visit.

- Liver assessments will be conducted at Screening, Baseline, Day 1, Day 7 (2x/week), Weeks 2, 4, 6, 8, 12, 16, 20 (2x/week), 24, 28, 32, 36, 40, 44, 48, 52, Months 15, 18, 21, 24, 27, 30, 33, 36/EOS, and at any Early Termination Visit.

  The liver panel includes total and direct bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), albumin, and total protein. Liver panel parameters will be presented in figures for each subject.

Chemistry, metabolic, hematology, and liver assessment data will be summarized by presenting descriptive statistics of actual values and changes from baseline at each visit. Shift tables (change from baseline relative to the normal range) may be constructed for selected laboratory parameters.

7.4 Vital Signs

Vital sign data will be summarized by presenting descriptive statistics of actual values and changes from baseline at each visit. Vital sign parameters include respiratory rate, temperature, systolic blood pressure, diastolic blood pressure, and heart rate. Height and weight will be summarized by presenting descriptive statistics of actual values. Changes from baseline will be presented for weight. A listing of vital signs will also be provided.

Vital sign assessments will be conducted at Screening, Baseline, Days 0, 1, 7, Weeks 2, 4, 6, 8, 12, 16, 20, 24, 36, 48, Months 15, 18, 21, 24, 27, 30, 33, 36/EOS, and at any Early Termination Visit.

7.5 Physical Examination

A listing will be provided for all physical examination abnormalities.

Physical examination assessments will be conducted at Screening, Baseline, Days 0, 1, 7, Weeks 2, 4, 6, 8, 12, 16, 20, 24, 36, 48, Months 15, 18, 21, 24, 27, 30, 33, 36/EOS, and at any Early Termination Visit.

7.6 Electrocardiogram (ECG)

A listing will be provided for all electrocardiogram (ECG).

Electrocardiogram (ECG) assessments will be conducted at Screening, Baseline, Days 7, Weeks 24, 48, Months 18, 24, 30, 36/EOS, and at any Early Termination Visit.

7.7 Echocardiogram (ECHO)

A listing will be provided for all echocardiogram (ECHO).

Echocardiogram (ECHO) assessments will be conducted at Screening, Week 48, Months 24, 36/EOS, and at any Early Termination Visit.

7.8 Neurologic Cranial Nerve Exam and Muscle Strength Test

The results of the Neurologic Cranial Nerve Exam and Muscle Strength Test will be provided in a listing. Change from baseline values will be presented for Muscle Strength Test. The number and percentage for Neurologic Cranial Nerve Exam will be presented.

Neurologic cranial nerve exam and muscle strength test assessments will be conducted at Baseline, Week 24, Week 48, Months 18, 24, 30, 36/EOS, and at any Early Termination Visit.

7.9 Serial α–fetoprotein (AFP) Testing

Serial α–fetoprotein (AFP) testing data will be summarized by presenting descriptive statistics of actual values and changes from baseline at each visit. A listing will be provided for all Serial α–fetoprotein (AFP) testing.

Serial α–fetoprotein (AFP) testing assessments will be conducted at Screening, Weeks 4, 8, 12, 24, 48, Months 18, 24, 30, 36/EOS, and at any Early Termination Visit.

7.10 Adrenocorticotropic Hormone (ACTH) Stimulation

The results of the ACTH stimulation tests will be listed.

ACTH stimulation assessments will be conducted at Baseline (prior to prednisone) and Week 20.

8. SMC ANALYSIS

An external SMC with appropriate medical and scientific expertise will have oversight of the study.

The SMC will be convened after the completion of each cohort to advise whether it is safe to proceed with the next dose cohort and to provide recommendations on pediatric dosing and expansion of any cohort. The SMC may also be convened at any time if there are excessive or unexpected toxicities associated with the conduct of the protocol. Specifically, the SMC will be convened if the following occurs:

- Any one Grade 3 or higher AE, or any two Grade 2 AEs in the same system organ class that last more than 2 weeks with therapy, provided these AEs are not related to the primary MPS II disease or treatment of the MPS II disease.
- SAE not related to the primary MPS II disease.
- Death of a subject.
- Development of a malignancy.

The SMC will then evaluate all data to advise whether the changes should be made to the study or whether accrual and dosing should be halted. In addition, no further dosing of subjects will be performed until a substantial amendment is submitted to the regulatory authority(ies) for review, and the amendment has been approved by the site IRB/IEC or equivalent. The SMC may also recommend changes to the enrollment of cohorts based on cumulative adult and pediatric safety and efficacy data from similar ongoing first-in-human clinical trials that are sponsored by Sangamo and that use in vivo rAAV2/6-based gene transfer of ZFNs. Specifically, study SB-318-1502 in MPS I subjects uses identical ZFNs components (SB-47171 and SB-47898) as the present study in combination with a different donor cDNA (encoding human alpha-iduronidase) (Clinicaltrials.gov NCT02702115). Given the similarities of the approaches, relevant data from study SB-318-1502 and other trials sponsored by Sangamo may be shared with the SMC to expand the clinical experience, particularly as it relates to safety and dose, and such data can be used by the SMC to inform its recommendations for the present study.

When no further enrolling or dosing decisions are required of the SMC, the SMC will no longer meet. Sangamo will continue to review subject safety data on an ongoing basis.

9. SAMPLE SIZE AND POWER CALCULATIONS

This study will enroll up to 32 subjects (2 subjects in each of 8 cohorts, with potential enrollment of approximately 2 additional subjects in any cohort). The sample size for this study was not based on statistical considerations, but is considered sufficient to provide preliminary assessments of the safety and tolerability of SB-913 in subjects with MPS II, as well as biochemical changes related to the pathophysiology of MPS II. Subjects who prematurely discontinue the study prior to the 12 months of study follow-up (i.e., subjects who were enrolled

but not dosed, were lost to follow-up, or discontinued prematurely for another reason) may be replaced at the discretion of Sangamo.

10. APPENDICES

10.1 Appendix A: Schedule of Events

PROCEDURE	Screening (p)	Baseline	Hospital or Acute Care Facility		Day	Week														Month								EIV
					7	2	4	6	8	12	16	20	24	28*	32*	36	40*	44*	48	52*	15	18	21	24	27	30	33	36 EOS[s]	
	(win 3 months of Baseline)	(win 21 days prior to SB-913 infusion)	Day 0	Day 1	(+/-1 day)	(+/-2 days)				(+/-1 week)											(+/-1 month)								
Informed Consent	X																											
Medical History	X																											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X																											
Demographics	X																											
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X		X	X	X	X	X	X	X	X
Vital Signs (a)	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X		X	X	X	X	X	X	X	X
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ERT Administration Log	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
JROM (b)		X											X						X			X		X		X		X	X
Neurologic Cranial Nerve Exam and Muscle Strength Testing of Upper Extremities (b)		X											X						X			X		X		X		X	X
12-Lead ECG	X	X			X								X						X			X		X		X		X	X
ECHO	X																		X					X				X	X
Chest X-ray	X																												
Pregnancy Test (c)	X	X	X				X		X	X	X	X	X			X			X										
Clinical Laboratory Tests	X	X		X		X	X	X	X	X	X	X	X			X			X		X	X	X	X	X	X	X	X	X
Liver Panel (d)	X	X		X (e)									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MPS II Gene Sequencing (f)	X																												
SNP Analysis (f)	X																												
Viral Load	X																												
Neutralizing Antibodies to AAV2/6	X																												
GAG Testing in Urine	X (g)	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IDS/GAG Testing in Blood (h)	X	X				X	X	X	X	X	X	X	X			X			X		X	X	X	X	X	X	X	X	X	X
Circulating AFP	X						X		X	X			X						X			X		X		X		X	X
Vector Genome PCR in Plasma				X (12 hr post-infusion)																									
Vector Genome PCR in Plasma, Saliva, Urine, Stool, and Semen (i)		X			X	X	X		X	X	X	X	X			X			X										
PFTs (b)	X	X											X						X			X		X		X		X	X
6MWT (b)		X											X						X			X		X		X		X	X

PROCEDURE	Screening (p)	Baseline	Hospital or Acute Care Facility		Day	Week														Month								ETV
					7	2	4	6	8	12	16	20	24	28*	32*	36	40*	44*	48	52*	15	18	21	24	27	30	33	36 EOS[4]	
	(win 3 months of Baseline)	(win 21 days prior to SB-913 infusion)	Day 0	Day 1	(+/-1 day)	(+/-2 days)				(+/-1 week)											(+/-1 month)								
VABS-II	X	X											X						X			X		X		X		X	X
Neurocognitive Abilities Assessment	X																												
Neurocognitive Abilities Testing (j)		X											X						X			X		X		X		X	X
MRI of Liver	X												X						X			X		X		X		X	X
MRI of Brain and Cervical Spine (k)		X																	X					X				X	X
ACTH Stimulation (Cosyntropin) Test (l)		X (prior to prednisone)										X																	
Liver Biopsy (m)		X											X						X										
Lumbar Puncture (m)		X											X						X										
Immunogenicity Assays (n)		X					X			X			X			X			X			X		X					
Prednisone (or equivalent corticosteroid) Administration (o)		X	X			X																							
SB-913 Infusion			X																										

* Week 28, 32, 40, 44, and 52 study visits have assessments that do not require evaluation at the clinical site, and therefore may be conducted at home if the subject is remote. Blood and urine samples at these visits may be collected by a qualified home health nurse. Assessments for AEs, concomitant medications and ERT administration log may be conducted remotely over the phone by study staff.

§ Study subjects may participate in the LTFU Study after 12 months of follow-up in this study, in which case an EOS visit may be conducted any time after Week 52 but before the next scheduled study visit. Study participants who wish to enroll in the LTFU Study with less than 12 months of follow-up in this primary study may be considered on a case-by-case basis at the judgement of the Principal Investigator and after consultation with the Sponsor. In these cases, the EOS visit may be conducted at any time on this study.

a. Vital signs (height, weight, systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature; for frequency, refer to the Study Reference Manual).

b. As permitted by subject's capacity.

c. Serum pregnancy test will be performed at Screening and Baseline visits. Urine pregnancy test will be performed on the Day 0 visit if >7 days from Baseline pregnancy test. Urine pregnancy tests will be performed until Week 48 or until 3 consecutive plasma samples are negative for AAV2/6, whichever occurs first.

d. Liver panel does not need to be drawn as a separate sample if samples for Clinical Laboratory Tests are obtained at the same visit.

e. Liver panel will be performed twice a week for the first 20 weeks post-SB-913 infusion, and may be conducted at home if the subject is remote. Blood samples will be drawn 2-4 days apart when possible, except for the first week when it will be drawn on the Day 1 and Day 7 visits. Liver function tests will subsequently be conducted at all indicated study visits.

f. For adult subjects (cohorts 1 through 4), the assay will be performed on blood or saliva samples; for pediatric subjects (cohorts 5 through 8), saliva samples are preferred.

g. During Screening, samples for GAG testing in urine will be collected on 3 separate days, each collection occurring at least 7 days after the previous. All samples for GAG testing in the urine must be collected at least 7 days after ERT administration [+/-1 day] but prior to the next ERT infusion.

h. For IDS/GAG testing in blood, samples must be obtained 7 days after ERT administration (+/- 1 day) and prior to the next ERT infusion. GAG and IDS levels in blood will both be measured concurrently from the same blood sample.

i. Each type of sample (plasma, saliva, urine, stool, semen) will be collected until 3 consecutive specimens of that sample type are reported as negative or undetectable for vector genome. Collection of semen samples may be waived for male pediatric subjects (cohorts 5 through 8) at the discretion of Principal Investigator.

j. As permitted by subject's capacity. Neurocognitive abilities testing in pediatric subjects will be done by VABS-II and by WASI-II, WPPSI-IV, or BSID-III, as appropriate based on the Neurocognitive Abilities Assessment performed at Screening.

k. Baseline MRI of brain and cervical spine may be obtained at the Screening visit (together with MRI for liver) instead of at the Baseline visit at Principal Investigator's discretion.

l. Should prednisone or equivalent corticosteroid treatment be continued or repeated due to increased transaminase activity, the ACTH stimulation test will be repeated at the end of taper. Vital signs should be monitored and recorded every hour during the ACTH stimulation test.

m. Unless contraindicated by a Principal Investigator or physician.

n. May be waived for pediatric subjects (cohorts 5 through 8) at the discretion of the Principal Investigator to minimize required blood volumes.

o. See Appendix 3.

p. For subjects who are re-screening for participation in the study, assessments including ECHO, chest X-Ray, PFTs, and MRI of liver and/or brain and cervical spine performed for the Screening of a subject in the previous 6 months may be used for evaluation of inclusion/exclusion criteria at the judgement of the Principal Investigator. Further, genetic marker analysis including SNP analysis and MPS II sequencing will not be repeated as results of these assessments do not change over time.

10.2 Appendix B: ERT Withdrawal Schedule of Events

PROCEDURE*	ERT Withdrawal Visit (a)	ERT Withdrawal Monitoring Visits Week, +/- 2 days (b)								ERT Withdrawal Follow-Up Visit (within 12 weeks of ERT withdrawal) (c)
		1	2	3	4	6	8	10	12	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Physical Examination	X									X
Vital Signs (d)	X									X
AE Assessment	X	X	X	X	X	X	X	X	X	X
ERT Administration Log	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests	X									X
Liver Panel (e)	X	X	X	X	X	X	X	X	X	X
GAG Testing in Urine	X	X	X	X	X	X	X	X	X	X
IDS / GAG Testing in Blood	X	X (g)	X	X (g)	X	X	X	X	X	X
PFTs (f)	X									X
6MWT (f)	X									X
ERT Clinical Assessment										X

* Assessments associated with ERT withdrawal that are duplicated at regular scheduled study visits should be waived if visits are combined (see Appendix 1).

a) ERT Withdrawal visit may occur at or at any time after the Week 12 visit (refer to Section 11.4 for additional guidance).

b) ERT Withdrawal Monitoring visits will take place on a weekly basis for the first 4 weeks, and on a biweekly basis for the last 8 weeks following the ERT Withdrawal visit until the ERT Withdrawal Follow-Up visit. ERT Withdrawal Monitoring visits have assessments that do not require evaluation at the clinical site, and may therefore be conducted at home if the subject is remote. Blood and urine samples at these visits may be collected by a qualified home health nurse. Assessments for AEs and concomitant medications may be conducted by study staff over the phone.

c) The ERT Withdrawal Follow-Up visit can occur at any time up to 12 weeks after ERT withdrawal at the discretion of the Principal Investigator. ERT does not need to be restarted at the end of the ERT Withdrawal Follow-Up visit.

d) Vital signs (weight, systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature; refer to the Study Reference Manual).

e) Liver panel does not need to be drawn as a separate sample if Clinical Laboratory Tests are obtained at the same visit.

f) As permitted by subject's capacity.

g) May be waived for pediatric subjects (cohorts 5 through 8) at the discretion of the Principal Investigator to minimize required blood volumes.

10.3 Appendix C: Immunosuppression Regimen

Weight of Subject (kg)	Oral Prednisone (mg/day)					
	Day -2 to Day 1	**Week 1**	**Week 2**	**Week 3-16**	**Week 17-19**	**Week 20**
≥ 60	60	60	30	15	5	STOP
55	60	60	30	15	5	STOP
50	50	50	25	15	5	STOP
45	45	45	25	15	5	STOP
40	40	40	20	10	5	STOP
35	35	35	20	10	5	STOP
30	30	30	15	10	5	STOP
<30	1 mg/kg	1 mg/kg	0.5 mg/kg	0.25 mg/kg	0.25 mg/kg every other day	STOP

Prednisone or equivalent corticosteroid regimen is commenced 2 days prior to Day 0 of SB-913 infusion and given once daily unless otherwise stated. Subject's liver function will be monitored twice a week while on prednisone or equivalent corticosteroid. Liver panel shall be drawn 2-4 days apart when possible, except for the first week when it will be drawn on Day 1 and Day 7 visits. Tapering of prednisone or equivalent corticosteroid will only proceed if ALT/AST activity levels are stable or declining (based on the 2 assessments of the preceding week).

If subjects develop increased ALT > 2 fold baseline while on prednisone or equivalent corticosteroid or after stopping prednisone, the prednisone regimen or equivalent corticosteroid may be adjusted or restarted at the Principal Investigator's discretion after consultation with the Medical Monitor. Twice a week liver panel testing should continue until the prednisone course or equivalent corticosteroid has been terminated.

An ACTH stimulation (cosyntropin) test will be performed prior to the first prednisone or equivalent corticosteroid dose and again at the end of the scheduled taper to ensure that the adrenal cortical function has not been suppressed. Should prednisone or equivalent corticosteroid treatment be repeated due to increased transaminase activity, the ACTH stimulation test will be repeated at the end of taper at the Principal Investigator's discretion.

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Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	11/2/2020 9:14:37 AM
Certified Delivered	Security Checked	11/9/2020 1:55:57 PM
Signing Complete	Security Checked	11/9/2020 1:56:40 PM
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