**Clinical Study Protocol**

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| **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) |
| **Date:** | 12Dec2019 |
| **BB-IND:** | 17006 |
| **EudraCT:** | 2018-000192-33 |
| **NCT#:** | NCT03041324 |

# Clinical Study Protocol

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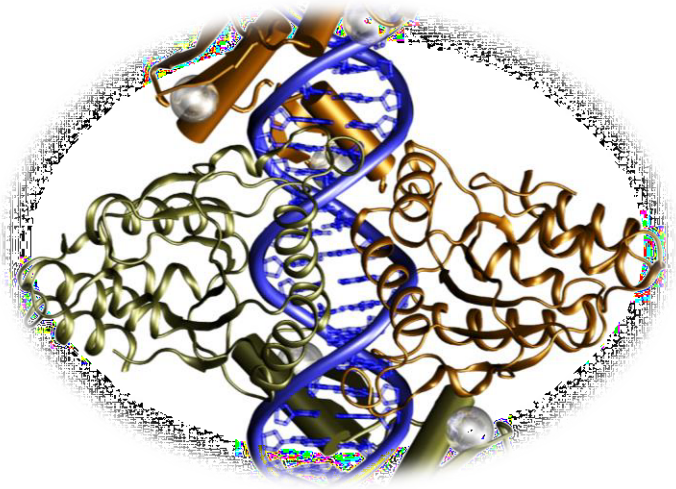

**Protocol Number:** SB-913-1602

**BB-IND:** 17006

**EudraCT:** 2018-000192-33

**Sponsor:** Sangamo Therapeutics, Inc.
7000 Marina Blvd.
Brisbane, CA 94005
Phone: (510) 970-6000
Fax: (510) 970-6009

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**Sponsor:** Sangamo Therapeutics, Inc.
7000 Marina Blvd
Brisbane, CA 94005
Phone: (510) 307-7296
Fax: (510) 970-6009

**Medical Monitor:** Weston Miller, M.D.
Phone: (510) 307-7296
Fax: (510) 323-7519
wmiller@sangamo.com

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**Amendment 6:** November 02, 2018
**Amendment 7:** December 12, 2019

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This study will be conducted in compliance with the protocol, the International Council for Harmonisation (ICH) Guidelines, Good Clinical Practices, and applicable regulatory requirements, including the U.S. Code of Federal Regulations.

# Sangamo Therapeutics, Inc.

## Clinical Approval Signature Page

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_____ _____

Weston Miller, M.D.
Medical Director
Sangamo Therapeutics, Inc.

Date

_____ _____

Didier Rouy, M.D., Ph.D.
Protocol Review Committee Chair
Sangamo Therapeutics, Inc.

Date

# Sangamo Therapeutics, Inc.

## Investigator Agreement Page

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I have read all pages of this clinical study protocol for which Sangamo Therapeutics, Inc. is the Sponsor. I agree to conduct the study as outlined in the protocol, and to comply with all terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH guidelines and applicable local regulations. I will ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH guidelines to enable them to work in accordance with the provisions of these documents.

_____ _____

Investigator Signature Date

_____

Investigator Printed Name

_____

Site Name

_____

Site Address

## TABLE OF CONTENTS

## LIST OF FIGURES

# LIST OF TABLES

| SB-913-1602 Study Protocol Synopsis | |
|---|---|
| **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)** | |
| **Sponsor** | Sangamo Therapeutics, Inc. |
| **Investigational Products** | SB-913 is a combination of 3 recombinant adeno-associated virus serotype 2/6 (rAAV2/6) vectors that encode:<br>• ZFN 1 (SB-47171): Left-side zinc finger nuclease (ZFN) that targets base pairs 447-461 of the albumin locus relative to the transcription initiation site, labeled as SB-A6P-ZLEFT.<br>• ZFN 2 (SB-47898): Right-side ZFN that targets base pairs 468-485 of the albumin locus relative to the transcription initiation site, labeled as SB-A6P-ZRIGHT.<br>• hIDS Donor (SB-IDS): DNA repair template that encodes a promotorless human iduronate-2-sulfatase (hIDS) transgene, labeled as SB-A6P-HNT. |
| **Study Sites** | Approximately 12 to 15 sites worldwide. |
| **Study Design** | Multicenter, open-label, single-dose, dose-ranging study with sequentially enrolled age cohorts: age $\geq$18 (adult cohorts 1 through 4), age 12-17 (pediatric cohorts 5 and 6), and age 5-11 (pediatric cohorts 7 and 8). |
| **Study Rationale** | Mucopolysaccharidosis type II (MPS II, Hunter Syndrome) is a recessive, X-linked, lysosomal storage disease caused by deficiency of iduronate-2-sulfatase (IDS). IDS is an enzyme that is required for the degradation of the glycosaminoglycans (GAGs) dermatan sulfate (DS) and heparan sulfate (HS). Deficiency of IDS is the result of mutations in the gene encoding IDS. The deficiency results in an inability by affected individuals to degrade GAGs, which in turn leads to accumulation of GAGs within lysosomes throughout the body, with consequent multi-organ dysfunction and damage. Affected individuals may develop developmental and neurocognitive delay, hepatosplenomegaly, valvular heart disease, upper airway obstruction, joint stiffness, skeletal deformities, and hearing loss.<br>MPS II has a diseases spectrum that spans from early onset, severe disease with somatic and cognitive involvement, to attenuated disease with later onset of somatic manifestations and little or no central nervous system (CNS) involvement, wherein clinical severity depends on the nature of the mutation in the IDS gene and the degree of residual IDS enzyme activity.<br>MPS II is currently treated with enzyme replacement therapy (ERT) using Elaprase® (idursulfase) or equivalent. ERT has been shown to improve pulmonary function, hepatosplenomegaly, and exercise capacity. However, limitations of ERT include the need for life-long treatment; development of neutralizing antibodies; inability to cross the blood brain barrier (with consequent lack of efficacy in the brain); continued cardiac, musculoskeletal, and upper airway complications; and the inconvenience of weekly intravenous (IV) infusions. Hematopoietic stem cell transplantation has been attempted to |

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| | limit the neurologic deterioration, however, the procedure is associated with significant morbidity and the effectiveness of this course of treatment is unclear.<br>The present study uses ZFN gene-specific targeted insertion of a hIDS donor transgene into the liver albumin genome locus in subjects with MPS II to provide long-term production of hIDS. |
| **Objectives** | **Primary Objective:**<br>• To evaluate the safety and tolerability of SB-913.<br>**Secondary Objectives:**<br>• To evaluate change from Baseline over time in the following assessments:<br>o IDS activity in blood.<br>o GAG testing in urine.<br>o Frequency of ERT administration.<br>• AAV2/6 clearance.<br>**Exploratory Objectives**:<br>• To evaluate change from Baseline over time in the following assessments:<br>o GAG testing in tissues (including blood, liver tissue, and cerebrospinal fluid [CSF]).<br>o Gene modification at the albumin locus in the liver.<br>o Imaging, functional, and neurocognitive testing related to MPS II.<br>o Immune response to AAV 2/6, ZFNs and IDS.<br>From consenting subjects, residual samples may be used for future research objectives. |
| **Endpoints** | **Primary Endpoint:**<br>• Incidence of treatment-emergent AEs (including SAEs).<br>• Additional safety evaluations include:<br>o Routine hematology, chemistry and liver function laboratory tests, vital signs, physical exam, electrocardiogram (ECG), echocardiogram (ECHO), and concomitant medications.<br>o Cranial nerve exam and muscle strength testing.<br>o Serial α-fetoprotein (AFP) testing and magnetic resonance imaging (MRI) of liver to evaluate for liver mass.<br>**Secondary Endpoints:**<br>• Change from Baseline in:<br>o IDS activity measured in blood.<br>o Total GAG, DS GAG, and HS GAG levels (expressed as ratio to creatinine) measured in urine.<br>o Monthly and annualized frequency and dose of idursulfase (or equivalent ERT).<br>• AAV2/6 clearance measured by vector genomes in plasma, saliva, urine, stool, and semen by PCR. |

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| | **Exploratory Endpoints:**<br>• Change from Baseline in:<br>o Total GAG, DS GAG, and HS GAG levels measured in tissues (including blood, liver tissue, and CSF).<br>o Percentage and durability of gene modification at the albumin locus in liver tissue obtained at biopsy.<br>o Forced vital capacity measured by pulmonary function tests (PFTs)<br>o Distance walked measured by six-minute walk test (6MWT).<br>o Joint range of motion (JROM).<br>o MRI of liver to evaluate liver and spleen volume.<br>o MRI of brain and cervical spine to evaluate clinical soft tissue and/or bone<br>o 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).<br>o Histopathological exam of liver tissue.<br>o Immune response to AAV 2/6, ZFNs, and IDS measured in serum. |
| **Study Population** | Subjects with MPS II disease, sequentially enrolled in 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). |
| **Number of Subjects** | Up to 32. |
| **Inclusion & Exclusion Criteria** | **Inclusion Criteria**<br>1. Signed informed consent.<br>2. ≥5 years of age:<br>a. Adult cohorts 1 through 4: ≥18 years of age;<br>b. Pediatric cohorts 5 and 6: 12 to 17 years of age; and<br>c. Pediatric cohorts 7 and 8: 5 to 11 years of age.<br>3. Clinical diagnosis of MPS II (based on evidence of hepatosplenomegaly, dysostosis multiplex by X-ray, valvular heart disease, or obstructive airway disease); IDS deficiency confirmed by gene sequencing.<br>4. Sexually mature subjects must agree to use a barrier contraceptive method for prevention of AAV transfer as follows: for female subjects this means that the subjects' partners must use a condom from dosing with SB-913 and until at least 3 consecutive plasma samples after administration of SB-913 are negative for AAV2/6; for male subjects this means that the subjects must use a condom and must refrain from sperm donation from the time of SB-913 administration until at least 3 consecutive semen samples after administration of SB-913 are negative for AAV2/6. In addition, female participants of child-bearing potential must consent to use a highly effective method of contraception.<br>5. MRI negative for liver mass as read by a radiologist. |

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| | **Exclusion Criteria**<br>1. Known to be unresponsive to ERT.<br>2. Neutralizing antibodies in serum (immune response) to AAV2/6.<br>3. Serious intercurrent illness or clinically significant organic disease (unless secondary to MPS II) such as cardiovascular, hepatic, pulmonary, neurologic, or renal disease.<br>4. Receiving antiviral therapy for hepatitis B or C, or with active hepatitis B (HBV DNA positive or HBV surface antigen positive) or hepatitis C (HCV RNA viral load) or human immunodeficiency virus (HIV)-1/2 (HIV RNA viral load or HIV antibody positive); to be considered negative for hepatitis C after treatment of an active HCV infection, viral assays in 2 samples collected at least 6 months apart must be negative.<br>5. Lack of tolerance to idursulfase treatment with significant infusion-associated reactions (IARs) or occurrence of anaphylaxis.<br>6. Polymorphisms in the ZFN-targeted region of the albumin locus.<br>7. Liver fibrosis score of 3 or 4 on a 0 to 4 point scale (Desmet et al. 1994) if subject has had a liver biopsy within 2 years of Screening.<br>8. Markers of hepatic dysfunction as evidenced by one or more of the following:<br>a) Platelet count <100,000/µL<br>b) Albumin ≤3.2 g/dL<br>c) Total bilirubin >1.5 x upper limit of normal (ULN) and direct bilirubin ≥0.5 mg/dL<br>d) Alkaline phosphatase >2.0 x ULN<br>e) ALT or AST >2.0 x ULN<br>9. Creatinine ≥ 1.5 mg/dL<br>10. Weight < 20 kg at Screening visit.<br>11. Pregnant or breastfeeding female.<br>12. Contraindication to the use of corticosteroids.<br>13. Current treatment with systemic (IV or oral) immunomodulatory agent or steroid use (topical treatment allowed, e.g., for asthma or eczema).<br>14. History of active malignancy in past 5 years (non-melanoma skin cancer or cervical cancer *in situ* permitted).<br>15. Participation in prior investigational drug or medical device study within the previous 3 months.<br>16. Prior treatment with a gene therapy product.<br>17. History of alcohol or substance abuse that in the opinion of the Principal Investigator may interfere with study compliance.<br>18. History of therapeutic non-adherence.<br>19. Elevated or abnormal circulating AFP.<br>20. Any other reason that, in the opinion of the Principal Investigator or Medical Monitor, would render the subject unsuitable for participation in the study. |

**Dose & Rationale for Dose Selection**

The doses to be evaluated were selected based on results of studies in non-human primates and emerging human safety data from this study. Current nonclinical data support the use of a 1:1:8 ZFN1:ZFN2:hIDS Donor ratio. The configurations of ZFNs and hIDS Donor rAAV2/6 vectors for the doses are illustrated in the table below.

| 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+13 | 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 |

**Treatment Plan & Schedule**

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

| Cohort # | Age Range (y) | 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. Review by an independent, external Safety Monitoring Committee (SMC) 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 (see Section 12.3). 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 (see Pediatric Dosing).

Approximately 2 additional subjects may be added to any cohort after SMC review of study data if safety criteria are met (see Safety Monitoring Committee), with up to a total of 32 subjects in the study.

Subjects who received ERT prior to study enrollment will continue to receive ERT during the study and remain on their current schedule per standard of care unless they undergo ERT withdrawal (see ERT Withdrawal). However, ERT will be omitted during the week of the SB-913 infusion to facilitate accurate baseline testing (e.g.; of GAG levels in urine, and of IDS activity in blood) and to allow a week free of ERT after the SB-913 infusion.

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| | To minimize the potential immune response to the AAV capsid protein, the engineered ZFNs, or the endogenous hIDS, and to preserve hepatic function, prednisone or equivalent corticosteroid will be administered prophylactically starting 2 days prior to SB-913 infusion and will be tapered over a period of approximately 20 weeks (see Appendix 3).<br><br>The 3 components of SB-913 (ZFN1, ZFN2, and hIDS Donor) will each be added to 200 mL of diluent (refer to the Pharmacy Manual) and adjusted to 0.25% human serum albumin. Total infusion volumes will depend on the subject's cohort assignment and body weight (kg). IV infusions will be administered while the subject is in the hospital or acute care facility (refer to the Pharmacy Manual). The subject will remain in the hospital or acute care facility for at least 24 hours after completion of 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.<br><br>After being discharged from the hospital or acute care facility, study visits are scheduled on Day 7; Weeks 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52; and Months 15, 18, 21, 24, 27, 30, 33, and 36.<br><br>Liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total and direct bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), albumin, and total protein levels) will be conducted for evaluation of AAV-mediated immunogenicity twice a week during the first 20 weeks after SB-913 infusion and may be conducted at home if the subject is remote. Blood samples for liver function tests will be drawn 2-4 days apart when possible, except for the first week when they will be drawn on the Day 1 and Day 7 visits. Liver function tests will subsequently be conducted at all study visits.<br><br>If, in spite of pretreatment with prednisone or equivalent corticosteroid, there is evidence of transaminitis, the dose of prednisone or equivalent corticosteroid will be increased on a case-by-case basis, and liver function will be assessed twice a week until normalization of liver enzymes, and then per protocol thereafter. |
| **Dose Escalation** | Within each cohort, treatment will be staggered so that each subsequent subject will not be infused until the preceding subject has been observed for at least 4 weeks.<br><br>Dose escalation to the next cohort will not occur until at least 4 weeks after the last subject in the preceding cohort has been dosed and the safety data from the prior cohort has been reviewed by the SMC and the SMC has agreed to dose escalate.<br><br>Dosing and dose escalation will be paused if a Grade 3 or higher AE occurs, or if two Grade 2 AEs occur within the same organ class and persist for 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. In such an event, the SMC will be convened to assess for potential dose-limiting toxicity (DLT) and to provide recommendations on whether to expand the cohort at the same dose level, to dose de-escalate, or to continue the study as planned (refer to the Stopping Rules). |

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| **Pediatric Dosing** | Pediatric dosing will not be initiated until adult safety data has been obtained and reviewed by the SMC, and only after the following conditions have been met:<br>• ≥6 months of safety data from 2 adults treated with SB-913 at any dose; and<br>• ≥4 weeks of safety data from 2 adults treated with SB-913 at the intended pediatric dose.<br>Younger pediatric subjects (Cohorts 7 and 8) will not be dosed until older pediatric subjects (Cohorts 5 and 6) have been dosed at the same dose level and ≥4 weeks of safety data from each older subject has been reviewed by the SMC. |
| **ERT Withdrawal** | The goal of SB-913 treatment is to abrogate or decrease the need for enzyme replacement therapy, by using engineered zinc finger nucleases (ZFNs) to site-specifically integrate a corrective copy of the enzyme iduronate-2-sulfatase (hIDS) transgene into the genome of the subject's own hepatocytes in vivo, resulting in life-long, liver-specific expression of IDS. Therefore, subjects who have received SB-913 may no longer require weekly administration of ERT, and may be considered for withdrawal of ERT (if applicable).<br>ERT withdrawal will be a controlled process with additional safety monitoring to reduce potential risk to the subject, and is an optional part of the study.<br>ERT withdrawal may be initiated by the Principal Investigator after consultation with the Sponsor, and only in subjects who are willing and who meet all of the following criteria:<br>• Are ≥12 weeks post-administration of SB-913.<br>• Are medically stable and can tolerate temporary discontinuation of ERT in the judgement of the Principal Investigator.<br>• Agree to additional safety monitoring and lab testing until ERT Withdrawal Follow-Up visit (see Appendix 2).<br>ERT does not need to be restarted after the ERT Withdrawal Follow-Up visit. However, ERT may be re-initiated at any time based on clinical circumstances or at the judgement of the Principal Investigator. |
| **Study Duration** | The duration of 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.<br>Upon completion of the study, subjects will be asked to participate in a separate Long-term Follow-Up (LTFU) Study to monitor the long-term safety of SB-913. To alleviate study burden, study subjects may participate in the LTFU Study after at least 12 months of follow-up in this study. 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. |
| **Safety Monitoring Committee** | An external SMC with appropriate medical and scientific expertise will provide advice to Sangamo regarding patient safety throughout the study. The SMC will be convened after completion of each cohort to determine if 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 |

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| | are excessive or unexpected toxicities associated with the conduct of the protocol. Specifically, the SMC will be convened if the following occurs:<br>• 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.<br>• SAE not related to the primary MPS II disease.<br>• Death of a subject.<br>• Development of a malignancy.<br>The SMC will then evaluate all data to determine if changes should be made to the study or if accrual should be halted.<br>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.<br>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. |
| **Safety Monitoring & Mitigation Plan** | The liver function (total and direct bilirubin, alkaline phosphatase, ALT, AST, LDH, albumin, and total protein) of subjects will be monitored closely throughout the study.<br>Key potential anticipated risks are:<br>• Development of transaminitis due to cell-mediated immunity to the AAV capsid protein, the engineered ZFNs, or the endogenous IDS; to minimize the potential immune response and to preserve hepatic function, prednisone or equivalent corticosteroid will be administered prophylactically starting 2 days prior to SB-913 infusion and will be tapered over approximately 20 weeks (see Appendix 3).<br>• Reduction in albumin synthesis; this is not expected given the small fraction (<1%) of transduced cells in which the albumin locus will be disrupted, and has not been observed in animal studies in which levels of transduction and albumin locus disruption exceeded by several fold those expected in humans.<br>• Off-target modification at the structural maintenance of chromosomes flexible hinge domain containing 1 (SMCHD1) locus; this is not expected given that no off-target activity has been observed at clinically relevant levels of albumin on-target activity in human cells *in vitro*. |

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| **Stopping Rules** | The SMC will be convened to assess whether changes should be made to the study or whether the study should be stopped if any of the following criteria are met:<br>• Completion of a cohort.<br>• 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.<br>• SAE not related to the primary MPS II disease.<br>• Death of a subject.<br>• Development of a malignancy.<br>The study may also be stopped for any of the following reasons:<br>• Sangamo Therapeutics, Inc. (Sangamo), in consultation with the SMC or Regulatory Agency, decides for any reason that subject safety may be compromised by continuing the study.<br>• Sangamo decides to discontinue development of SB-913.<br>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. |
| **Sample Size** | This study will enroll up to a total of 32 subjects (2 subjects in each of 8 cohorts, with potential enrollment of approximately 2 additional subjects in any cohort). To obtain an evaluable sample size, subjects who prematurely discontinue the study prior to the 12 months of study follow-up (i.e., subjects who were enrolled but not dosed, or were lost to follow-up) may be replaced at the discretion of Sangamo. |
| **Statistical Methods** | The primary objective of this study is to evaluate the safety and tolerability of SB-913. All statistical summaries will be descriptive in nature (e.g., means, standard deviations, and percentages). All subjects who receive any portion of the SB-913 infusion will be included in the analyses, even those who withdraw prematurely from the study. All results will be presented separately for each of the SB-913 dose levels. All analyses, summaries, and listing will be performed using SAS version 9.2 or later.<br>**Primary Safety Analyses**<br>Treatment-emergent AEs will be summarized overall and by treatment cohort. For each subject, the maximum reported severity of each AE will be used in the summaries by severity grade. In addition, all SAEs and AEs related to study treatment will be summarized.<br>Laboratory data will be summarized for each time-point at which specimens are collected. Change-from-Baseline values may be calculated for selected laboratory parameters. Shift-tables (Change-from-Baseline relative to the normal range) may be constructed for selected laboratory parameters. |

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| | **Secondary Analyses**<br>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.<br>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 annualized total dose and number of infusions. Duration of ERT withdrawal may also be analyzed.<br>AAV2/6 clearance measured by vector genomes in the different samples will be plotted over time by treatment cohort. |

## ABBREVIATIONS

| | |
|---|---|
| AAV | adeno-associated virus |
| AAV2/6 | adeno-associated virus serotype 2/6 |
| ACTH | adrenocorticotropic hormone |
| AE | adverse event/experience |
| AFP | α-fetoprotein |
| ALT | alanine aminotransferase (SGPT) |
| ANOVA | analysis-of-variance |
| AR | adverse reaction |
| AST | aspartate aminotransferase (SGOT) |
| BSC | BioSafety Committee |
| BSID-III | Bayley Scales of Infant Development |
| CNS | central nervous system |
| CRF | case report form |
| CSF | cerebrospinal fluid |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | dose-limiting toxicity |
| DNA | deoxyribonucleic acid |
| DS | dermatan sulfate |
| DSB | double-strand break |
| ECG | electrocardiogram |
| ECHO | echocardiogram |
| eCRF | electronic CRF |
| ELISA | enzyme linked immunoassay |
| EOS | End of Study |
| ERT | enzyme replacement therapy |
| ETV | early termination visit |
| FDA | Food and Drug Administration |
| FIX | Factor IX |
| FSHD | facioscapulohumeral muscular dystrophy |
| GAG | glycosaminoglycan |
| HBV | hepatitis B virus |
| HCC | hepato-cellular carcinoma |
| HCV | hepatitis C virus |
| HDR | homology-directed repair |
| HEENT | head, eyes, ears, nose, and throat |
| hFIX | human Factor IX |
| HIV | human immunodeficiency virus |
| hIDS | human IDS |
| HS | heparan sulfate |
| IAR | infusion-associated reaction |
| IATA | International Air Transport Association |
| ICH | International Council for Harmonisation |
| IDS | iduronate-2-sulfatase |
| IEC | institutional ethics committee |
| IRB | institutional review board |

| | |
|---|---|
| ITR | inverted terminal repeat |
| IV | intravenous |
| JROM | joint range of motion |
| LDH | lactate dehydrogenase |
| LTFU | long-term follow-up |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MPS II | Mucopolysaccharidosis II |
| MRI | magnetic resonance imaging |
| mRNA | messenger RNA |
| NHEJ | non-homologous end-joining |
| NIH | National Institutes of Health |
| OHR | Office for Human Research |
| PBS | phosphate buffered saline |
| PCR | polymerase chain reaction |
| PFT | pulmonary function test |
| rAAV | recombinant adeno-associated virus |
| rAAV2/6 | recombinant adeno-associated virus serotype 2/6 |
| RNA | ribonucleic acid |
| RSI | reference safety information |
| SAE | serious adverse event |
| SMC | Safety Monitoring Committee |
| SMCHD1 | structural maintenance of chromosomes flexible hinge domain containing 1 |
| SNP | single-nucleotide polymorphism |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent AE |
| ULN | upper limit of normal |
| VABS-II | Vineland Adaptive Behavior Scales |
| vg | viral genomes |
| WASI-II | Wechsler Abbreviated Scale of Intelligence, Second Edition (Shapiro et al. 2015) |
| WPPSI-IV | Wechsler Preschool and Primary Scale of Intelligence |
| ZFN | zinc finger nuclease |
| ZFP | zinc finger protein |
| 6MWT | 6-minute walk test |

# 1. INTRODUCTION

## 1.1 Mucopolysaccharidosis II

Mucopolysaccharidosis type II (MPS II), also referred to as Hunter Syndrome, is an X-linked, recessive lysosomal storage disorder that predominantly affects males (Burton & Giugliani 2012). The incidence of MPS II is reported as 0.3 to 0.71 per 100,000 live births (Burton & Giugliani 2012). Applying the more conservative median life expectancy of 21.7 years for the attenuated form of the disease (the life expectancy for the severe form of the disease is 11.8 years; Burrow et al. 2008; Young & Harper 1982) to the yearly incidence yields an estimated prevalence of about 629 individuals with MPS II currently living in the US.

MPS II is associated with mutations in the gene encoding iduronate-2-sulfatase (IDS). The IDS gene maps to genomic location Xq28, and comprises 9 exons spread over 24 kb. The IDS enzyme degrades the glycosaminoglycans (sulfated carbohydrate polymers; GAGs) dermatan sulfate (DS) and heparan sulfate (HS). Mutations in the IDS gene diminish or eliminate IDS enzyme activity, which results in the accumulation of toxic GAGs in urine and body tissues, with consequent multi-organ dysfunction and damage.

Depending on the specific type of IDS mutation (more than 150 different mutations have been described) and the level of the resulting residual IDS enzyme activity, patients will develop either the early onset, severe disease with somatic and cognitive involvement, or the attenuated disease with later onset of somatic manifestations and little or no central nervous system (CNS) involvement (Sukegawa-Hayasaka et al. 2006). Major deletions and rearrangements in the IDS gene are always associated with the severe form of the disease.

It has been estimated that about two-thirds of all MPS II patients present with the severe form of the disease. These patients start to show physical and neurocognitive developmental delays between 18 months and 3 years of age. Other symptoms include hepatosplenomegaly, hyperactivity, aggressiveness, neurologic deterioration, joint stiffness, skeletal deformities (including abnormal spinal bones), coarse facial features with enlarged tongue, heart valve thickening, upper airway obstruction, hearing loss, and hernias. The life expectancy of untreated patients is mid-teenage years, with death typically resulting from neurologic deterioration and/or cardiorespiratory failure.

Patients with the attenuated forms of the disease share most of these clinical manifestations but with less severe symptoms and slower disease progression. In addition, there is no or only mild CNS involvement. Death in untreated patients typically occurs at 20-30 years, and typically results from cardiac or respiratory disease.

The only approved therapy for MPS II is enzyme replacement therapy (ERT; using Elaprase, [idursulfase] or equivalent). In contrast to MPS I, hematopoietic stem cell transplantation has shown to have limited efficacy (Martin et al. 2008). ERT has been shown to improve pulmonary function, hepatosplenomegaly, and exercise capacity, and to lead to improved health-related quality of life. Response to ERT depends on the severity of disease at the time of treatment initiation (Muenzer et al. 2012). Drawbacks of ERT include the need for life-long treatment; development of neutralizing antibodies; inability to cross the blood brain barrier (with consequent lack of efficacy in the brain); continued cardiac, musculoskeletal, and upper airway complications; and the inconvenience of weekly intravenous (IV) infusions. These drawbacks underscore the urgent need to develop a broader array of curative therapies for MPS II.

The objective and rationale for the proposed SB-913 investigational therapy is to abrogate or decrease the need for ERT using *in vivo* genome editing. The proposed treatment employs recombinant adeno-associated virus (rAAV) comprising engineered zinc finger nucleases (ZFNs) to site-specifically integrate a corrective copy of the human IDS (hIDS) gene into the genome of subjects' own hepatocytes *in vivo*. Integration of the hIDS transgene is targeted to intron 1 of the albumin locus, resulting in stable, high level, liver-specific expression and secretion of hIDS into the blood. Placement of the hIDS transgene under the control of the highly expressed endogenous albumin locus is expected to provide life-long, liver-specific expression of hIDS in MPS II patients.

## 1.2 Development of Zinc Finger Nucleases for Genome Editing

ZFNs are proteins developed for genome editing. They combine the DNA recognition specificity of zinc finger proteins (ZFPs) with the nuclease domain of the type IIS restriction endonuclease *FokI* to create double-strand breaks (DSBs) at pre-determined target sites in the genome. Repair of the DSBs typically leads to the introduction of mutations that result in functional knockouts of the target gene products.

ZFPs contain tandem arrays of Cys2-His2 zinc fingers, each recognizing approximately 3 base pairs of DNA. The *FokI* nuclease domain has no sequence specificity, and must dimerize to cut DNA. Consequently, DNA cleavage activity is achieved by 2 independent ZFNs consisting of ZFPs directed to adjacent sequences in the correct spatial orientation (i.e., on opposite sides of the DNA with 5 or 6 base pairs of sequence between the recognition sites), each bound to a *FokI* nuclease.

Sangamo Therapeutics, Inc. (Sangamo) has engineered a ZFN pair consisting of a 5-finger (SB-47171) ZFP and a 6-finger (SB-47898) ZFP that bind with an adjacent 33 base pairs (combined) site on intron 1 of the human albumin locus. Following the DSBs created by the *FokI* nuclease domain, the DNA can be repaired by either homology-directed repair (HDR) or non-homologous end-joining (NHEJ). The co-delivery of a DNA repair template encoding the hIDS transgene for insertion at the break results in the targeted integration of the transgene into intron 1 of the human albumin locus (see Figure 1).

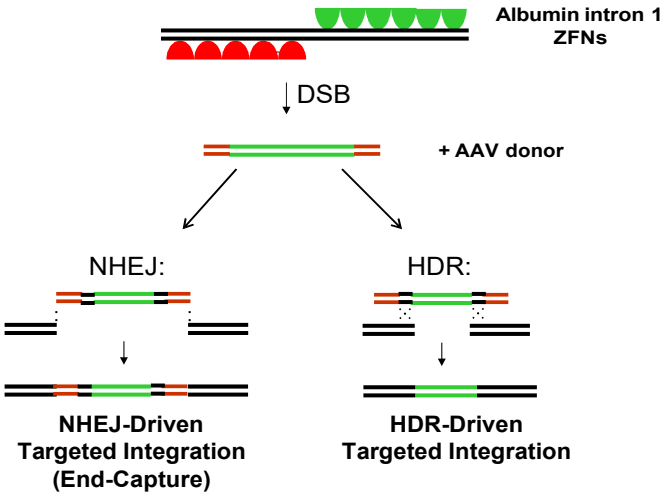



**Figure 1. ZFN-Induced DSBs Stimulate Targeted Integration of an AAV Donor via NHEJ or HDR.**

## 1.3 Pharmacology Studies with SB-913

### 1.3.1 *In vitro* Studies

A series of studies using mouse, non-human primate, or human primary hepatocytes and a human hepatoma cell line were conducted to demonstrate that species-specific albumin ZFNs and hIDS Donor rAAV2/6 vectors can affect site-specific integration at the albumin locus and expression and secretion of active hIDS.

A study using HepG2 subclones characterized the hIDS transcripts generated by either NHEJ or HDR following transduction of the cells with SB-913. The HepG2 subclones were also used to examine hIDS enzymatic activity, intracellular processing, and enzyme secretion and uptake ability by human primary hepatocytes mediated by post-translational modification-like glycosylation.

#### 1.3.1.1 Pharmacologic Activity in Murine and Cynomolgus Monkey Hepatocytes

Surrogate mouse or non-human primate ZFNs and hIDS Donor with mouse or non-human primate homology arms were tested in primary mouse or cynomolgus monkey hepatocytes *in vitro*. Following transduction, both mouse and cynomolgus monkey hepatocytes secreted active hIDS into the culture supernatant.

#### 1.3.1.2 Pharmacologic Activity in Human Hepatocytes

SB-913 was tested *in vitro* in 2 human hepatocyte systems: primary human hepatocytes and the human hepatoma cell line HepG2. As shown in Figure 2, following SB-913 transduction, both cell systems secreted active hIDS into the culture supernatant.

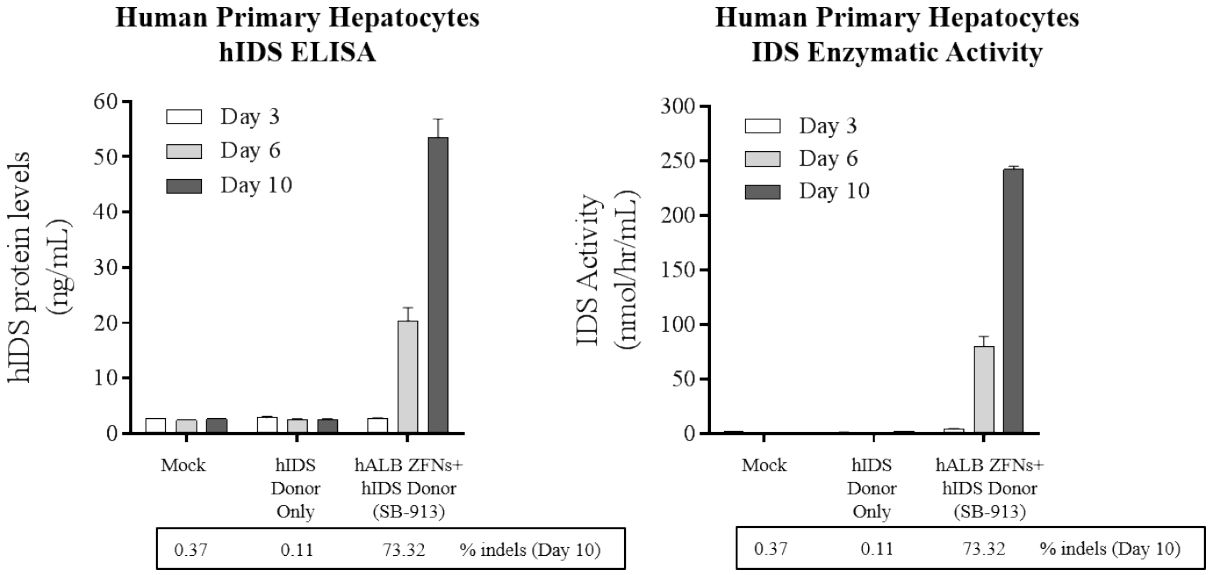



**Figure 2. Human IDS (hIDS) Levels and Activity in Supernatants of SB-913-treated Human Primary Hepatocytes.**

Human primary hepatocyte cultures were treated with hIDS Donor only (1.2e6 vg/cell) or SB-913 (6e5 for each ZFN + 1.2e6 hIDS Donor). hIDS was measured by ELISA and enzymatic activity assay after 3, 6, and 10 days of culture. Data are plotted as mean ± SD (n=2 for mock; n=3 each for hIDS Donor only and SB-913).

Subclones of transduced HepG2 were used for analysis of the transcription profile of the modified albumin locus. The data showed that only the expected human albumin-hIDS fusion mRNA transcript was expressed, and that the secreted hIDS protein was enzymatically active independent of the mechanism of integration by either NHEJ or HDR. The albumin allele without integrated hIDS expressed normal levels of wild-type albumin transcripts despite small indels at the ZFN cut site in albumin intron 1.

Characterization of the hIDS protein secreted from the HepG2 subclones showed that the hIDS protein was normally processed into the mature protein, having the expected normal glycosylation pattern, with a mix of high-mannose, hybrid, and complex oligosaccharides. High glycosylation allows the protein to be taken up by unmodified human primary hepatocyte cells, and then to be processed normally to the mature and active forms of hIDS, which results in a 7-10 fold increase of IDS activity.

These results demonstrated that SB-913 can transduce primary human hepatocytes and hepatoma cells, and introduce the hIDS transgene into the human albumin locus. And that after SB-913 transduction, human hepatocyte cells express, splice, and secrete highly active hIDS protein, which can be taken up by target cells and carry out its function in the lysosome.

### 1.3.2 *In vivo* Studies

The *in vivo* pharmacology studies included a 1-month proof-of-concept study in C57BL/6 male mice, a 3-month pilot study in 4-month old male MPS II mice, a 4-month hybrid pharmacology/toxicology study in 2-month old male MPS II mice, and a 90-day pilot pharmacology, biodistribution, and toxicology study in cynomolgus monkeys. A 1-month lot qualification study was also conducted in C57BL/6 mice.

For the 3 mouse studies, the AAV2/8 mouse surrogate ZFNs and hIDS Donor components were administered at a ratio of ZFN1:ZFN2:hIDS Donor of 1:1:8 (C57BL/6 and 4-month MPS II mouse) or 1:1:10 (3-month MPS II mouse). For the monkey study, the rAAV2/6 non-human primate surrogate ZFNs and hIDS Donor components were administered at a ratio of ZFN1:ZFN2:hIDS Donor of 1:1:8.

#### 1.3.2.1 Pharmacologic Proof-of-Concept in C57BL/6 Mice

Male mice were injected with either rAAV2/8 vectors encoding mouse albumin ZFNs and hIDS Donor (ZFN+Donor), or with the hIDS Donor only (Donor only). As shown in see Figure 3, Panel A, by Day 21 post-injection plasma hIDS enzymatic activity in the ZFN+Donor mice (38-220 nmol/hr/mL) was more than 100-fold above the normal physiological levels seen in wild-type or Donor only mice (0.5-1.5 nmol/hr/mL). When tissues from these mice were analyzed, the ZFN+Donor mice displayed 90-fold higher levels of IDS activity in the liver (where it is produced from the albumin locus; 154 ± 32.9 nmol/hr/mg) and 5-fold higher levels in the spleen (where it is taken up from the plasma; 18 ± 5.5 nmol/hr/mg) (see Figure 3, Panels B-C). The targeted integration of the hIDS transgene at the mouse albumin locus was confirmed by PCR analysis of liver genomic DNA (data not shown).

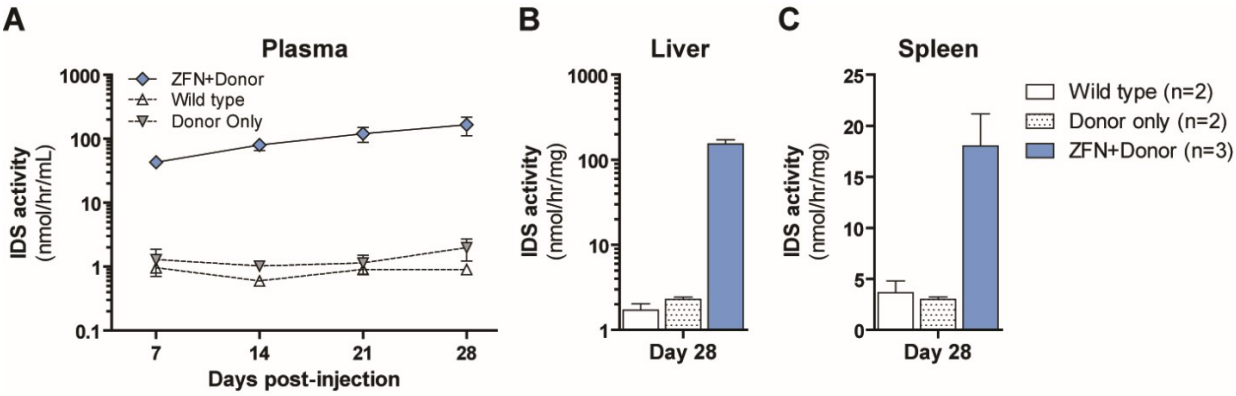



**Figure 3. ZFN-driven Targeting of hIDS to Mouse Albumin Intron 1 Results in Supraphysiological IDS Activity in the Liver, Plasma, and Spleen of Wild-type Mice.**

C57BL/6 wild-type mice (8-10 weeks old) were IV injected with 1.2e12 vg of the rAAV2/8 SB-mu-IDS Donor alone (Donor only) or together with 1.5.00E+11 of each rAAV2/8 mouse albumin ZFN vector (SB-48641+SB-31523; ZFN+Donor; total AAV dose was approximately 7.5.00E+13 vg/kg for a 20 gram mouse). IDS enzymatic activity was assayed at the indicated time points in plasma (**A**), liver (**B**), and spleen (**C**). Group size for plasma analysis: ZFN+Donor: n=12 at Day 7, n=6 at Days 14-21, n=3 at Day 28; Wild-type: n=6 at Day 7, n=4 at Day 14, n=at Day 21, n=2 at Day 28; Donor only: n=5 at Day 7, n=4 at Days 14-21, n=2 at Day 28. Group size decreases after Day 7 as subsets of mice were euthanized to allow for additional molecular characterization.

This 1-month proof-of-concept study demonstrated the ability of the mouse surrogate vectors to integrate and express the hIDS transgene from the mouse albumin locus in the liver *in vivo*. Upon integration, hIDS was expressed from the liver, secreted into the plasma, and subsequently taken up by secondary tissues in an active form.

### 1.3.2.2 3-Month Pharmacologic Proof-of-Concept in MPS II Mice

To demonstrate the feasibility of the therapeutic approach in a relevant disease model, a study was conducted in MPS II (IDS knockout) mice. Because MPS II is X-linked, only male mice were used for this study. The MPS II mouse model has been shown to exhibit phenotypic features typical for MPS II such as skeletal abnormalities, neurological deficits, shortened lifespan, and increased GAG levels in tissues and urine. The model has been successfully used to study ERT and AAV-mediated gene therapy (Muenzer et al. 2002; Cardone et al. 2006).

Adult male MPS II mice were injected with rAAV2/8 vectors encoding mouse albumin ZFNs and hIDS Donor (ZFN+Donor) or with hIDS Donor alone (Donor only). In contrast to wild-type and Donor only mice, ZFN+Donor mice showed levels of ZFN activity (as determined by deep sequencing of the mouse albumin locus) of 31-40% (Day 21) and 54-61% (Day 93) indels. In addition, IDS enzymatic activity was clearly increased in the ZFN+Donor mice, by Day 14 post-injection exceeded levels in wild-type mice by more than 100-fold (56 ± 22 nmol/hr/mL vs 0.55 ± 0.08 nmol/hr/mL), and remained elevated throughout the duration of the study (see Figure 4, Panel A). Liver IDS activity of ZFN+Donor mice (2366 ± 264 nmol/hr/mg) was 100-fold higher than in wild-type control mice (see Figure 4, Panel B), and elevated IDS activity was also detected in spleen (346 ± 60 nmol/hr/mg), heart (32 ± 10 nmol/hr/mg) and lungs (60 ± 12 nmol/hr/mg) (see Figure 4, Panel C).

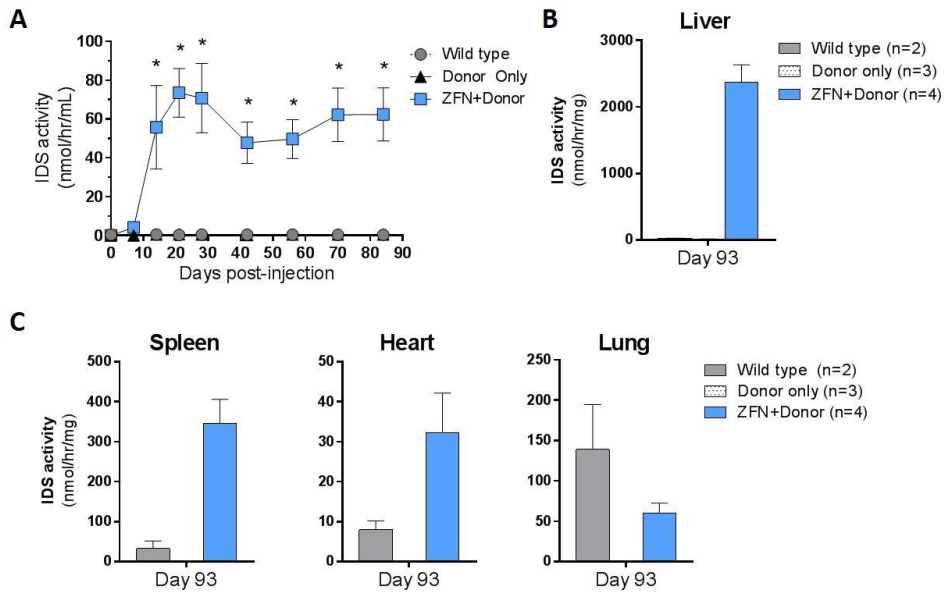



**Figure 4. ZFN-driven Targeting of hIDS to Mouse Albumin Intron 1 Results in High Levels of IDS Activity in the Liver, Plasma, and Tissues of MPS II Mice.**

MPS II mice (4 months old) were IV injected with 1.5.00E+12 vg/mouse of rAAV2/8 SB-mu-IDS donor alone (Donor only) or together with 1.5.00E+11 vg/kg of each rAAV2/8 mouse albumin ZFN vector (SB-31523+SB-48641; ZFN+Donor; total AAV dose = 9e13 vg/kg for a 20 gram mouse). **A.** Plasma was collected at the indicated time points and assayed for IDS activity. Group size for plasma analysis: ZFN+Donor: n=7 up to Day 21, n=4 thereafter; Wild-type: n=2; Donor only: n=5 up to Day 21, n=3 thereafter. Group size decreases after Day 21 as a subset of mice were euthanized to allow for additional molecular characterization. *p<0.0001 vs wild-type group (two-way repeated-measures analysis-of-variance [ANOVA] followed by Dunnett's multiple comparison test). **B. & C.** At necropsy (Day 93), tissues were collected, flash frozen, and later homogenized and assayed for IDS activity.

To assess the functional impact of this increase in IDS activity, levels of GAGs were analyzed in the mice. As shown in Figure 5, Panel A, urinary GAG levels were decreased in ZFN+Donor mice compared to Donor only and wild-type control mice. As shown in Figure 5, Panel B, reduced GAG levels were also observed in a variety of tissues in these mice.

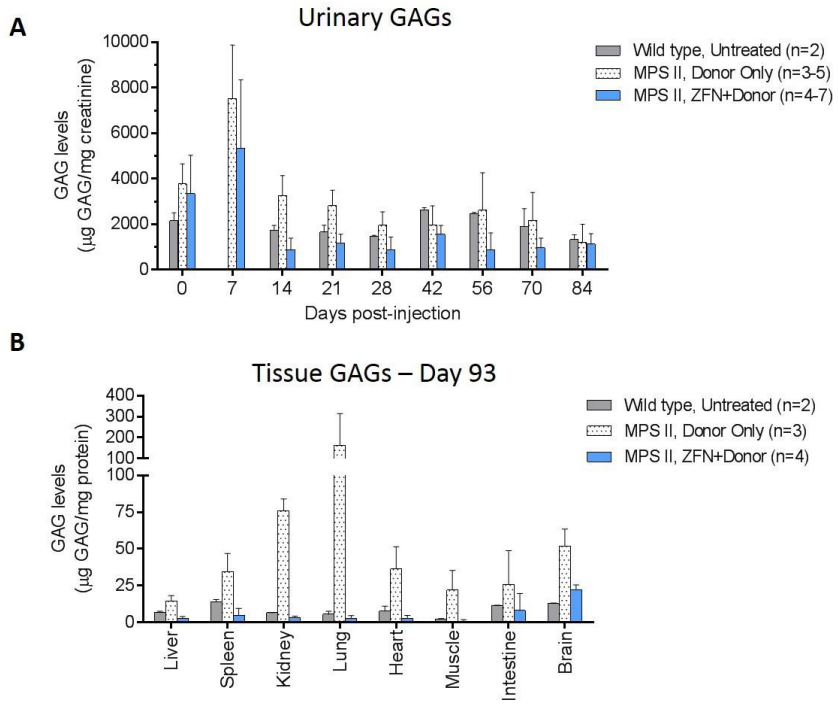



**Figure 5. ZFN-driven Targeting of hIDS to Mouse Albumin Intron 1 Results in GAG Biomarker Reduction in Urine and Tissues of MPS II Mice.**

Mice were treated as described for Figure 4. **A.** Urine was collected on the indicated days and assayed for GAG levels using the Blyscan GAG assay. Data represent mean ± SD. **B.** Tissues were harvested at necropsy on Day 93 post-dosing, and protein extracts were assayed for GAG levels using the Blyscan GAG assay. Data represent mean ± SD.

These data demonstrate ZFN-driven integration of the hIDS transgene into the mouse albumin locus in the liver *in vivo*, after which hIDS is expressed in the liver, secreted into the plasma and subsequently taken up by secondary tissues in an active form where it functionally corrects the IDS deficiency of MPS II mice.

#### 1.3.2.3 4-Month Pharmacologic Proof-of-Concept in MPS II Mice (Neurocognitive Preventive Model)

Although GAG accumulation in urine and tissues are evident in the MPS II (IDS knockout) mice at an early age, neurocognitive deficits only become apparent after 5 months of age. Therefore, a longer term study was conducted starting with younger animals.

Two-month old male MPS II mice were injected with rAAV2/8 vectors encoding mouse albumin ZFNs and hIDS Donor (ZFN+Donor) at escalating doses (see Table 1) or with hIDS Donor alone (Donor only). In contrast to wild-type mice, MPS II mice, and Donor only mice, ZFN+Donor mice showed levels of ZFN activity (as determined by deep sequencing of the mouse albumin locus) that increased with administered dose from 12.6 ± 3.6% indels (low dose) to 31.7 ± 3.5% indels (mid dose) to 49.3 ± 2.1% indels (high dose) at 1 month, and from 26.4 ± 3.6% indels (low dose) to 43.5 ± 5.6% indels (mid dose) to 56.0 ± 2.5% indels (high dose) at 4 months. In addition, IDS activity in plasma was clearly increased in the ZFN+Donor mice in a dose-dependent manner, exceeded levels in wild-type mice by more than 100-fold by Day 14 (61 ± 7 nmol/hr/mL vs 0.29 ± 0.03 nmol/hr/mL), and remained elevated throughout the duration of the study (see Figure 6, Panel A). Liver IDS activity in the high dose ZFN+Donor mice was more than 200-fold higher than in wild-type mice (5355 ± 1989 nmol/hr/mL vs 26 ± 2 nmol/hr/mL) (see Figure 6, Panel B), and elevated IDS activity was also detected in all secondary tissues examined, with at least one ZFN+Donor mouse surpassing wild-type levels in the spleen, kidney, heart, and muscle (see

Figure 6, Panel C). Significant increases of IDS activity were also observed in the ZFN+Donor high dose mice in the lung (36% of wild-type) and the brain (1.5% of wild-type).

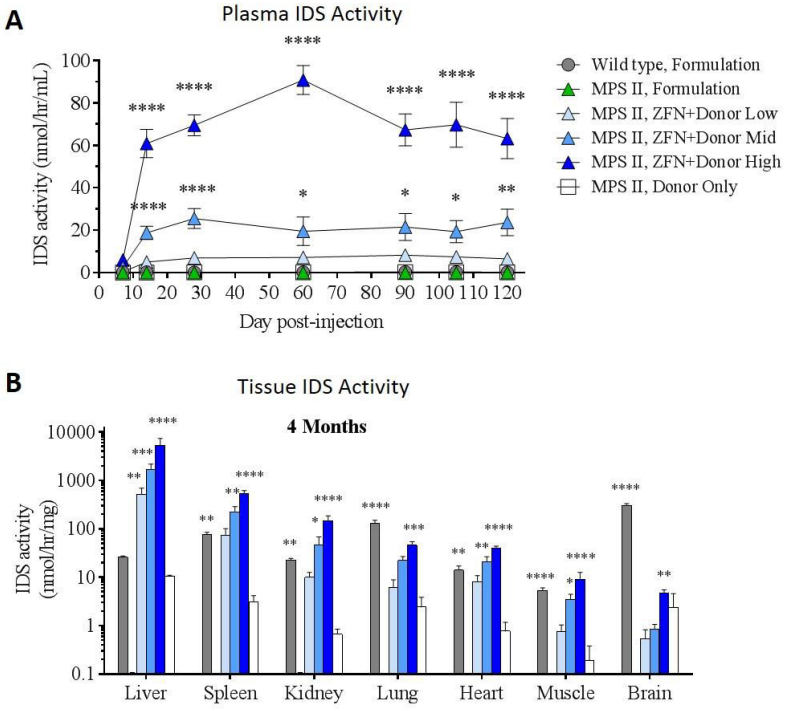



**Figure 6. ZFN-driven Targeting of hIDS to Mouse Albumin Intron 1 Results in High Levels of IDS Activity in the Liver, Plasma and secondary Tissues of MPS II Mice.**

Male MPS II mice (2 months old) were intravenously injected with rAAV2/8 SB-mu-IDS donor alone (Donor only) or together with rAAV2/8 mouse albumin ZFN vector (SB-31523+SB-48641; ZFN+Donor) at the doses indicated in Table 1**.** IDS enzymatic activity was assayed at the indicated time points in the plasma (A) and tissues (**B**). For IDS activity in plasma, data represent mean ± SEM of 4-13 animals/group. Animals No. 1323 and No. 1264 were excluded from the data analysis. *p<0.05, **p<0.01, ****p<0.0001 vs. wild-type group (two-way repeated-measures ANOVA followed by Dunnett's multiple comparison test). For tissue IDS activity, data represent mean ± SEM of 4-10 animals/group. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs. formulation-treated MPS II control group (Kruskal-Wallis test followed by Dunn's multiple comparisons test).

**Table 1. Dose Levels and Group Designations for 4-month MPS II Proof-of-Concept Study.**

| Group | Group Designation | Genotype | No. of Animals | Each ZFN Dose (vg/mouse) | IDS Donor Dose (vg/mouse) | Total AAV Dose (vg/mouse) | Total AAV Dose (vg/kg)[1] |
|---|---|---|---|---|---|---|---|
| 1 | Formulation buffer control | C57BL/6 (wild-type) | 13 | 0 | 0 | 0 | 0 |
| 2 | Formulation buffer control | MPS II | 13 | 0 | 0 | 0 | 0 |
| 3 | ZFN+Donor low dose | MPS II | 8 | 2.5e10 | 2.0e11 | 2.5.00E+11 | 1.25.00E+13 |
| 4 | ZFN+Donor mid dose | MPS II | 8 | 5.0e10 | 4.0e11 | 5.0e11 | 2.5.00E+13 |
| 5 | ZFN+Donor high dose | MPS II | 13 | 1.5.00E+11 | 1.2e12 | 1.5.00E+12 | 7.5.00E+13 |
| 6 | Donor Only | MPS II | 8 | 0 | 4.0e11 | 4.0e11 | 2.0e13 |

vg = vector genomes; [1]Total AAV dose (vg/kg) using an estimated 0.02 kg body weight.

To assess the functional impact of this increase in IDS activity, levels of GAGs were analyzed in the mice. As shown in Figure 7, Panel A, GAG levels in peripheral tissues were decreased in ZFN+Donor mice compared to Donor only MPS II mice and MPS II mice at 1 month post-dosing. As shown in Figure 7, Panels B & C, reduced GAG levels were also observed in a variety of peripheral tissues at 4 months post-dosing.

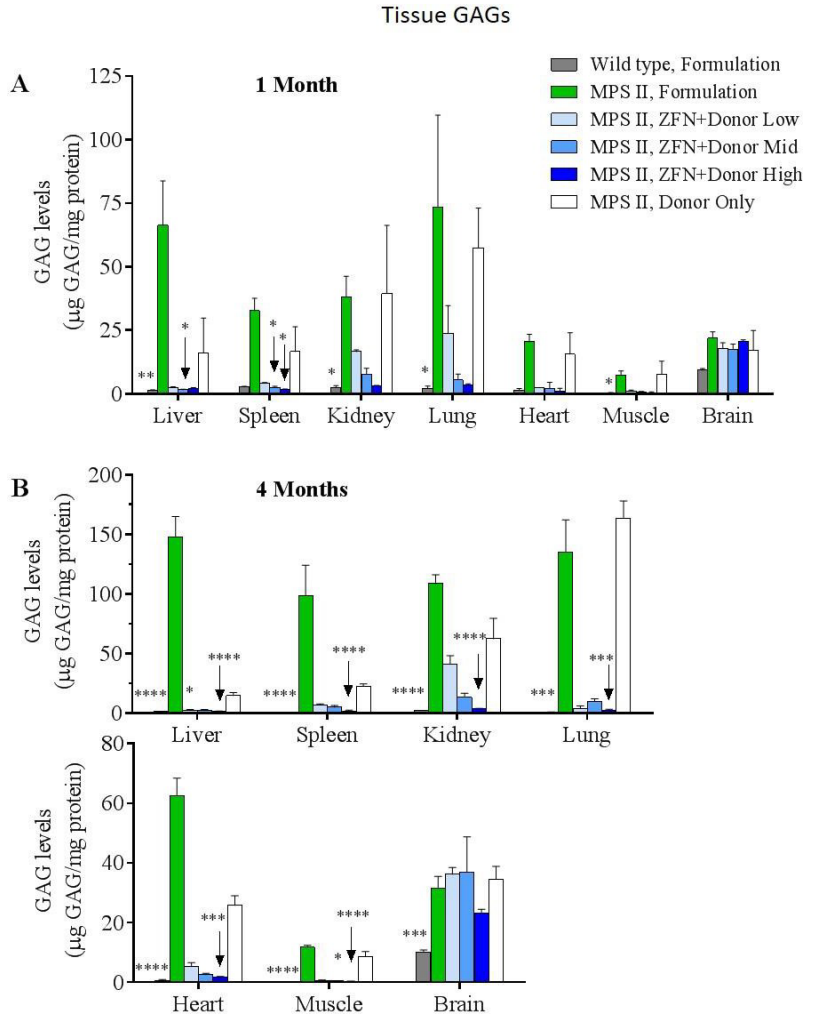



**Figure 7. ZFN-driven Targeting of hIDS to Mouse Albumin Intron 1 Results in GAG Biomarker Reduction in Tissues of MPS II Mice.**

Mice were treated as described for Figure 6. GAG levels were determined using the Blyscan GAG assay. Data represent mean ± SD of 2-3 animals/group (1 month) or mean ± SEM of 4-10 animals/group (4 months). *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs. the formulation-treated MPS II control group (Kruskal-Wallis test followed by Dunn's multiple comparisons test). Arrows indicate groups of low read-out.

The cognitive performance of the mice was tested during the final week prior to necropsy using the Barnes Maze Test, one of the cognitive tests in which MPS II mice have previously shown learning deficits. The mice were trained on the Barnes maze for 6 days, at 4 trials a day, with a maximum time limit of 3 minutes per trial and intervals between consecutive trials of 12-15 minutes per mouse. As shown in Figure 8, high dose ZFN+Donor mice performed significantly better than MPS II mice, and were statistically indistinguishable from wild-type mice.

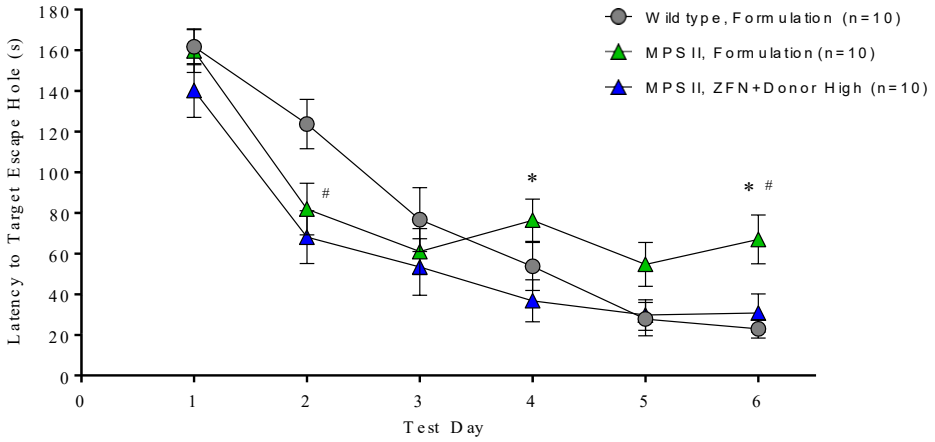



**Figure 8. ZFN-driven Targeting of hIDS to Mouse Albumin Intron 1 Results in Significant Cognitive Benefits in the Barnes Maze.**

Mice were treated as described for Figure 7. Cognitive performance was assessed using the Barnes maze test at ~4 months post-dosing. Data represent mean ± SEM of the time it took the animals to find the target escape hole (average of 4 trials each day) over 6 days of testing. *p<0.05 vs. MPS II, ZFN+Donor high dose, #p<0.05 vs. wild-type (two-way repeated-measures ANOVA followed by Dunnett's multiple comparison test).

These data demonstrate dose-dependent ZFN-driven integration of the hIDS transgene into the mouse albumin locus in the liver *in vivo*, leading to sustained high levels of functional correction of IDS activity in a broad array of tissues, including in the brain, and resulting in significant cognitive benefits.

### 1.4 Clinical Experience with Zinc Finger Nucleases

This is a first in-human study for SB-913. As of 11 September 2018, 6 subjects with MPS II have been enrolled and have received SB-913 at doses of up to 5.00E+13 vg/kg. SB-913 was well tolerated, and reported AEs were mostly mild (Grade 1) in severity and unrelated to the study treatment. No SAEs related to SB-913 were reported. (For further details, see Section 8.1).

Another cell therapy modified by ZFNs, SB-728-T, has to date been administered to over 70 subjects with HIV infection in 4 Phase I studies: one study sponsored by the University of Pennsylvania, and the other 3 studies sponsored by Sangamo. SB-728-T is autologous enriched CD4+ T-cells that have been transduced *ex vivo* with ZFNs, resulting in modification of the CCR5 gene. A donor transgene was not co-infused with this therapy. The ZFNs were delivered with a replication deficient recombinant Ad5/35 viral vector (and subsequently by electroporation of mRNA), which through transient episomal expression delivered these nucleases to transduced cells. The two ZFNs bind to a composite 24-base pair sequence found specifically in the region encoding the first transmembrane domain of the CCR5 gene, just upstream from the naturally occurring CCR5 delta 32 mutation. Expression of the CCR5-specific ZFNs induces a DSB that is repaired, but in approximately 30% of transduced cells leads to the insertion of random sequences or deletions. The sequence insertions and deletions disrupt the CCR5 coding sequence, leading to frame shift mutations and termination of CCR5 protein expression. SB-728-T infusions were well tolerated with mostly mild and moderate reversible infusion-related AEs. The most common AEs were skin odor abnormal (caused by the DMSO required for cell freezing), fatigue, upper respiratory tract infection, headache, chills, fever, and pyrexia. SAEs were reported in 3 subjects: 2 subjects experienced SAEs assessed as unrelated to SB-728-T (including an event of

polysubstance abuse leading to unresponsiveness in a subject with a history of substance abuse, and an event of cellulitis/MRSA abscess in a subject with a suspected history of intravenous drug abuse); and 1 subject experienced SAEs of fever, chills, joint pain, and back pain 1 day after SB-728-T infusion, which were attributed to an infusion reaction and assessed as related to the study treatment.

There have been no reports of malignancy in these studies as of 11 SEP 2018.

## 1.5 Dose Justification

The selection of 5.00E+12 vg/kg as the clinical starting dose of SB-913 takes into account 2 critical objectives: 1) administration of sufficient amounts of the 3 SB-913 AAV vectors to enter the hepatocytes, transduce the cells, express hIDS, and provide high enough levels of both ZFNs to induce DSBs in the cells; and 2) administration of a safe starting dose.

Preclinical data from Sangamo's SB-FIX program supports a minimal effective single ZFN dose each of 1.20E+12 vg/kg to ensure adequate nuclease activity to allow insertion of the human Factor IX (hFIX) cDNA donor into the target site and yield circulating hFIX levels of about 1% normal. The selected total SB-913 starting dose of 5.00E+12 vg/kg at a 1:1:8 ratio of ZFN1:ZFN2:hIDS Donor contains a ZFN dose of 5.00E+11 vg/kg (per ZFN), which is 2.4-fold less than the minimally effective ZFN dose (1.2e12 vg/kg) for SB-FIX in cynomolgus monkeys. As described above, the ZFN architecture and *in vitro* potency for the SB-913 and SB-FIX products are similar, allowing extrapolation from SB-FIX to SB-913 ZFN activity.

The total SB-913 starting dose of 5.00E+12 vg/kg provided approximately a half-log margin of safety for ZFN activity, and is anticipated to be minimally pharmacologically active. Clinically significant levels of hIDS activity may be expected at SB-913 dose levels of 1.00E+13 vg/kg and 5.00E+13 vg/kg, which contain single ZFN dose levels of 1.00E+12 vg/kg and 5.00E+12 vg/kg, respectively. As the predictive value of non-human primate dosing data to human pharmacologic activity is not known, this half-log safety margin with a starting dose of 5.00E+12 vg/kg (total AAV2/6) provided a conservative starting dose for this first-in-human trial, and the half-log increments in dose escalation should bring the clinical dose level into the non-human primate predictive range for ZFN activity and hIDS expression.

Dosing is further informed by the cumulative study data on 6 subjects who received SB-913 at 3 different doses that was reviewed by the SMC on 08 October 2018. Based on these data, the SMC recommended expansion of Cohort 3 (5.00E+13 vg/kg dose) and opening of the first pediatric cohort (Cohort 5) with dosing at 5.00E+13 vg/kg, as well as consideration of a higher dose (see Section 8.1 for additional details).

The selection of 1.20E+14 vg/kg as the highest dose of SB-913 in Cohort 4 is based on data obtained in preclinical studies in which AAV2/6 ZFN and cDNA donor were administered to mice and cynomolgus monkeys at dose levels up to 1.50E+14 vg/kg. Neither increase in liver enzymes nor adverse microscopic findings were observed in the mice. Transient increases in liver enzymes, as well as mild, generally reversible, hepatic inflammation, likely related to the expressed human protein and/or AAV vector, were observed in the cynomolgus monkeys. The safety results from these nonclinical studies thus support human dosing of SB-913 at up to 1.20E+14 vg/kg, which provides a 1.25-fold dose multiple to the highest tested dose in cynomolgus monkeys.

In addition to Sangamo's studies, other clinical trials using AAV-based gene therapy have provided evidence that that a total AAV dose of up to 2.00E+14 vg/kg can be administered to humans with an acceptable safety profile (Mendell et al. 2017).

## 1.6 Targeted Patient Population

The targeted patient population of this study will be subjects with MPS II disease. Subjects will be sequentially enrolled in 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). The pediatric cohorts will be enrolled only after review of cumulative adult safety data by an independent, external Safety Monitoring Committee (SMC).

Currently, the treatment of choice for this patient population is ERT using Elaprase® (idursulfase) or equivalent. ERT has been shown to improve pulmonary function, hepatosplenomegaly, and exercise capacity, and to lead to improved health related quality of life. However, it has proven ineffective in addressing the CNS involvement (due to the inability of the enzyme to cross the blood brain barrier), the progressive joint and orthopedic complications, and the cardiac problems. Further drawbacks include the need for life-long treatment, development of neutralizing antibodies, and the inconvenience of weekly IV infusions. Given that MPS II is primarily a disease of children that is devastating and progressive, pediatric cohorts will be enrolled after safety assessment of adult subjects who have received SB-913.

SB-913 is expected to provide life-long, liver-specific expression of IDS.

## 1.7 Risk Benefit Assessment and Study Hypothesis

MPS II is a recessive lysosomal storage disorder that results from mutations in the gene encoding IDS. Deficiency or decreased levels of the enzyme results in the accumulation of toxic levels of metabolites such as GAGs in the urine, blood, and body tissues. Clinical severity varies depending upon residual IDS activity.

The objective for the proposed SB-913 investigational therapy is to abrogate or decrease the need for ERT by *in vivo* genome editing. The proposed treatment employs engineered ZFNs to site-specifically integrate a corrective copy of the hIDS transgene into the genome of a subject's own hepatocytes *in vivo*. Integration of the hIDS transgene is targeted to intron 1 of the albumin locus, resulting in stable, high level, liver-specific expression and secretion of hIDS into the blood. Placement of the hIDS transgene under the control of the highly expressed endogenous albumin locus is expected to provide permanent, liver-specific expression of hIDS for the lifetime of an MPS II patient and improve current clinical outcomes of ERT therapy.

The major risk of therapy with SB-913, which is presumed AAV capsid protein immunogenicity, and possible immunological responses involving the expressed hIDS in the liver post-infusion, will be closely monitored in this study (see Section 8). An immune response is likely to be generated to AAV capsid protein based upon previous gene therapy studies in Hemophilia, but can be ameliorated with a short course of steroids. Whether an immune response will develop against hIDS remains to be determined. Most MPS II patients who receive ERT with Elaprase develop IgG antibodies to IDS.

Another potential risk is the effect on albumin synthesis. However, given the intronic location of the ZFN target site and that < 1% of albumin loci in expressing hepatocytes are predicted to be disrupted, SB-913 should have a minimal clinical impact on overall hepatic albumin production.

Another potential risk is the off-target modification at the structural maintenance of chromosomes flexible hinge domain containing 1 (SMCHD1) locus. This is not expected given that no off-target activity has been observed at clinically relevant levels of albumin on-target activity in human cells *in vitro* (see Section 8.1.2).

# 2. STUDY OBJECTIVES

## 2.1 Primary Objectives

- To evaluate the safety and tolerability of SB-913.

## 2.2 Secondary Objectives

- To evaluate change from Baseline over time in the following assessments:
  - IDS activity in blood.
  - GAG testing in urine.
  - Frequency of ERT administration.
- AAV2/6 clearance.

## 2.3 Exploratory Objectives

- To evaluate change from Baseline over time in the following assessments:
  - GAG levels in tissues (including blood, liver tissue, and cerebrospinal fluid [CSF]).
  - Gene modification at the albumin locus in the liver.
  - Imaging, functional, and neurocognitive testing related to MPS II.
  - Immune response to AAV 2/6, ZFNs and IDS.

From consenting subjects, residual samples may be used for future research objectives. Such future research objectives may include analysis of biomarkers of severity of disease, response to therapy (e.g. cytokines, soluble cell surface proteins, soluble receptors), and functional improvements (e.g., neurological function, musculoskeletal function), as well as determination of AAV virus inhibition, function, immunogenicity, or pharmacodynamics (e.g., antibodies, soluble receptors, AAV viral receptor inhibitors, cytokines, co-existing alternate serotype antibodies). For more details, refer to the Study Reference Manual.

# 3. STUDY DESIGN

## 3.1 Overview

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 inclusion/exclusion criteria are eligible to participate in this study.

## 3.2 Number of Subjects

Up to a total of 32 subjects will be enrolled in this study.

## 3.3 Dose

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+13 | 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 |

## 3.4 Study Duration

The duration of study participation will be approximately 39 months for each subject (see Figure 9), divided into approximately 3 months for Screening followed by 36 months for treatment and study follow-up.

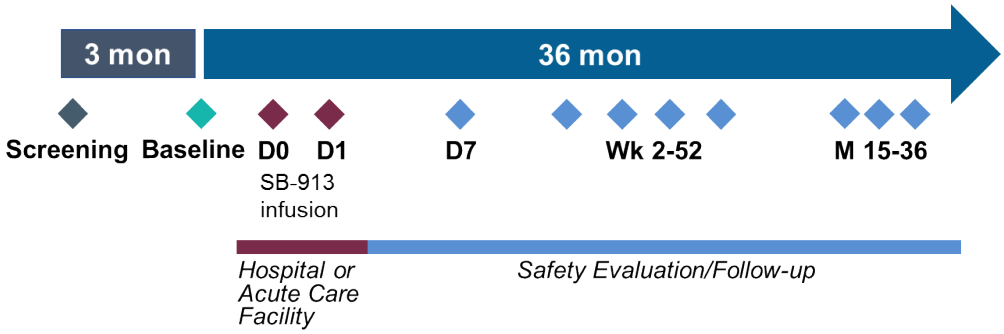



**Figure 9. Schema of Study Visits.**

Upon completion of the study, subjects will be asked to participate in a separate Long-term Follow-Up (LTFU) Study to monitor the long-term safety of SB-913. To alleviate study burden, study subjects may participate in the LTFU Study after at least 12 months of follow-up in this study. 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.

## 3.5 Study Schedule

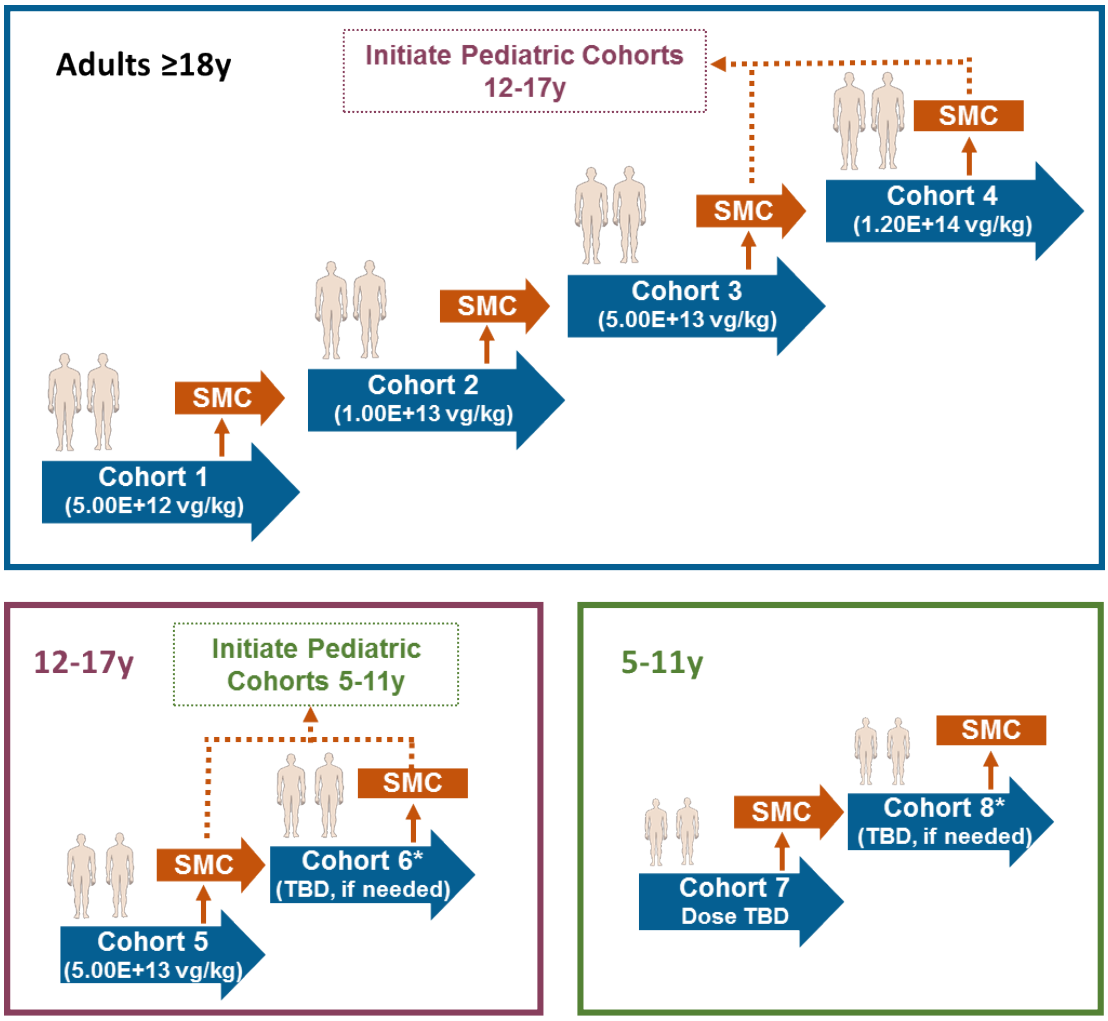
Subjects who satisfy all eligibility criteria will be enrolled into one of the following treatment cohorts:

| Cohort # | Age Range (y) | 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 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 (see Section 12.3). 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 (see Pediatric Dosing).

Approximately 2 additional subjects may be added to any age cohort after SMC review of study data if safety criteria are met (see Safety Monitoring Committee), with up to a total of 32 subjects in the study.




*TBD, to be determined based on SMC Review*
**will be enrolled if dose adjustment is indicated after SMC Review of study data*

**Figure 10. Schema of Cohort Enrollment.**

Blue box = adult subjects age ≥18 years; purple box = pediatric subjects age 12-17; green box = pediatric subjects age 5-11; orange box = SMC review; dashed orange line = SMC recommendation on pediatric dosing.

Subjects who received ERT prior to study enrollment will continue to receive ERT during the study and remain on their current schedule per standard of care unless they undergo ERT withdrawal (see Section 11.4). However, ERT will be omitted during the week of the SB-913 infusion to facilitate accurate baseline testing (e.g.; of GAG levels in urine, blood, and of IDS activity in blood) and to allow a week free of ERT after the SB-913 infusion.

To minimize the potential immune response to the AAV capsid protein, the engineered ZFNs, or the endogenous IDS, and to preserve hepatic function, prednisone or equivalent corticosteroid will be administered prophylactically starting 2 days prior to SB-913 infusion and will be tapered over a period of approximately 20 weeks (see Appendix 3).

The 3 components of SB-913 (ZFN1, ZFN2, and hIDS Donor) will each be added to 200 mL of diluent (refer to the Pharmacy Manual) and adjusted to 0.25% human serum albumin. Total infusion volumes will depend on a subject's cohort assignment and body weight (kg). IV infusions will be administered while the subject is in the hospital or acute care facility (refer to the Pharmacy Manual).

The subject will remain in the hospital or acute care facility for at least 24 hours after completion of 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, study visits are scheduled on Day 7; Weeks 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52; and Months 15, 18, 21, 24, 27, 30, 33, and 36 (see Section 6 and Appendix 1).

Liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total and direct bilirubin, alkaline phosphatase, LDH, albumin, and total protein levels) will be conducted for evaluation of AAV mediated immunogenicity twice a week during the first 20 weeks after SB-913 infusion and may be conducted at home if the subject is remote. Blood samples for liver function tests will be drawn 2-4 days apart when possible, except for the first week when they will be drawn on the Day 1 and Day 7 visits. Liver function tests will subsequently be conducted at all study visits.

Previous studies with IV AAV8 FIX gene therapy have shown that liver transaminitis due to AAV immunogenicity occurs between 2 and 9 weeks after infusion and resulted in loss of FIX expression, and that rapid institution of prednisone can control this immunogenicity. If in spite of pretreatment with prednisone or equivalent corticosteroid in this study there is evidence of transaminitis, the dose of prednisone or equivalent corticosteroid will be increased on a case-by-case basis, and liver function will be assessed twice a week until normalization of liver enzymes, and then per protocol thereafter.

# 4. SUBJECT SELECTION

## 4.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in the study:

1. Signed informed consent.
2. ≥5 years of age:
   a) Adult cohorts 1 through 4: ≥18 years of age;
   b) Pediatric cohorts 5 and 6: 12 to 17 years of age; and
   c) Pediatric cohorts 7 and 8: 5 to 11 years of age.
3. Clinical diagnosis of MPS II (based on evidence of hepatosplenomegaly, dysostosis multiplex by X-ray, valvular heart disease, or obstructive airway disease); IDS deficiency confirmed by gene sequencing.
4. Sexually mature subjects must agree to use a barrier contraceptive method for prevention of AAV transfer as follows: for female subjects this means that the subjects' partners must use a condom from dosing with SB-913 until at least 3 consecutive plasma samples after administration of SB-913 are negative for AAV2/6; for male subjects this means that the subjects must use a condom and must refrain from sperm donation from the time of SB-913 administration until at least 3 consecutive semen samples after administration of SB-913 are negative for AAV2/6. Additionally, female subjects of child-bearing potential must consent to use a highly effective method of contraception.
5. Magnetic resonance imaging (MRI) negative for liver mass as read by a radiologist.

## 4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. Known to be unresponsive to ERT.
2. Neutralizing antibodies in serum (immune response) to AAV2/6.
3. Serious intercurrent illness or clinically significant organic disease (unless secondary to MPS II) such as cardiovascular, hepatic, pulmonary, neurologic, or renal disease.
4. Receiving antiviral therapy for hepatitis B or C, or with active hepatitis B (HBV DNA positive or HBV surface antigen positive) or hepatitis C (HCV RNA viral load) or human immunodeficiency virus (HIV)-1/2 (HIV RNA viral load or HIV antibody positive); to be considered negative for hepatitis C after treatment of an active HCV infection, viral assays in 2 samples collected at least 6 months apart must be negative.
5. Lack of tolerance to idursulfase treatment with significant infusion-associated reactions (IARs) or occurrence of anaphylaxis.
6. Polymorphisms in the ZFN-targeted region of the albumin locus.
7. Liver fibrosis score of 3 or 4 on a 0 to 4 point scale (Desmet et al. 1994) if subject has had a liver biopsy within 2 years of Screening.
8. Markers of hepatic dysfunction as evidenced by one or more of the following:
   a) Platelet count <100,000/μL

b) Albumin ≤3.2 g/dL

c) Total bilirubin >1.5 x upper limit of normal (ULN) and direct bilirubin ≥0.5 mg/dL

d) Alkaline phosphatase >2.0 x ULN

e) ALT or AST >2.0 x ULN

9. Creatinine ≥ 1.5 mg/dL.
10. Weight < 20 kg at Screening visit.
11. Pregnant or breastfeeding female.
12. Contraindication to the use of corticosteroids.
13. Current treatment with systemic (IV or oral) immunomodulatory agent or steroid use (topical treatment allowed, e.g., for asthma or eczema).
14. History of active malignancy in past 5 years (non-melanoma skin cancer or cervical cancer *in situ* permitted).
15. Participation in prior investigational drug or medical device study within the previous 3 months.
16. Prior treatment with a gene therapy product.
17. History of alcohol or substance abuse that in the opinion of the Principal Investigator may interfere with study compliance.
18. History of therapeutic non-adherence.
19. Elevated or abnormal circulating α-fetoprotein (AFP).
20. Any other reason that, in the opinion of the Principal Investigator or Medical Monitor, would render the subject unsuitable for participation in the study.

# 5. INFORMED CONSENT

Informed consent must be obtained from the subject as institutional policy allows before any study-related screening activity is undertaken that is not part of routine care. Informed consent may be obtained separately for Screening blood tests only (to determine eligibility based on neutralizing antibodies to AAV 2/6 and single-nucleotide polymorphism [SNP] analysis) prior to obtaining full study Informed Consent, if allowed by the local institutional review board (IRB) or institutional ethics committee (IEC) or equivalent. The subject's legally authorized representative may also provide informed consent for subject participation if allowed by the local IRB/IEC or equivalent. The Principal Investigator or designated personnel will explain to each subject or the subject's legally authorized representative the nature of the study, its purpose, the procedures, the expected duration, alternative therapies available, and the benefits and risks of participation. The subject or the subject's legally authorized representative will receive an information and consent document, with the opportunity to ask questions, and will be informed that participation is voluntary, and that the subject can withdraw from the study at any time without any impact upon the subject's future clinical care. The subject or the subject's legally authorized representative will receive a copy of the signed and dated written informed consent form and any other written information required for the study. Each subject will be re-consented at the time of any informed consent amendment, as applicable, and will be provided a copy of the signed and dated revised consent form.

# 6. STUDY METHODOLOGY

Prior to initiation of this study, the study site shall be approved by the IRB/IEC or equivalent. Subjects must be willing to participate in all study procedures related to this protocol. The following sections describe all study procedures. Additional detailed instructions will be provided in the Study Reference Manual, Laboratory Manual, and Pharmacy Manual. A table of all study procedures is presented in the Schedule of Events (see Appendix 1).

## 6.1 Screening

The objective of the Screening visits is to identify subjects who meet the stated inclusion and exclusion criteria and who are willing and able to participate in the study.

Screening may take up to approximately 3 months and may be performed across several visits.

The following assessments and procedures will be performed:

- Obtain a signed and dated subject informed consent form and authorization document to use and disclose medical information prior to performing any study-specific procedures.
- Obtain a complete medical history.
- Review and record concomitant medications.
- Review the inclusion and exclusion criteria.
- Assign a subject number.
- Collect demographic information.
- Physical examination.
- Vital signs.
- Assessment of AEs.
- ERT administration log.
- 12-lead electrocardiogram (ECG).
- Echocardiogram (ECHO).
- Chest x-ray.
- Pregnancy test (for females of childbearing potential only).
- Clinical laboratory tests.
- Liver panel.
- MPS II gene sequencing.
- SNP analysis.
- Viral load.
- Neutralizing antibodies to AAV2/6.

- GAG testing in urine (collect samples on 3 separate days, each collection occurring at least 7 days after the previous, and all collections occurring at least 7 days after ERT administration [+/-1 day] but prior to the next ERT infusion).
- IDS / GAG testing in blood (collect 7 days after ERT administration [+/-1 day]).
- Circulating AFP level.
- Pulmonary function tests (PFTs).
- VABS-II (Vineland Adaptive Behavior Scales) test.
- Neurocognitive abilities assessment.
- MRI of liver.

Subjects may be re-screened in the judgement of the Principal Investigator and after consultation with Sangamo. For subjects who are re-screening for participation in the study, the following assessments performed in the previous 6 months may be used for evaluation of inclusion/exclusion criteria at the judgement of the Principal Investigator:

- ECHO.
- Chest X-Ray.
- PFTs.
- MRI of liver and/or brain and cervical spine.

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.

### 6.2 Subject Enrollment

Before a subject is assigned to a dose cohort, the study site personnel must verify that the subject fulfills all eligibility criteria.

The pediatric cohorts will be enrolled only after review of cumulative adult safety data by an independent, external SMC.

### 6.3 Baseline

Baseline assessments will be performed within 21 days prior to SB-913 infusion.

In subjects receiving ERT, ERT shall be withheld during the week of the administration of SB-913 to enable accurate baseline testing.

The following assessments and procedures will be performed:

- Review and record concomitant medications.
- Physical examination.
- Vital signs.
- Assessment of AEs.
- ERT administration log.
- Joint range of motion (JROM).

- Neurologic cranial nerve exam and muscle strength testing of the upper extremities.
- 12-lead ECG.
- Pregnancy test (for females of childbearing potential only).
- Clinical laboratory tests.
- Liver panel.
- GAG testing in urine.
- IDS / GAG testing in blood.
- Vector genome PCR in plasma, saliva, urine, stool, and semen (males only).
- PFTs.
- 6-minute walk test (6MWT).
- Neurocognitive abilities tests by WASI-II (Wechsler Abbreviated Scale of Intelligence), WPPSI-IV (Wechsler Preschool and Primary Scale of Intelligence), or BSID-III (Bayley Scales of Infant Development), and by VABS-II.
- MRI of brain and cervical spine.
- Adrenocorticotropic hormone (ACTH) stimulation (cosyntropin) test (prior to prednisone or equivalent corticosteroid).
- Liver biopsy.
- Lumbar puncture.
- Immunogenicity assays.
- Prednisone or equivalent corticosteroid administration (starting 2 days before SB-913 infusion).

### 6.4 Day 0 (SB-913 Infusion)

Subjects will receive the SB-913 infusion at a hospital or acute care facility, remain there for at least 24 hours after the infusion for observation, and be discharged when all AEs and vital signs are stable.

The following assessments and procedures will be performed:

- Review and record concomitant medications.
- Physical examination.
- Vital signs (for frequency, refer to the Study Reference Manual).
- Assessment of AEs.
- ERT administration log.
- Pregnancy test (females of childbearing potential only, and if >7 days from Baseline pregnancy testing).
- Prednisone or equivalent corticosteroid administration.
- Infusion of SB-913 via a peripheral vein catheter.

### 6.5 Day 1

All subjects will remain in the hospital or acute care facility for at least 24 hours after completion of SB-913 infusion. Subjects will be discharged when all AEs and vital signs are stable.

The following assessments and procedures will be performed:

- Review and record concomitant medications.
- Physical examination.
- Vital signs (continued measurement from Day 0).
- Assessment of AEs.
- Clinical laboratory tests.
- Liver panel.
- Vector genome PCR in plasma (12 hours after end of SB-913 infusion).
- Prednisone or equivalent corticosteroid administration.

### 6.6 Day 7 (+/- 1 day)

The following assessments and procedures will be performed:

- Review and record concomitant medications.
- Physical examination.
- Vital signs.
- Assessment of AEs.
- ERT administration log.
- 12-lead ECG.
- Liver panel.
- Vector genome PCR in plasma, saliva, urine, stool, and semen (males only).
- Prednisone or equivalent corticosteroid administration.

### 6.7 Weeks 2, 4, 6, and 8 (+/- 2 days)

The following assessments and procedures will be performed unless otherwise stipulated:

- Review and record concomitant medications.
- Physical examination.
- Vital signs.
- Assessment of AEs.
- ERT administration log.
- Pregnancy test (females of childbearing potential only; at Weeks 4 and 8 only).
- Clinical laboratory tests.

- Liver panel (twice weekly; may be conducted at home if subject is remote).
- GAG testing in urine.
- IDS / GAG testing in blood.
- Circulating AFP level (at Weeks 4 and 8 only).
- Vector genome PCR in plasma, saliva, urine, stool, and semen (males only) (at Weeks 2, 4, and 8 only).
- Immunogenicity assays (at Week 4 only).
- Prednisone or equivalent corticosteroid administration.

### 6.8 Weeks 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 (+/- 1 week)

The following assessments and procedures will be performed unless otherwise stipulated:

- Review and record concomitant medications.
- Physical examination (at Weeks 12, 16, 20, 24, 36, and 48 only).
- Vital signs (at Weeks 12, 16, 20, 24, 36, and 48 only).
- Assessment of AEs.
- ERT administration log.
- JROM (at Weeks 24 and 48 only).
- Neurologic cranial nerve exam and muscle strength testing of the upper extremities (at Weeks 24 and 48 only).
- 12-lead ECG (at Weeks 24 and 48 only).
- ECHO (at Week 48 only).
- Pregnancy test (females of childbearing potential only; at Weeks 12, 16, 20, 24, 36, and 48 only).
- Clinical laboratory tests (at Weeks 12, 16, 20, 24, 36, and 48 only).
- Liver panel (twice weekly until Week 20; then at Weeks 24, 28, 32, 36, 40, 44, 48, and 52; may be conducted at home if subject is remote until Week 20 and at Weeks 28, 32, 40, 44, and 52).
- GAG testing in urine.
- IDS / GAG testing in blood (at Weeks 12, 16, 20, 24, 36, and 48 only).
- Circulating AFP level (at Weeks 12, 24, and 48 only).
- Vector genome PCR in plasma, saliva, urine, stool, and semen (males only) (at Weeks 12, 16, 20, 24, 36, and 48 only).
- PFTs (at Weeks 24 and 48 only).
- 6MWT (at Weeks 24 and 48 only).

- Neurocognitive abilities tests by WASI-II, WPPSI-IV, or BSID-III, and by VABS-II (at Weeks 24 and 48 only).
- MRI of liver (at Weeks 24 and 48 only).
- MRI of brain and cervical spine (at Week 48 only).
- ACTH stimulation (cosyntropin) test (at Week 20 only or at end of prednisone or equivalent corticosteroid taper; see Appendix 3).
- Liver biopsy (at Weeks 24 and 48 only).
- Lumbar puncture (at Weeks 24 and 48 only).
- Immunogenicity assays (at Weeks 12, 24, 36, and 48 only).
- Prednisone or equivalent corticosteroid administration (through Week 20 only).

### 6.9 Months 15, 18, 21, 24, 27, 30, 33, and 36/End of Study (+/-1 month)

Subjects will be evaluated every 3 months in Years 2 and 3 after SB-913 infusion.

An End of Study (EOS) visit will be conducted at Month 36.

At the EOS visit, subjects will be asked to participate in the LTFU Study. 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 anytime 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, EOS visit may be conducted anytime when transition to the LTFU study is imminent . Informed consent will be obtained prior to participating in the LTFU Study.

The following assessments and procedures will be performed unless otherwise stipulated:

- Review and record concomitant medications.
- Physical examination.
- Vital signs.
- Assessment of AEs.
- ERT administration log.
- JROM (at Months 18, 24, 30, and 36/EOS only).
- Neurologic cranial nerve exam and muscle strength testing of the upper extremities (at Months 18, 24, 30, and 36/EOS only).
- 12-lead ECG (at Months 18, 24, 30, and 36/EOS only).
- ECHO (at Months 24 and 36/EOS only).
- Clinical laboratory tests.
- Liver panel.
- GAG testing in urine.

- IDS / GAG testing in blood.
- Circulating AFP level (at Months 18, 24, 30, and 36/EOS only).
- PFTs (at Months 18, 24, 30, and 36/EOS only).
- 6MWT (at Months 18, 24, 30, and 36/EOS only).
- Neurocognitive abilities tests by WASI-II, WPPSI-IV, or BSID-III, and by VABS-II (at Months 18, 24, 30, and 36/EOS only).
- MRI of liver (at Months 18, 24, 30 and 36/EOS only).
- MRI of brain and cervical spine (at Months 24 and 36/EOS only).
- Immunogenicity assays (at Months 18 and 24 only).

### 6.10 Early Termination

Subjects who discontinue from the study prematurely or are withdrawn from the study will be asked to return to the study site for an early termination visit (ETV).

It is at the discretion of the Principal Investigator, in consultation with the Medical Monitor, to waive any procedure if the procedure has been performed within the standard interval of scheduled study visits per protocol.

The following assessments and procedures will be performed:

- Review and record concomitant medications.
- Complete physical exam.
- Vital signs.
- Assessment of AEs.
- ERT administration log.
- JROM.
- Neurologic cranial nerve exam and muscle strength testing of the upper extremities.
- 12-lead ECG.
- ECHO.
- Clinical laboratory tests.
- Liver panel.
- GAG testing in urine.
- IDS / GAG testing in blood.
- Circulating AFP level.
- PFTs.
- 6MWT.
- Neurocognitive abilities tests by WASI-II, WPPSI-IV, or BSID-III, and by VABS-II.

- MRI of liver.
- MRI of brain and cervical spine.

### 6.11 ERT Withdrawal (any time after Week 12)

Subjects who are willing and who are at least 12 weeks post administration of SB-913 may be considered for withdrawal of ERT by the Principal Investigator after consultation with the Sponsor. For ERT withdrawal, subjects must be medically stable and agree to increased safety monitoring and lab testing until the ERT Withdrawal Follow-Up visit.

The ERT Withdrawal visit may occur concurrently or independent of a regular scheduled visit.

The ERT Withdrawal visit should be combined with a regular scheduled visit whenever possible to reduce study burden.

The following assessments and procedures will be performed:

- Review and record concomitant medications.
- Complete physical exam.
- Vital signs.
- Assessment of AEs.
- ERT administration log.
- Clinical laboratory tests.
- Liver panel.
- GAG testing in urine.
- IDS / GAG testing in blood.
- PFTs.
- 6MWT.

### 6.12 ERT Withdrawal Monitoring (ERT Withdrawal Weeks 1, 2, 3, 4, 6, 8, 10, and 12 [+/-2 days])

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 should be combined with regular scheduled visits whenever possible to reduce study burden.

ERT Withdrawal Monitoring visits may be conducted at home if the subject is remote.

The following assessments and procedures will be performed:

- Review and record concomitant medications.
- Assessment of AEs.
- ERT administration log.

- Liver panel.
- GAG testing in urine.
- IDS / GAG testing in blood.

### 6.13 ERT Withdrawal Follow-Up (up to 12 weeks post-ERT Withdrawal visit)

The ERT Withdrawal Follow-Up visit can occur at any time up to 12 weeks after the ERT Withdrawal visit at the discretion of the Principal Investigator.

The following assessments and procedures will be performed:

- Review and record concomitant medications.
- Complete physical exam.
- Vital signs.
- Assessment of AEs.
- ERT administration log.
- Clinical laboratory tests.
- Liver panel.
- GAG testing in urine
- IDS / GAG testing in blood.
- PFTs.
- 6MWT.
- ERT clinical assessment.

# 7. INVESTIGATIONAL PRODUCT AND OTHER STUDY MEDICATIONS

## 7.1 SB-913

SB-913 is a combination of 3 recombinant adeno-associated virus serotype 2/6 (rAAV2/6) vectors that encode:

- ZFN 1 (SB-47171): Left-side ZFN that targets base pairs 447-461 of the albumin locus relative to the transcription initiation site (ZFN 1 product vials are labeled as SB-A6P-ZLEFT).
- ZFN 2 (SB-47898): Right-side ZFN that targets base pairs 468-485 of the albumin locus relative to the transcription initiation site (ZFN 2 product vials are labeled as SB-A6P-ZRIGHT).
- hIDS Donor (SB-IDS): DNA repair template that encodes a promotorless hIDS transgene (hIDS Donor product vials are labeled as SB-A6P-HNT).

Purified lots of recombinant vector are formulated in phosphate buffered saline (PBS) containing $CaCl_2$, $MgCl_2$, NaCl, Sucrose & Kolliphor (Poloxamer) P 188, and filled at volumes of either 5 mL or 10 mL into vials, which are then stored at ≤-65°C. The lots are tested for identity, sterility, potency, and stability.

### 7.1.1 Inventory, Storage, and Handling of the Drug Product

The SB-913 components required for subject treatment will be shipped to the study center with dry ice and temperature monitoring device, and will be required to be stored at ≤ -65ºC (with temperature monitoring) prior to administration.

A Clinical Certificate of Analysis for each SB-913 component will accompany each shipment. The vials will have a label affixed containing the following information: vector identity, lot number, concentration, volume, storage conditions, manufacturer, date of manufacturing, sponsor, and "Caution: For investigational use only".

Subject-specific kits, comprised of the three SB-913 components in the quantities required based on the subject's weight and cohort will be prepared for shipment to the study center. Kit labels will contain the following additional information: subject ID number, protocol number, and quantity.

The study center is required to maintain complete records of all study products received during the course of this study, as well as of labeled product that is dispensed. At the conclusion or termination of this study, return or destruction of all drug supplies must be coordinated with Sangamo (refer to the Pharmacy Manual for additional details).

The Principal Investigator agrees not to supply labeled product to any person other than study personnel and subjects in this study.

### 7.1.2 SB-913 Administration

Side effects following SB-913 infusions may include transient fever, chills, and/or nausea. These symptoms can be treated with acetaminophen (Tylenol or Paracetamol) 650 mg by mouth and diphenhydramine hydrochloride (Benadryl) 25-50 mg by mouth or IV or equivalent medication. These medications may be repeated every 3-4 hours as needed.

SB-913 will be shipped to the study site prior to the scheduled infusion.

On Day 0, after the subject has arrived at the hospital or acute care facility and has been confirmed to be eligible for infusion, the three SB-913 rAAV2/6 vector components (ZFN1, ZFN2, and hIDS Donor) will be thawed by placing the vials at room temperature. Then each component will be added to 200 mL of diluent (refer to the Pharmacy Manual) and adjusted to 0.25% human serum albumin. Total infusion volumes will be calculated according to a subject's cohort assignment and body weight (kg). Once the SB-913 infusion is prepared it should be transported at room temperature to the infusion facility at the hospital or acute care facility, and be kept at room temperature prior to infusion. SB-913 will be infused while monitoring the subject's vital signs (temperature, heart rate, respiratory rate, and blood pressure) pre-, during, and post-infusion until discharge (for frequency, refer to the Study Reference Manual).

For detailed instructions for thawing and infusing SB-913, refer to the Pharmacy Manual.

### 7.1.3 Precautions

SB-913 is an investigational product, and there is a potential risk of severe hypersensitivity reaction (e.g., anaphylaxis). Emergency medical equipment must be available during the infusion in case the subject has an allergic response, severe hypotensive crisis, or any other reaction to the infusion. Vital signs (temperature, heart rate, respiratory rate, and blood pressure) must be taken before, during, and after infusion (see Appendix 1 and refer to the Study Reference Manual). In the unlikely event that the subject develops sepsis or systemic bacteremia following SB-913 infusion, appropriate cultures and medical management should be initiated.

All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to the instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

### 7.1.4 Dose Modifications

No dose modifications are possible within an individual subject since this is a single infusion study.

## 7.2 Concomitant Medication and Supportive Care

The Principal Investigator will record all concomitant medications, including over-the-counter medicinal products, dietary supplements, herbal medications, and medications given in treatment of AEs, taken by a subject from Screening throughout the course of the study on the concomitant medications page in the subject's case report form (CRF).

Subjects who received ERT prior to study enrollment should continue to receive ERT during the study as per standard of care unless they undergo ERT withdrawal (see Section 11.4), except during the week of the SB-913 infusion, and such treatment should be recorded on the concomitant medications page.

Treatment with prednisone or equivalent corticosteroid and pre-treatment with acetaminophen (Tylenol or Paracetamol) and diphenhydramine hydrochloride or equivalent medication should also be recorded on the concomitant medications page.

# 8. SAFETY AND POTENTIAL RISKS

## 8.1 SB-913

The 3 individual rAAV vectors encoding the individual albumin ZFNs and the hIDS Donor are packaged as AAV serotype 2/6 made in a Baculovirus expression system. These rAAV vectors are non-replicating, and efficiently transduce non-dividing cells such as liver hepatocytes. rAAV vectors do not actively integrate into the host cell genome and do not encode any viral proteins. The SB-913 rAAV2/6 vectors are pseudotyped vectors with both inverted terminal repeats (ITRs) being derived from AAV2 ITRs, and the virus is packaged in the presence of the AAV2 rep gene and AAV6 cap gene. Tissue tropism of these pseudotyped vectors is completely dependent on the properties of the capsid proteins encoded by the AAV6 cap gene. The AAV2/6 serotype was chosen based on pilot studies *in vitro* and *in vivo* in mice that demonstrated that rAAV2/6 effectively delivered the hIDS transgene cassette to liver hepatocytes, resulting in expression of IDS in the systemic circulation.

As of 11 September 2018, 6 subjects with MPS II have been enrolled and have received SB-913 at doses of up to 5.00E+13 vg/kg. SB-913 was well tolerated, and reported AEs were mostly mild (Grade 1) in severity and unrelated to the study treatment.

Four subjects reported AEs assessed as related to SB-913 by the Principal Investigator. The AEs included flushing in a subject 3 days after dosing; flushing and erythema in a subject on the day of dosing, and ALT increased and AST increased in this same subject 60 days after dosing; cold sweat, dizziness, and asthenia in one subject 4 days after dosing; and 2 events of pruritus in a subject 2 and 6 days after dosing. Each of these events was mild (Grade 1) in severity, and resolved without treatment. No persistent transaminitis has been observed in any subject after SB-913 infusion as of the data cutoff date.

No SAEs assessed as related to SB-913 were reported. Two SAEs were reported in 2 subjects, and each was assessed by the Principal Investigator as not related to SB-913 but rather secondary to the subjects' underlying MPS II disease. An SAE of acute bronchitis was reported approximately 3 weeks after SB-913 infusion in a subject with a history of chronic obstructive pulmonary disease (COPD) for which the subject was similarly hospitalized 2 years prior, tracheobronchomalacia, and sleep apnea. An SAE of atrial fibrillation was reported approximately 7 weeks after SB-913 infusion in a subject with a history of mitral valve stenosis, pulmonic valve stenosis, aortic stenosis, left atrial enlargement, and heart palpitations.

The immune system of subjects in this study may be exposed to antigens arising from the foreign AAV capsid protein, the endogenous hIDS, and the engineered ZFNs. Clinical studies to date suggest an immune response will be generated to AAV capsid protein, but whether an immune response will develop against hIDS remains to be determined as it is unknown whether antibodies will develop against a protein with a glycosylation pattern derived from human hepatocyte production of the enzyme. ZFPs are ubiquitous as the DNA-binding domains of transcription factors in human cells, so may have limited immunogenic potential; in contrast the *FokI* nuclease domain of the ZFN is of bacterial origin. In extensive evaluations in non-human primates, no consistent evidence for humoral or cell-mediated adaptive immune responses to engineered ZFN components has been found.

Although AAV is a replication defective virus, humans are naturally infected during childhood, probably in conjunction with a helper virus infection such as adenovirus. Therefore, pretreatment

neutralizing antibodies to AAV will affect transduction by forming immune complexes with the infused vector, and thereby prevent hepatocyte transduction. Furthermore, following transduction, memory CD8 T cells may be reactivated and eliminate transduced hepatocytes that express AAV protein-derived epitopes. As described earlier, results from clinical studies suggest that immunosuppression, for example with corticosteroids, may be necessary to achieve sustained hIDS expression.

In the proposed study, subjects will be screened for neutralizing antibodies to AAV2/6. Subjects that test positive to neutralizing antibodies to AAV2/6 will not be enrolled in this study. Cell-mediated immunity to the viral capsid may be attenuated/abrogated with a course of immunosuppression since the viral capsid is not encoded in the vector. Therefore, in this study, subjects will receive pretreatment with oral prednisone or equivalent corticosteroid starting 2 days prior to SB-913 infusion and as described in Appendix 3. If any subject develops increased aminotransferases in spite of the prednisone or equivalent corticosteroid treatment, the prednisone or equivalent corticosteroid regimen may be adjusted or restarted after consultation with the Medical Monitor.

### 8.1.1 Potential On-Target Effect on Albumin

Albumin is the most abundant plasma protein, accounting for 55-60% of plasma proteins. The total body albumin pool is about 250 to 300 g for a healthy 70 kg adult, with approximately 42% of this in the plasma compartment and the remainder in the extravascular space. The latter is recirculated into the vascular compartment via the lymphatics. Albumin synthesis in humans occurs only in the liver. The rate of albumin synthesis in a healthy adult is 12-25 g/day, but varies depending on the nutritional and health status of an individual. The capacity to increase albumin synthesis is limited (2-2.7x normal) since much of the liver synthetic machinery is already devoted to albumin synthesis at rest. Daily albumin degradation is approximately 14 g/d or ~5% of total body protein turnover. Albumin is broken down in most organs of the body, with 40-60% being degraded by muscle and skin, ~15% by the liver, and ~10% each by kidney and gastrointestinal tract.

The function of albumin is well established and includes maintenance of plasma oncotic pressure, acid-base balance, antioxidant function, and anticoagulant effects. It also binds to numerous compounds, such as hydrophobic organic anions, long chain fatty acids, bilirubin, hematin, and hormones such as thyroxine. Despite the importance of albumin, approximately 30 individuals with analbuminemia have been described, in which mutations in the albumin gene result in mRNA splicing errors and premature stop codons (Watkins et al. 1994). These subjects do have some circulating albumin (<1 g/L), possibly due to gene leakage. The subjects' bodies appear to compensate by slowing the rate of albumin degradation. Surprisingly, these subjects have minimal pathology, limited to peripheral edema, lipodystrophy (lower limb obesity), fatigue, and hyperlipidemia (Minchiotti, et al. 2013; Prinsen & van der Velden 2004; Nicholson et al. 2000). The hemodynamic effects of analbuminemia are minor, consisting of a minor reduction in oncotic pressure (16 vs 25 mm Hg) and arterial pressure leading to increased renin and aldosterone secretion.

Given the rate of albumin production by the liver (12-25 g/day), it can be estimated that the conversion by SB-913 of as little as 0.01% of albumin alleles to hIDS synthesis would yield potentially therapeutically beneficial IDS levels (>1% of normal) in plasma (Muenzer et al. 2006; Elaprase FDA summary of approval). The loss of such a small proportion of albumin production is expected to have no adverse consequences. At the individual cell level, the targeted locus is

completely dispensable, since albumin has no autocrine role. At the organism level, heterozygous disruption of albumin yields no symptoms, and even homozygous disruption is tolerated as described above. Therefore, disrupting < 1% of the albumin alleles is predicted to have no adverse phenotype. Moreover, given the intronic location of the ZFN target site, ZFN cleavage and subsequent DNA repair in the absence of hIDS integration (e.g., small insertion and deletion mutations at the site of ZFN cleavage) will be functionally inert with respect to albumin expression. A recent review of the genetic targeting of the albumin locus to treat hemophilia in murine models highlights the usefulness of targeting a highly active heterologous gene like albumin; neither transaminitis nor perturbations in serum albumin levels were observed, and few off-target integration sites were detected (Davidoff & Nathwani 2016).

### 8.1.2 Potential Off-Target Effects

An unbiased integration site assay was established to identify ZFN cleavage sites and subsequent insertion of a donor oligonucleotide duplex in the genome (based on Gabriel et al. 2011). This assay allows for evaluation of all potential integration sites within the genome. The integration site assay was run using the SB-913 ZFNs (SB-47171 and SB-47898), and yielded a ranked list of 39 candidate cleavage sites. As expected, the top ranked locus in the human genome was the intended target site within albumin intron 1. A follow-up indel analysis performed in human primary hepatocytes transduced with rAAV2/6 encoding the SB-913 ZFNs revealed significant modification only at the on-target site in albumin intron 1 (6.1% for low dose and 33.5% for high dose) but at no other candidate cleavage site.

For the SB-FIX program (BB-IND 16721), which uses ZFNs highly similar to the SB-913 ZFNs, the integration site assay revealed a single, low activity off-target site. Due to the similarity of the ZFN reagents, this off-target site was also considered for further analysis in the SB-913 program. The off-target site was mapped to exon 38 (out of 48 exons) of the SMCHD1 gene. SMCHD1 has been linked to chromosome X-inactivation, tumor suppression, DNA damage repair, and facioscapulohumeral muscular dystrophy (FSHD) type 2.

A mouse knockout (by genetrap/gt) of the murine homolog of SMCHD1 has been generated (Blewitt et al. 2008). Although male knockout mice (Smchd1 gt/gt) develop normally, female knockout mice exhibit embryonic lethality due to problems with X chromosome inactivation and misregulation of CpG methylation. This indicates a role for SMCHD1 in embryogenesis in the female mouse, and suggests that only the loss of both SMCHD1 copies in female patients could potentially pose a problem. Furthermore, it is unclear whether X-inactivation would have any impact on liver hepatocytes, which are often polyploid. Male knockout mice show normal embryonic development but increased lethality after birth (Leong et al. 2013); surviving mice appear normal and show no predisposition or susceptibility to tumor formation. When the male knockout mice were crossed into a premalignant Eu-Myc transgenic mouse model, some hematopoietic cancers were detected in homozygotes (Leong et al. 2013).

It has been suggested that SMCHD1 is recruited to the site of DNA damage and that its depletion could alter DNA damage response signaling and cell survival (Tang et al. 2014). However, no evidence for decreased cell survival or spontaneous activation of apoptosis (cleaved Parp1) or DNA damage markers (Kap-1 phosphorylation) was seen during *in vitro* dose titration studies with up to 45% SB-913 ZFN on-target activity.

SMCHD1 mutations have been associated with FSHD type 2, which is an autosomal dominant muscular dystrophy affecting facial, shoulder girdle, upper arm, and other muscle tissues

(Larsen et al. 2015). FSHD type 1 is linked to the contraction of macrosatellite D4Z4 repeats and misregulation of the DUX4 transcript in myoblasts (Statland & Tawil 2014). The far less common FSHD type 2 (about 5% of all cases) has been linked to mutations in SMCHD1 (Lemmers et al. 2012). However, SB-913 ZFN expression should be restricted to hepatocytes due to the use of the liver-specific ApoE/hAAT promotor, and no liver-related symptoms have been reported with FSHD. Moreover, *in vivo* studies with the surrogate mouse SB-913 ZFNs revealed no significant modification of the albumin locus in tissues other than liver tissue, confirming the ZFN's tissue-specific expression.

Dose titration studies carried out *in vitro* in human hepatocytes with SB-913 ZFNs showed that the SMCHD1 off-target site was modified only at low levels, nearly 100-fold below those observed at the albumin intron 1 on-target site, and modification levels were generally within the range seen in mock-treated cells or control samples. Only at higher doses of AAV2/6 SB-913 ZFNs, which corresponded to an on-target activity of more than 20%, were the levels of off-target modification at SMCHD1 consistently above background. *In vitro* studies established that non-human primate albumin ZFN surrogate reagents cut the conserved SMCHD1 off-target in similar fashion with about 100-fold less efficiency than at the albumin on-target locus. Accordingly, analysis of non-human primate *in vivo* samples with on-target ZFN activity of up to 2.1% found no significant off-target activity at the SMCHD1 locus. These results suggest that the observed dose-dependent off-target activity behavior in cultured cells is predictive of the *in vivo* situation in non-human primates and potentially humans.

### 8.1.3 Carcinogenicity

There is a risk that people who receive gene transfer may develop tumors derived from their genetically modified cells. This risk has been seen with viral gene transfer vectors that integrate randomly into the cellular DNA where they may affect genes controlling cell proliferation. The rAAV2/6 vector donor will integrate specifically in the albumin ZFN DSB site. In toxicity studies, no tumors were identified. For evaluation of liver carcinogenicity the current study adopts the hepato-cellular carcinoma (HCC) screening recommendation for high risk subjects (e.g., chronic hepatitis C or B), which includes monitoring AFP and liver MRI. Liver biopsy will be performed if there is an abnormal AFP and a >2 cm mass in the liver (El-Serag & Davila 2011).

## 8.2 Prednisone (or Equivalent Corticosteroid)

Prednisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract.

The following adverse reactions have been associated with the use of glucocorticoids:

- Thinning of bones (osteoporosis), which may lead to fractures or compressions, especially true of vertebral bodies (backbone).
- Loss of blood supply to bones (aseptic necrosis), which may cause severe bone pain, fractures (especially of the hip and shoulder), and which may require surgical correction.
- High blood pressure (hypertension).
- Increased pressure in the eye (glaucoma).
- Permanent clouding of vision in one or both eyes (cataracts).
- Weight gain with increased appetite and fluid retention.

- Facial fullness.
- Increase in body hair and acne, and tendency to easy bruising and thinning of the skin.
- Increased risk of infections while on high dose continuous steroid therapy.
- Interference with growth.
- Muscle cramps and joint pain.
- Changes in the menstrual cycle.
- Elevations in blood sugar (diabetes).
- Suppression of adrenal glands' ability to make necessary cortisone at times of stress (adrenal insufficiency).
- Irritation of stomach and esophagus with possible ulcer type symptoms and, rarely, bleeding.
- Emotional disturbances.

Dietary guidelines will be provided to subjects while on prednisone or equivalent corticosteroid to help alleviate some of the side effects including blood sugar elevation, associated with the use of glucocorticoids (refer to the Study Reference Manual).

# 9. STUDY ASSESSMENTS

## 9.1 Medical History

A complete medical history, including concomitant medications, will be obtained to assess study eligibility. All clinically-significant medical conditions, surgeries, and procedures should be recorded. If the subject is not normally seen at the study center, it may be necessary to obtain medical records to confirm study eligibility. For details, refer to the Study Reference Manual.

## 9.2 Demographics

Demographic data on each subject (e.g., age, gender, race, ethnicity) will be obtained at the Screening visit.

## 9.3 Concomitant Medications

Current concomitant medications will be recorded. For details, refer to the Study Reference Manual.

## 9.4 Physical Examination

Physical examinations will be conducted on each subject at the specified visit and will include at minimum: general appearance, head, eyes, ears, nose, and throat (HEENT); as well as cardiovascular, dermatologic, respiratory, gastrointestinal, musculoskeletal, and neurologic systems. For details, refer to the Study Reference Manual and the Physical Exam Guidelines.

## 9.5 Vital Signs

Vital signs, including height, weight, systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature will be recorded. For details, refer to the Study Reference Manual.

## 9.6 Joint Range of Motion (JROM)

Since MPS II subjects are known to suffer from joint stiffness and skeletal deformities, a series of JROM assessments will be conducted, as permitted by the subject's capacity. For details refer to the Study Reference Manual and the Physical Exam Guidelines.

## 9.7 Neurological Cranial Nerve Exam and Muscle Strength Testing of Upper Extremities

Mutations in SMCHD1, a gene identified as a low-level off target of SB-913, have been associated with FSHD type 2. No detectable modification to SMCHD1 in muscle or nerve cells by SB-913 is expected at the doses used in this study. Nevertheless, for safety evaluation of SB-913, facial and upper body muscle strength will be tested, as permitted by the subject's capacity. For details, refer to the Study Reference Manual and the Physical Exam Guidelines.

## 9.8 Electrocardiogram (ECG)

12-lead ECGs will be obtained to monitor cardiac function/conduction. For details, refer to the Study Reference Manual.

## 9.9 Echocardiogram (ECHO)

Standard 2-dimensional Doppler ECHOs will be obtained to evaluate cardiac function. The measurements will include chamber volumes, ventricular wall thickness, left ventricular ejection fraction, regional wall motion, and valvular morphology and function. For details, refer to the Study Reference Manual and the Imaging Guidelines.

### 9.10 Chest X-Ray

Chest X-Rays (also known as AP radiograph of the chest) will be obtained to evaluate the general health and study eligibility of the subject per the Principal Investigator's clinical judgement. For details, refer to the Imaging Guidelines.

### 9.11 Pregnancy Testing and Contraception Requirements

Pregnancy testing will be conducted on all female subjects of childbearing potential (for details, refer to the Laboratory Manual).

A female subject is considered of childbearing potential (i.e. fertile) following menarche and until becoming post-menopausal unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Female subjects of childbearing potential with a positive pregnancy test at Screening will not be enrolled in the study.

Female subjects of childbearing potential will have a serum pregnancy test at the Screening and Baseline visits. Urine pregnancy test will be performed on the Day 0 visit if >7 days from Baseline pregnancy test. Subsequently, urine pregnancy tests will be done at the indicated visits (see Section 6 and Appendix 1) until at least 3 consecutive plasma samples after administration of SB-913 are negative for AAV2/6. Additional pregnancy tests will be performed at any visit at which pregnancy status is in question. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result, or can be performed if pregnancy test by urine is not feasible at the discretion of the Principal Investigator.

Pregnancy in a subject or a subject's partner must be reported to the Sponsor (see Section 10.7).

Both male and female sexually mature subjects must agree to use a barrier contraceptive method for prevention of AAV transfer as follows: for female subjects this means that the subjects' partners must use a condom from dosing with SB-913 and until at least 3 consecutive plasma samples after administration of SB-913 are negative for AAV2/6; for male subjects this means that the subjects must use a condom and must refrain from sperm donation from the time of SB-913 administration until at least 3 consecutive semen samples after administration of SB-913 are negative for AAV2/6.

Additionally, female participants of child-bearing potential who have not undergone a total hysterectomy or bilateral salpingo-oophorectomy and are sexually active must consent to use a highly effective method of contraception as listed below from dosing with SB-913 and until at least 3 consecutive plasma samples after administration of SB-913 are negative for AAV2/6. Examples of highly effective methods of contraception include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (e.g., oral, intravaginal, transdermal).
- Progestogen-only hormonal contraception associated with inhibition of ovulation (e.g., oral, injectable, implantable).
- Intrauterine device or intrauterine hormone-releasing system.
- Bilateral tubal occlusion.

- Male partner sterilization, also called vasectomy.
- Sexual abstinence (i.e., refraining from heterosexual intercourse during the entire period of risk associated with SB-913, when this is in line with the preferred and usual lifestyle of the subject).

For details, refer to the Laboratory Manual.

### 9.12 Clinical Laboratory Tests

Clinical laboratory tests are summarized in Table 2. For details, refer to the Laboratory Manual.

**Table 2. Clinical Laboratory Tests.**

| **Hematology** | **Urine** (with microscopic examination) | **Serum Chemistry** |
|---|---|---|
| Complete blood count with differential and platelet count | Glucose | Sodium (Na) |
| | Protein | Potassium (K) |
| | Bilirubin | Chloride (Cl) |
| | Blood | Carbonate ($CO_3^{2-}$) |
| | pH | Calcium (Ca) |
| | Specific gravity | Phosphate ($PO_4^{3-}$) |
| | | Blood urea nitrogen |
| | | Creatinine |
| | | Glucose |
| | | Uric acid |
| | | Lactate dehydrogenase (LDH) |

For pediatric cohorts, assessments requiring blood draws should be obtained over multiple days if needed to ensure that no greater than 0.8 mL/kg of blood is drawn in any 24-hour period.

### 9.13 Liver Panel

Liver function testing will include assessment of AST, ALT, total and direct bilirubin, alkaline phosphatase, LDH, albumin, and total protein levels. Since liver function testing is important to closely monitor for transaminitis due to AAV-mediated immunogenicity in this study, it is strongly recommended that subjects refrain from consuming alcohol and from taking liver-toxic medications and herbal supplements for the study period of one year after SB-913 administration. Liver panel will be performed twice a week for at least the first 20 weeks post-SB-913 infusion and may be conducted at home if the subject is remote. Blood samples for liver panel shall be drawn 2-4 days apart when possible, except for the first week when they will be drawn on the Day 1 and Day 7 visits. Subsequent to discontinuation of prednisone or equivalent corticosteroid, liver panel will be performed at all study visits for the duration of the study. Liver panel does not need to be drawn as a separate blood sample if Clinical Laboratory Tests are obtained at the same visit. For details, refer to the Laboratory Manual.

### 9.14 MPS II Gene Sequencing

MPS II gene sequencing will be performed at Screening to confirm the clinical diagnosis of MPS II. The assay may be performed on blood or saliva samples; however for pediatric subjects (cohorts 5 through 8), saliva samples are strongly preferred. For details, refer to the Laboratory Manual.

### 9.15 Single-Nucleotide Polymorphism (SNP) Analysis

A SNP assay will be performed at Screening to identify polymorphisms in the ZFN-targeted region of the albumin locus. The assay may be performed on blood or saliva samples; however for pediatric subjects (cohorts 5 through 8), saliva samples are strongly preferred. Subjects with polymorphisms in the ZFN-targeted region of the albumin locus are not eligible to participate in this study. For details, refer to the Laboratory Manual.

### 9.16 Viral Load

Testing for HIV, HBV, and HCV will be conducted at Screening. Subjects with a diagnosis of HIV or evidence of active HBV or HCV infection are not eligible to participate in this study. For details, refer to the Laboratory Manual.

### 9.17 Neutralizing Antibodies to AAV2/6

The level of neutralizing antibodies to AAV2/6 will be measured at Screening to assess the subject's pre-existing immune response to AAV2/6. Subjects with elevated pre-existing neutralizing antibodies to AAV2/6 are not eligible to participate in this study. For details, refer to the Laboratory Manual.

### 9.18 GAG Testing in Urine and Blood

GAGs are metabolites that accumulate in MPS II due to lack of active IDS enzyme. GAG accumulation is responsible for diffuse organ toxicity and damage in MPS II. To monitor the effect of SB-913 administration, GAG levels (including total GAG, DS GAG, and HS GAG) will be measured in urine and tissues (including blood, liver tissue, and CSF) throughout this study. Samples GAG testing in blood and urine 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. For details, refer to the Laboratory Manual.

### 9.19 Circulating AFP Level

Clinical laboratory measurement of AFP will be performed to monitor for potential development of malignancy. Subjects with elevated abnormal circulating AFP at Screening are not eligible to participate in this study. For details, refer to the Laboratory Manual.

### 9.20 Vector Genome PCR

Plasma, saliva, urine, stool, and semen (males only) samples will be analyzed by PCR to determine clearance of SB-913 vector genomes. Each type of sample (plasma, saliva, urine, stool, semen) should 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 pediatric subjects (cohorts 5 through 8) at the discretion of the Principal Investigator. For details, refer to the Laboratory Manual.

### 9.21 Pulmonary Function Tests (PFTs)

MPS II is often associated with significant pulmonary complications. PFTs are a common method for evaluating respiratory function, and will be conducted in this study as permitted by the subject's capacity. For details, refer to the Study Reference Manual.

### 9.22 6-Minute Walk Test (6MWT)

A 6MWT will be performed, as permitted by subject's capacity, to measure endurance following the American Thoracic Society Guidelines. For details, refer to the Study Reference Manual.

### 9.23 Neurocognitive Abilities Tests

WASI-II, WPPSI-IV, and BSID-III are widely-used neurocognitive tests that have been validated and are easily administered. Given the broad age-range of study participants and variability of CNS involvement due to MPS II, the appropriate test will be determined for each subject at Screening visit following a neurocognitive abilities assessment. Based on this initial evaluation, either the WASI-II, WPPSI-IV, or the BSID-III will be administered to each subject beginning at the Baseline visit. The same test should be used throughout the duration study when possible to allow for longitudinal evaluation.

The VABS-II test is given to all subjects and provides a measure of adaptive behaviors, including ability to cope with environmental changes, to learn new skills, and to demonstrate independence.

The tests will be administered by a trained psychologist or psychometrist to determine neurocognitive function over time after SB-913 administration. Neurocognitive testing will be conducted as permitted by the subject's capacity. For details, refer to the Study Reference Manual.

### 9.24 MRI of Liver

MRI of the liver is commonly used to evaluate liver pathology in patients with MPS II, and will be performed in this study to evaluate liver and spleen volumes, as well as to screen and monitor for the potential development of liver masses. For details, refer to the Study Reference Manual and the Imaging Guidelines.

### 9.25 MRI of Brain and Cervical Spine

MRI of the brain and cervical spine is commonly used to evaluate neurological and skeletal complications in patients with MPS II, and will be performed in this study to evaluate for changes in clinical soft tissue and/or bone appearance. The baseline MRI of brain and cervical spine may be obtained at Screening (together with MRI for liver) instead of at Baseline at the Principal Investigator's discretion. For details, refer to the Study Reference Manual and the Imaging Guidelines.

### 9.26 Adrenocorticotropic Hormone Stimulation (Cosyntropin) Test

An ACTH stimulation test will be performed prior to beginning and discontinuing a prednisone or equivalent corticosteroid regimen to evaluate adrenocortical function. During the test, vital signs should be monitored and recorded every hour. For details, refer to the Study Reference Manual.

### 9.27 IDS Testing in Blood

IDS activity in blood will be measured to determine whether IDS is being produced and is active. IDS activity measurements may be conducted on plasma, serum, whole blood, dried blood spot, leukocytes, or other blood component. Samples must be obtained 7 days after ERT administration (+/- 1 day) and prior to the next ERT infusion. IDS and GAG testing in blood will both be measured concurrently from the same blood sample. For details, refer to the Laboratory Manual.

### 9.28 Liver Biopsy

The proposed mechanism of action of SB-913 is to introduce the hIDS transgene into a precise location in the albumin locus. To determine the efficiency of SB-913, liver tissue will be obtained by liver biopsy, unless contraindicated by the Principal Investigator or physician, and analyzed by histopathologic examination, testing for GAG levels, and high-throughput sequencing of the albumin locus. Further, subjects with an elevated AFP or MRI mass suspicious for HCC or greater than 2 cm will undergo liver biopsy. Histopathologic examination and genomic analysis will be performed to determine the origin and nature of the tumor. For details, see Appendix 4 and refer to the Study Reference Manual.

### 9.29 Lumbar Puncture

MPS II often causes neurocognitive decline due to a buildup of GAGs in the brain. To determine if GAG levels in the CSF are changed after SB-913 administration, lumbar punctures will be performed on all subjects, unless contraindicated by Principal Investigator or physician. CSF samples may also be tested for cell count, total protein, glucose, and other MPS-related biomarkers. For details, refer to the Study Reference Manual.

### 9.30 Immunogenicity Assays

Exploratory research assays, including total antibodies to AAV2/6, ZFN, and IDS immunogenicity will be performed. At the discretion of the Principal Investigator, this assessment may be waived for pediatric subjects (cohorts 5 through 8) to reduce required blood volumes. For details, refer to the Laboratory Manual.

### 9.31 Laboratory Assessments in Pediatric Subjects

Although safety monitoring of subjects with clinical laboratory testing is necessary in this study, the potential impact of taking multiple blood samples in children must be assessed at all times. Therefore, all blood draws in pediatric cohorts should be minimized when possible to ensure the safety and welfare of the subjects, particularly in the case of younger children. In accordance with accepted guidance, no more than 1% of total blood volume (0.8 mL/kg) should be drawn in pediatric subjects in any 24-hour period unless medically-indicated based on the judgement of the Principal Investigator (Veal et al, 2014). In addition, it is encouraged to utilize procedures to minimize any pain and distress associated with blood sampling when possible, such as use of intravenous catheters, collection from central catheters if in place, use of local anesthesia for needle sticks, etc. (For details, refer to the Laboratory Manual).

### 9.32 ERT Administration Log

Frequency of ERT administration will be studied before and after administration of SB-913. Therefore, each dose of ERT given to the subject from the time of Screening will be recorded on the ERT Administration Log, including date and time of start and stop of ERT infusion. At each indicated visit, documentation of all ERT administration since the last visit must be obtained and confirmed. An assumed standing schedule (e.g., weekly) should not be used.

### 9.33 ERT Clinical Assessment

A clinical assessment of the need for ERT must be conducted at the ERT Withdrawal Follow-Up visit. The Principal Investigator should determine if chronic weekly ERT infusions will be resumed or if the subject may continue without ERT, and indicate the decision on the appropriate eCRF. The assessment will be made based on the clinical judgement of the Principal Investigator and in

consultation with the Medical Monitor, taking into account all information available (which may include but is not limited to AEs, clinical laboratory testing, IDS levels, GAG levels, 6MWT, PFTs, and other available data). The ERT Clinical Assessment may be completed again at any time post-ERT withdrawal if there is a clinically significant change in the status of the subject's ERT administration.

# 10. SAFETY MONITORING AND ADVERSE EVENTS

## 10.1 Definitions

### 10.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or a clinical trial subject administered a medicinal product. An AE does not necessarily have a causal relationship with the administered treatment. The term can include any of the following events that develop or increase in severity during the course of the study:

- Any sign, symptom, or physical examination finding that worsens in nature, severity, or frequency compared to Baseline, whether thought to be related or unrelated to the condition under study.
- Any clinically significant laboratory abnormality or laboratory abnormality that requires medication or hospitalization.
- All reactions associated with the use of the study treatment, including those occurring as a result of an overdose, abuse, withdrawal phenomena, sensitivity, or toxicity to the study treatment.
- Concurrent illness.
- Injury or accident.

A pre-existing condition is one that is present prior to or at the start of the study, and is to be reported as part of the subject's medical history. It should be reported as an AE only if the frequency, intensity, or the character of the condition worsens during study participation.

### 10.1.2 Adverse Reaction

An adverse reaction (AR) is any untoward and unintended response to a medicinal product related to any dose administered. The phrase "response to a medicinal product" means that a causal relationship between the medicinal product and the AR is at least a reasonable possibility (i.e., there are facts [evidence] or arguments to suggest a causal relationship).

The definition of an AR also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

### 10.1.3 Unexpected Adverse Event or Adverse Reaction

An Unexpected AE or Unexpected AR is an AE or AR, the nature or severity of which is not consistent with the reference safety information (RSI) for the product (e.g., Investigator's Brochure).

### 10.1.4 Serious Adverse Event or Serious Adverse Reaction

An AE or AR is considered "serious" if, in the view of either the Principal Investigator or the Sponsor, it results in any of the following outcomes:

- Death.
- Life-threatening AE (i.e., AE in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions.
- Congenital anomaly/birth defect in the offspring of an exposed subject.
- Important medical event that may jeopardize the subject or may require an intervention to prevent one of the above characteristics/consequences (i.e., event may not result in death, be life-threatening, or require hospitalization, but based on appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, and development of drug dependency or drug abuse).

With regard to results obtained from tests in laboratory animals or *in vitro* testing, whether or not conducted by Sponsor, a SAE includes any event suggesting significant risk to human subjects.

### 10.1.5 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is any SAE that is assessed as both unexpected and, in the view of either the Principal Investigator or the Sponsor, as an AR.

## 10.2 Adverse Event Reporting Period

AEs will be monitored continuously during the study from the time that the subject has provided written informed consent through the subject's last day of study participation. Subjects will be queried and events will be assessed at each clinic visit. A treatment-emergent AE (TEAE) is any AE with an onset from any time from administration of the study treatment through the last study visit, whether or not it is considered causally related to the study treatment.

## 10.3 Recording of an Adverse Event

The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and determining that documentation of the event is adequate. He/she is responsible for determining the severity of the AE and its relationship to the investigational drug. The Principal Investigator may delegate these duties to sub-investigators but must assure that these sub-investigators are qualified to perform these duties under the supervision of the Principal Investigator.

All AEs will be recorded in the subject's CRF. The detailed description of the event will include appropriately graded severity of the AE and its relationship to the investigational product. 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 Common Terminology Criteria for Adverse Events version 4.03 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.

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

Any Grade 3 and 4 clinical laboratory results that represents an increase in severity from Baseline will be reported as an AE if it is not associated with a diagnosis already reported on the CRF. A Grade 1 or 2 clinical laboratory abnormality should be reported as an AE only if it is considered clinically significant by the Principal Investigator.

In the event of death, the cause of death should be recorded as the AE and reported as a SAE. "Death" is not the AE; "death" is an outcome. The term "death" should be reported as an SAE only if the cause of death is not known and cannot be determined. If an autopsy is performed, a copy of the autopsy report should be obtained if possible. The Principal Investigator should make every effort to obtain and send death certificates and autopsy reports to Sponsor.

### 10.4 Serious Adverse Event Reporting Period

All SAEs, whether or not unexpected or considered to be associated with the administration of study treatment, must be reported immediately to Sponsor or its designees, and must be submitted to Sponsor or its designees on an SAE Report form within 24 hours of the Principal Investigator's discovery of the event. Please refer to the study reference manual for SAE reporting guidelines and contacts.

The reporting period for all SAEs is from subject consenting through the last study visit.

The Principal Investigator is responsible for promptly notifying the IRB/IEC or equivalent in accordance with local regulations of all SAEs. The National Institutes of Health (NIH) requires that all investigators participating in gene transfer research to report all SUSARs. SUSARs will be reported to the appropriate regulatory authorities (FDA/MHRA or equivalent) according to the requirements for expedited safety reporting. Sangamo or its designee will assume the responsibility for reporting SUSARs to the FDA/MHRA or equivalent.

All "serious" events must be followed with appropriate medical management until resolved or stabilized.

## 10.5 Recording of a Serious Adverse Event

SAEs reported by telephone must be recorded on a written SAE Report Form provided by Sponsor or its designees. The SAE report form must be submitted to Sponsor or its designees within 24 hours.

The Medical Monitor will then advise the Principal Investigator regarding the nature of any further information or documentation that is required. Follow-up reports must be submitted within 24 hours from the time that the additional information becomes available.

## 10.6 SUSAR Reporting Obligations

Sponsor or its designee will submit SUSAR reports to appropriate regulatory authorities (including Competent Authorities in all Member States concerned), Ethics Committees, and Principal Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7-calendar days of first knowledge of the event and follow-up information submitted within an additional 8 days. All other SUSARs will be submitted within 15-calendar days of first knowledge of the event.

Principal Investigators are required to report any urgent safety matters to Sponsor or its designee within 24 hours. Sponsor or its designee will inform the regulatory authorities, ethics committees, and Principal Investigators of any events (e.g., change to the safety profile of the study treatment, major safety findings) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may affect the safety of subjects participating in the clinical trials, as required, in accordance with applicable laws and regulations. The reporting period for urgent safety issues is the period from the signing of the ICF through the last study visit.

The Principal Investigator will notify the IRB/IEC or equivalent of SAEs and urgent safety matters, in accordance with IRB/IEC or equivalent requirements and local laws and regulations. A copy of this notification must be provided to Sponsor or its designee.

## 10.7 Pregnancy and Pregnancy of a Partner Reporting

Pregnancies or pregnancies of partners occurring during this study are to be reported on the Pregnancy Reporting Form. In general, it is expected that pregnancies are reported in the same timeframe as SAEs. Regardless of whether the subject has discontinued participation in the study, the course of all pregnancies and any AEs will be followed to partum at minimum.

# 11. TREATMENT SCHEDULE, DOSE ESCALATION, AND STOPPING RULES

## 11.1 Schedule for Subject Treatment

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

| Cohort # | Age Range (y) | 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 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 (see Section 12.3). 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 (see Pediatric Dosing).

Approximately 2 additional subjects may be added to any cohort after SMC review of study data if safety criteria are met (see Safety Monitoring Committee), with up to a total of 32 subjects in the study.

## 11.2 Dose Escalation Rules

Within each cohort, treatment will be staggered so that each subsequent subject will not be infused until the preceding subject has been observed for at least 4 weeks.

Dose escalation to the next cohort will not occur until at least 4 weeks after the last subject in the preceding cohort has been dosed and the safety data from the prior cohort has been reviewed by the SMC and the SMC has agreed to dose escalate.

Dosing and dose escalation will be paused if a Grade 3 or higher AE occurs, or if two Grade 2 AEs occur within the same organ class and persist for 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. In such an event, the SMC will be convened to assess for potential dose-limiting toxicity (DLT) and to provide recommendations on whether to expand the cohort at the same dose level, to dose de-escalate, or to continue the study as planned (refer to the Stopping Rules).

## 11.3 Pediatric Dosing

Pediatric dosing will not be initiated until adult safety data has been obtained and reviewed by the SMC, and only after the following conditions have been met:

- ≥6 months of safety data from 2 adults treated with SB-913 at any dose; and
- ≥4 weeks of safety data from 2 adults treated with SB-913 at the intended pediatric dose.

Younger pediatric subjects (Cohorts 7 and 8) will not be dosed until older pediatric subjects (Cohorts 5 and 6) have been dosed at the same dose level and ≥4 weeks of safety data from each older subject has been reviewed by the SMC.

## 11.4 ERT Withdrawal

ERT using Elaprase (idursulfase) or equivalent is the only approved therapy for MPS II. ERT is beneficial but has significant drawbacks, which include the need for continuous life-long treatment; development of neutralizing antibodies; lack of efficacy in the brain (due to inability to cross the blood-brain barrier); continued cardiac, musculoskeletal, and upper airway complications; and the inconvenience and cost of weekly IV infusions (Tomanin et al, 2014).

The goal of SB-913 treatment is to abrogate or decrease the need for enzyme replacement therapy, by using engineered zinc finger nucleases (ZFNs) to site-specifically integrate a corrective copy of the enzyme iduronate-2-sulfatase (hIDS) transgene into the genome of the subject's own hepatocytes in vivo, resulting in life-long, liver-specific expression of IDS. Therefore, subjects who have received SB-913 may no longer require weekly administration of ERT, and may be considered for withdrawal of ERT (if applicable).

ERT withdrawal will be a controlled process with additional safety monitoring to reduce potential risk to the subject, and is an optional part of the study.

ERT withdrawal may be initiated by the Principal Investigator after consultation with the Sponsor, and only in subjects who are willing and who meet all of the following criteria:

- Are ≥12 weeks post-administration of SB-913.
- Are medically stable and can tolerate temporary discontinuation of ERT in the judgement of the Principal Investigator.
- Agree to additional safety monitoring and lab testing until ERT Withdrawal Follow-Up visit (see Appendix 2).

Study visits associated with ERT withdrawal may occur concurrently or independent of regular scheduled study visits, but should be combined with regular scheduled study visits whenever possible to reduce study burden. When combined, assessments associated with ERT withdrawal that are duplicated at the regular scheduled study visits should be waived (see Appendix 1). 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 after the ERT Withdrawal Follow-Up visit. However, ERT may be re-initiated at any time based on clinical circumstances or at the judgement of the Principal Investigator.

ERT withdrawal may be repeated if previously unsuccessful. However, ERT withdrawal may not be attempted until at least 12 weeks after ERT has been resumed, and only at the discretion of the Principal Investigator and in consultation with the Sponsor. Subjects undergoing repeat ERT withdrawal must be willing and meet the criteria for initial ERT withdrawal listed above.

Documentation of dosing and administration of all ERT should be obtained and recorded on the ERT Administration Log.

## 11.5 Study Stopping Rules

The safety data for all subjects within a cohort will be evaluated by the SMC at least 4 weeks after the last subject within that cohort was infused with SB-913. Safety data including AEs and clinical laboratory results (chemistry, hematology, etc.) will be evaluated to determine if it is safe to dose escalate. Subjects in the subsequent cohort may be screened and enrolled prior to the safety review

but will not be infused until the SMC has reviewed the data and approved the study for cohort escalation.

The SMC will also be convened to recommend whether the study should be stopped if any of the following criteria are met:

- 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 study may also be stopped for any of the following reasons:

- Sangamo, in consultation with the SMC or Regulatory Agency, decides for any reason that subject safety may be compromised by continuing the study.
- Sangamo decides to discontinue development of SB-913.

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

# 12. SUBJECT WITHDRAWAL/DISCONTINUATION, AND SAFETY MONITORING COMMITTEE

## 12.1 Subject Withdrawal and Discontinuation from Study

Subjects may withdraw or should be discontinued from study for any of the following reasons:

- Request by the subject to withdraw.
- Request of Sangamo or primary care provider if he or she thinks the study is no longer in the best interest of the subject.
- Pregnancy prior to SB-913 infusion.
- Subject judged by the Principal Investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the IRB/IEC or equivalent, Office for Human Research (OHR), regulatory authority (e.g. FDA/MHRA or equivalent), Principal Investigator, or Sangamo.

Subjects will be strongly encouraged to continue and comply with follow-up safety evaluations. If a subject withdraws consent or discontinues from the study post-study treatment, a conference between the Principal Investigator and Medical Monitor will take place to ensure that the subject understands the importance of the study follow-up and that the study treatment cannot be reversed even if a subject drops out of the study follow-up. If the subject agrees, a reduced follow-up testing schedule may be arranged including telephone call and safety labs to assess treatment-related AEs and disease status.

## 12.2 Safety Monitoring and Mitigation Plan

The liver function (total and direct bilirubin, alkaline phosphatase, ALT, AST, LDH, albumin, and total protein) of study subjects will be monitored closely throughout the study as indicated above in Section 9.13**.**

Key potential anticipated risks are:

- Development of transaminitis due to cell-mediated immunity to the AAV capsid protein, the engineered ZFNs, or the endogenous hIDS; to minimize the potential immune response and to preserve hepatic function, prednisone or equivalent corticosteroid will be administered prophylactically starting 2 days prior to the SB-913 infusion and will be tapered over a period of approximately 20 weeks (see Appendix 3).
- Reduction in albumin synthesis; this is not expected given the small fraction (<1%) of transduced cells in which the albumin locus will be disrupted, and has not been observed in animal studies, in which levels of transduction and albumin locus disruption exceeded by several fold those expected in humans.
- Off-target modification at the SMCHD1 locus; this is not expected given that no off-target activity has been observed at clinically relevant levels of albumin on-target activity in human cells *in vitro* (see Section 8.1.2).

## 12.3 Safety Monitoring Committee (SMC)

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.

# 13. STATISTICAL ANALYSIS AND DATA ANALYSIS

The primary objective of this study is to evaluate the safety and tolerability of SB-913. All statistical summaries will be descriptive in nature (e.g., means, standard deviations, and percentages). All subjects who receive any portion of the SB-913 infusion will be included in the analyses, even those who withdraw prematurely from the study. All results will be presented separately for each of the SB-913 dose levels. All analyses, summaries, and listings will be performed using SAS version 9.2 or later.

## 13.1 Determination of Sample Size

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.

## 13.2 Statistical Analyses

Efficacy analyses will be descriptive and exploratory in nature. Continuous variables will be summarized by means, standard deviations, medians, and ranges by cohort. Categorical variables will be summarized with counts and percentages per category by cohort.

## 13.3 Analysis of the Conduct of the Study

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

Demographic and baseline characteristics, such as age, sex, and race 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.

## 13.4 Primary Endpoint

The primary endpoint of this study is the incidence of treatment-emergent AEs (including SAEs).

Additional safety evaluations will include:

- Routine hematology, chemistry, and liver function laboratory tests, vital signs, physical exam, ECG, ECHO, and concomitant medications.
- Cranial nerve exam and muscle strength testing.
- Serial AFP testing and MRI of liver to evaluate for liver mass.

Safety assessment will be performed on all subjects. All reported AEs will be coded to a standard set of terms using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent adverse events 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 serious adverse events and AEs related to study treatment will be summarized.

Laboratory data will be summarized for each time-point at which specimens are collected. Change-from-Baseline values may be calculated for selected laboratory parameters. Shift-tables (Change-from-Baseline relative to the normal range) may be constructed for selected laboratory parameters.

### 13.5 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.

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.

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

### 13.6 Exploratory Endpoints

The following are exploratory endpoints for this study:

- Change from Baseline in:
  - Total GAG, DS GAG, and HS GAG levels measured in tissues (including blood, liver tissue, and CSF).
  - Percentage and durability of gene modification at the albumin locus in liver tissue obtained at biopsy.
  - Forced vital capacity measured by PFTs.
  - Distance walked measured by 6MWT.
  - 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, WPPSI-IV, or BSID-III, and by VABS-II.

- Histopathological exam of liver tissue.
- Immune response to AAV 2/6, ZFNs, and IDS measured in serum.

Analysis details for the exploratory endpoints will be provided in the Statistical Analysis Plan.

## 14. INVESTIGATOR OBLIGATIONS

The Principal Investigator will ensure that the study is conducted in compliance with the protocol, Declaration of Helsinki, ICH Guidelines for Good Clinical Practice (E6), and all regulatory and institutional requirements, including those for subject privacy, informed consent, IRB/IEC or equivalent approval, and record retention.

### 14.1 Informed Consent

No investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.

Sangamo will provide the Principal Investigator with a template for the consent form. State and local laws and/or institutional requirements may require the disclosure of additional information in the informed consent. The proposed consent form must be submitted to Sangamo prior to submission to the IRB/IEC or equivalent to ensure that it meets Sangamo standards for consent forms. The IRB/IEC or equivalent must approve the consent form. A copy of the approved form must be submitted to Sangamo.

Prior to the initiation of any procedures relating to the study, informed consent shall be documented by the use of a written consent form approved by the IRB/IEC or equivalent and signed and dated by the subject at the time of consent. A copy of the signed informed consent will be given to the person signing the form. The Principal Investigator must keep each subject's signed consent form on file for inspection by a regulatory authority at any time.

### 14.2 Institutional Review Board/Ethics Committee and BioSafety Committee

This protocol, informed consent document, and relevant substantive data are to be submitted to the appropriate IRB/IEC or equivalent and BioSafety Committee (BSC) for review and approval before the initiation of the study. Amendments to the protocol will also be submitted to the IRB/IEC or equivalent and BSC (as appropriate) prior to implementation of the change. A letter documenting the IRB/IEC or equivalent and BSC approval must be received by Sangamo prior to initiation of the study.

### 14.3 Protocol Amendments

Any changes to this protocol will be initiated by Sangamo in writing as a protocol amendment. The amendment must be submitted to the IRB/IEC or equivalent together with a revised informed consent form, if applicable. Written documentation of IRB/IEC or equivalent approval must be received before the amendment may take effect.

### 14.4 Subject Privacy

Subject medical information obtained for the purposes of this trial is confidential, and disclosure

to third parties other than those noted below is prohibited. Upon the subject's request and written permission, medical information may be given to the subject's personal physician or other appropriate medical personnel responsible for the subject's welfare. Data generated for this study must be available for inspection on request to representatives of the FDA/MHRA or equivalent, other national or local health authorities, Sangamo, and the associated IRB/IEC or equivalent.

Release of research results or data that reveal subject names or other identifiers, such as photographs, audio, or videotapes, must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individual Health information, 45 CFR 164.508. Written authorization must be obtained from the subject and IRB/IEC or equivalent prior to release of such information. Identifiable subject data may not be used for purposes of promoting the investigational product.

### 14.5 Reporting Obligations

Sangamo, the Sponsor of this study, is required to report to the regulatory authorities (e.g., FDA/MHRA or equivalent) annually on the status of the trial. Status reports must be filed by the Principal Investigator with his/her IRB/IEC or equivalent on an annual basis.

The Principal Investigator is also responsible for informing his/her IRB/IEC or equivalent of the progress of the study and for obtaining annual IRB/IEC or equivalent renewal. The IRB/IEC or equivalent must be informed at the time of completion of the study. The Principal Investigator should provide his/her IRB/IEC or equivalent (if required by the institution) with a summary of the results of the study.

# 15. ADMINISTRATIVE CONSIDERATIONS

## 15.1 Study Documentation

The Principal Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be suitable for inspection by Sangamo or the FDA/MHRA or equivalent at any time, and should consist of the following elements:

- Subject files containing the completed medical records, supporting source documentation, electronic CRFs, and the IRB/IEC or equivalent approved Informed Consent signed by subjects.
- Study files containing all versions of the IRB/IEC or equivalent approved protocol with all amendments, IRB/IEC or equivalent approved informed consent forms, copies of all pre-study documentation, Form FDA 1572, and all correspondence to and from the IRB/IEC or equivalent and Sangamo.

The Principal Investigator should maintain a list of appropriately qualified persons who are delegated to perform significant study-related studies. In addition, the Principal Investigator should maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on the source documents and electronic CRFs.

## 15.2 Record Retention

The Principal Investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the Principal Investigator shall retain these records until 2 years after the investigation is discontinued and the FDA/MHRA or equivalent are notified. Study records shall be kept for at least 25 years or the maximum period by applicable policy or regulation (whichever is greater). However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with Sangamo. It is the responsibility of Sangamo to inform the Principal Investigator as to when these documents no longer need to be retained.

## 15.3 Case Report Forms

The Principal Investigator is responsible for the quality of the data recorded on the CRF. The data recorded should be a complete and accurate account of the subject's record collected during the study.

Clinical data will be recorded on CRFs provided by Sangamo. All forms must be legible and complete. The Principal Investigator must review all entries for completeness and correctness. When changes or corrections are made on any CRF, an audit trail will be generated to record date and time when a change is made, who made the change, and reason for the change as needed. The original entry should not be obscured.

The Principal Investigator agrees to complete and sign CRFs in a timely fashion at the end of the study, and to make them available to the Study Monitor for full inspection. In addition, all data queries should be resolved promptly.

## 15.4 Termination of the Study

Sangamo retains the right to terminate the study and remove all the study materials from the study site at any time for any reason. Specific instances that may precipitate such termination are as follows:

- Completion of the study at an investigational site.
- Principal Investigator withdrawal from participation in study.
- Termination of study by Sangamo.

## 15.5 Study Monitoring

Sangamo, as Sponsor of this study, is responsible to regulatory authorities for ensuring the proper conduct of the study with regard to protocol adherence and validity of the data recorded on the CRFs presented to the regulatory authorities. Sangamo has therefore assigned a Clinical Monitor and a Medical Monitor to this study. Their duties are to aid the Principal Investigator and, at the same time, Sangamo in the maintenance of complete, legible, well-organized, and easily retrievable data. In addition, a Sangamo Study Monitor will ensure an understanding of the protocol, reporting responsibilities, and the validity of the data.

Individual study sites will be monitored by a Sangamo representative at appropriate intervals to assure satisfactory consenting process, data recording, and protocol adherence. To perform their roles well, the Sangamo monitors must be given direct access to primary subject data (source documents) that support data entered onto the CRFs. The Principal Investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. Each study center will also be routinely monitored by telephone and/or by email to keep abreast of subject status and to answer questions.

Regulatory authorities, the IRB/IEC or equivalent, and/or Sangamo's Clinical Quality Assurance group may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Principal Investigator, who must provide support at all times for these activities.

The Principal Investigator or designated person should agree, as a minimum requirement, to record the following information in the subject notes:

- Protocol identification number, brief description, or title of study.
- Date and statement that subject has given written informed consent.
- All study follow-up visit dates.
- AE as described in Section 10 of this protocol.

Entries in the subject notes must contain the signature or initials of the person making the entries.

The Study Monitor will perform source data verification at each monitoring visit.

## 15.6 Confidential Information and Publication

All information provided by Sangamo to the Principal Investigator and any data or results generated in the performance of this clinical trial are considered confidential and remain the sole property of Sangamo. The Principal Investigator shall maintain this information in confidence and use this information solely for in the conduct of the study unless otherwise expressly agreed to in writing by Sangamo.

The Principal Investigator understands and agrees that Sangamo shall have the right to use the data or results generated in the performance of the study for any purpose, including in registration documents for regulatory authorities in the U.S. or abroad, or for public dissemination in the form of papers, abstracts, posters, or other informational materials to be presented at scientific meetings, or published in professional journals, or as a part of an academic thesis. The Principal Investigator further understands and agrees that Sangamo shall have the right to first publication of the data or results of the study, which is intended to be a joint, multi-center publication of the study results made by Sangamo in conjunction with the Principal Investigators from all appropriate investigational sites contributing data, analysis, and comments. Authorship of publications resulting from this study will be based on customary standards for attribution of authorship taking into consideration factors such as significance of contribution to the design of the study, analysis and interpretation of the data, and critical review of the publication. Subsequent to the first publication of the study results by Sangamo, the Principal Investigator may publish the Principal Investigator's site specific data or results. If the Principal Investigator wishes to publish the Principal Investigator's site specific data or results, a copy of such proposed publications, papers, abstracts, or other written materials, or an outline of any proposed oral presentations, shall be submitted to Sangamo for review at least 60 days prior to submission of such written materials for publication, or any proposed oral presentation. Sangamo shall have the right to review and comment on such written material or outline, and to confirm the accuracy of the data described therein by comparison with that collected during the course of this study. In addition, Sangamo shall have the right to require the Principal Investigator to, and Principal Investigator shall, remove specifically identified confidential information of Sangamo (other than the data or results of the study) and/or delay the proposed publication for an additional 60 days to enable Sangamo to file patent applications.

## 15.7. Study Funding

The costs necessary to perform the study will be agreed to by the Principal Investigator and/or the management of the study facility, and will be documented in a separate financial agreement. All financial agreements will be signed by the Principal Investigator and Sangamo.

## 16. REFERENCES

Blewitt ME, Gendrel AV, Pang Z, Sparrow DB, Whitelaw N, Craig JM, Apedaile A, Hilton DJ, Dunwoodie SL, Brockdorff N, Kay GF, Whitelaw E. SmcHD1, containing a structural-maintenance-of-chromosomes hinge domain, has a critical role in X inactivation. Nat Genet. 2008 May;40(5):663-9.

Burrow TA, Leslie ND. Review of the use of idursulfase in the treatment of mucopolysaccharidosis II. Biologics. 2008 Jun;2(2):311-20.

Burton BK, Giugliani R. Diagnosing Hunter syndrome in pediatric practice: practical considerations and common pitfalls. Eur J Pediatr. 2012 Apr;171(4):631-9.

Cardone M, Polito VA, Pepe S, Mann L, D'Azzo A, Auricchio A, Ballabio A, Cosma MP. Correction of Hunter syndrome in the MPS II mouse model by AAV2/8-mediated gene delivery. Hum Mol Genet. 2006 Apr 1;15(7):1225-36.

Davidoff AM, Nathwani AC. Genetic Targeting of the Albumin Locus to Treat Hemophilia. N Engl J Med. 2016 Mar 31;374(13):1288-90.

Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology. 1994 Jun;19(6):1513-20.

El-Serag HB, Davila JA. Surveillance for hepatocellular carcinoma: in whom and how? Therap Adv Gastroenterol. 2011 Jan;4(1):5-10.

Gabriel R, Lombardo A, Arens A, Miller JC, Genovese P, Kaeppel C, Nowrouzi A, Bartholomae CC, Wang J, Friedman G, Holmes MC, Gregory PD, Glimm H, Schmidt M, Naldini L, von Kalle C. An unbiased genome-wide analysis of zinc-finger nuclease specificity. Nat Biotechnol. 2011 Aug 7;29(9):816-23.

Larsen M, Rost S, El Hajj N, Ferbert A, Deschauer M, Walter MC, Schoser B, Tacik P, Kress W, Müller CR. Diagnostic approach for FSHD revisited: SMCHD1 mutations cause FSHD2 and act as modifiers of disease severity in FSHD1. Eur J Hum Genet. 2015 Jun;23(6):808-16.

Lemmers RJ, Tawil R, Petek LM, Balog J, Block GJ, Santen GW, Amell AM, van der Vliet PJ, Almomani R, Straasheijm KR, Krom YD, Klooster R, Sun Y, den Dunnen JT, Helmer Q, Donlin-Smith CM, Padberg GW, van Engelen BG, de Greef JC, Aartsma-Rus AM, Frants RR, de Visser M, Desnuelle C, Sacconi S, Filippova GN, Bakker B, Bamshad MJ, Tapscott SJ, Miller DG, van der Maarel SM. Digenic inheritance of an SMCHD1 mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2. Nat Genet. 2012 Dec;44(12):1370-4.

Leong HS, Chen K, Hu Y, Lee S, Corbin J, Pakusch M, Murphy JM, Majewski IJ, Smyth GK, Alexander WS, Hilton DJ, Blewitt ME. Epigenetic regulator Smchd1 functions as a tumor suppressor. Cancer Res. 2013 Mar 1;73(5):1591-9.

Martin HR, Poe MD, Reinhartsen D, Pretzel RE, Roush J, Rosenberg A, Dusing SC, Escolar ML. Methods for assessing neurodevelopment in lysosomal storage diseases and related disorders: a multidisciplinary perspective. Acta Paediatr. 2008 Apr;97(457):69-75.

Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, Lowes L, Alfano L, Berry K, Church K, Kissel JT, Nagendran S, L'Italien J, Sproule DM, Wells C, Cardenas JA, Heitzer MD, Kaspar A, Corcoran S, Braun L, Likhite S, Miranda C, Meyer K, Foust KD, Burghes AHM, Kaspar BK. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. N Engl J Med. 2017 Nov 2;377(18):1713-22.

Minchiotti L, Galliano M, Caridi G, Kragh-Hansen U, Peters T Jr. Congenital analbuminaemia: molecular defects and biochemical and clinical aspects. Biochim Biophys Acta. 2013 Dec;1830(12):5494-502.

Muenzer J, Lamsa JC, Garcia A, Dacosta J, Garcia J, Treco DA. Enzyme replacement therapy in mucopolysaccharidosis type II (Hunter syndrome): a preliminary report. Acta Paediatr Suppl. 2002;91(439):98-9.

Muenzer J, Wraith JE, Beck M, Giugliani R, Harmatz P, Eng CM, Vellodi A, Martin R, Ramaswami U, Gucsavas-Calikoglu M, Vijayaraghavan S, Wendt S, Puga AC, Ulbrich B, Shinawi M, Cleary M, Piper D, Conway AM, Kimura A. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med. 2006 Aug;8(8):465-73.

Muenzer J, Bodamer O, Burton B, Clarke L, Frenking GS, Giugliani R, Jones S, Rojas MV, Scarpa M, Beck M, Harmatz P. The role of enzyme replacement therapy in severe Hunter syndrome-an expert panel consensus. Eur J Pediatr. 2012 Jan;171(1):181-8.

Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth. 2000 Oct;85(4):599-610.

Prinsen BH, de Sain-van der Velden MG. Albumin turnover: experimental approach and its application in health and renal diseases. Clin Chim Acta. 2004 Sep;347(1-2):1-14.

Shapiro EG, Nestrasil I, Rudser K, Delaney K, Kovac V, Ahmed A, Yund B, Orchard PJ, Eisengart J, Niklason GR, Raiman J, Mamak E, Cowan MJ, Bailey-Olson M, Harmatz P, Shankar SP, Cagle S, Ali N, Steiner RD, Wozniak J, Lim KO, Whitley CB. Neurocognition across the spectrum of mucopolysaccharidosis type I: Age, severity, and treatment. Mol Genet Metab. 2015 Sep-Oct;116(1-2):61-8.

Statland J, Tawil R. Facioscapulohumeral muscular dystrophy. Neurol Clin. 2014 Aug;32(3):721-8.

Sukegawa-Hayasaka K, Kato Z, Nakamura H, Tomatsu S, Fukao T, Kuwata K, Orii T, Kondo N. Effect of Hunter disease (mucopolysaccharidosis type II) mutations on molecular phenotypes of iduronate-2-sulfatase: enzymatic activity, protein processing and structural analysis. J Inherit Metab Dis. 2006 Dec;29(6):755-61.

Tang M, Li Y, Zhang X, Deng T, Zhou Z, Ma W, Songyang Z. Structural maintenance of chromosomes flexible hinge domain containing 1 (SMCHD1) promotes non-homologous end joining and inhibits homologous recombination repair upon DNA damage. J Biol Chem. 2014 Dec 5;289(49):34024-32.

Tomanin R, Zanetti A, D'Avanzo F, Rampazzo A, Gasparotto N, Parini R, Pascarella A, Concolino D, Procopio E, Fiumara A, Borgo A, Frigo AC, Scarpa M. Clinical efficacy of enzyme replacement

therapy in paediatric Hunter patients, an independent study of 3.5 years. Orphanet J Rare Dis. 2014 Sep 18;9:129.

Veal GJ. Blood volumes in pediatric clinical trials: a review of current regulations and guidance for research studies. Clin. Invest. (Lond.) 2014 4(11):1008-11.

Watkins S, Madison J, Galliano M, Minchiotti L, Putnam FW. Analbuminemia: three cases resulting from different point mutations in the albumin gene. Proc Natl Acad Sci U S A. 1994 Sep 27;91(20):9417-21.

Young ID, Harper PS, Newcombe RG, Archer IM. A clinical and genetic study of Hunter's syndrome. 2. Differences between the mild and severe forms. J Med Genet.1982 Dec;19(6):408-11.

# APPENDIX 1: SCHEDULE OF EVENTS

| 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[5] | |
| | (w/in 3 months of Baseline) | (w/in 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 | 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 | 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 | 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 | 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 | 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 |
| **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 |
| **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 |
| **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 |

# APPENDIX 1: SCHEDULE OF EVENTS (continued)

| 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[§] | |
| | (w/in 3 months of Baseline) | (w/in 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.

# APPENDIX 2: 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.

# APPENDIX 3: IMMUNOSUPPRESSION REGIMEN

| Weight of Subject (kg) | Oral Prednisone (mg/day) | | | | | |
|---|---|---|---|---|---|---|
| | Day -2 to Day 0 | 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. Blood for liver panel shall 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. 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 or equivalent corticosteroid, the prednisone or equivalent corticosteroid regimen 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 or equivalent corticosteroid course has been terminated.

An ACTH stimulation (cosyntropin) test will be performed prior to the first prednisone or equivalent corticosteroid dose and again during Week 20 or 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.

# APPENDIX 4: INSTRUCTION FOR LIVER BIOPSY SAMPLE COLLECTION AND TISSUE PREPARATION

SB-913 uses ZFN-gene specific targeted insertion of a hIDS donor transgene into the liver albumin genome locus in subjects with MPS II to provide long-term production of hIDS. To determine the efficiency of SB-913, liver tissue will be obtained by liver biopsy for analysis by histopathologic examination, testing for GAG levels, and site specific molecular analysis at the albumin locus. AFP levels will be monitored throughout the study, and abnormal results will be investigated by clinical evaluation and MRI. Any subject who has an elevated AFP and/or an MRI mass suspicious for HCC or greater than 2 cm will undergo liver biopsy. Histopathologic examination and integration site analysis will be performed to determine the origin and nature of the tumor.

Liver Biopsy Sample Collection and Tissue Preparation

Liver biopsy will be obtained at selected visits unless contraindicated by a Principal Investigator or physician. The liver biopsy should be divided into 3 samples when possible. One liver biopsy sample will be collected in 10% neutral buffered formalin and processed for histopathological evaluation. Two liver biopsy samples will be flash frozen in liquid nitrogen. Samples may be stored in a -80ºC freezer before shipment. The weight of liver tissue obtained from each biopsy sample will be forwarded to Sangamo.

The efficiency of SB-913 in targeting insertion of hIDS donor transgene to the liver will be measured by site specific molecular analysis of integration events at the albumin locus.

Additionally, the frequency of other genomic modification events like small insertions and deletions (indels) will be determined by Next Generation Sequencing (NGS) at the albumin locus and at the SMCHD1 locus, the only known off-target site of SB-913.

In addition, for any subject who undergoes liver biopsy due to an elevated AFP and/or an MRI mass suspicious for HCC, the albumin locus will be sequenced by NGS to examine the genetic diversity at the albumin ZFN cleavage site, which may provide information about the clonal origin of the suspicious mass. A single or limited number of modified albumin genotypes or AAV integration sites would indicate that the cells were derived from the clonal expansion of modified hepatocytes. A similar sequencing analysis will also be performed on the SMCHD1 locus to evaluate the genetic diversity at the only known off-target site of SB-913.