CLINICAL STUDY PROTOCOL

A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy via Zinc Finger Nuclease (ZFN) mediated targeted integration of SB-FIX in Subjects with Severe Hemophilia B

Protocol Number:	SB-FIX-1501
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EudraCT:	2017-004805-42
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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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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

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SB-FIX-1501 PROTOCOL SYNOPSIS

A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy via Zinc Finger Nuclease (ZFN) mediated targeted integration of SB-FIX in Subjects with Severe Hemophilia B	
Sponsor	Sangamo Therapeutics, Inc.
Investigational Products	SB-FIX is composed of three AAV2/6 vectors that encode: • Left ZFN (SB-42906) that targets bp 447-461 of the albumin locus, relative to the transcription initiation site (ZFN 1) • Right ZFN (SB-43043) that targets bp 468-485 of the albumin locus, relative to the transcription initiation site (ZFN 2) • Human FIX Donor cDNA with human albumin homology arms (SB- F9)
Study Design	Phase 1, open-label, ascending dose study
Study Rationale	Hemophilia B is an X-linked blood coagulation disorder due to a mutation of the factor IX (FIX) gene. FIX is a serine protease that is critical for the intrinsic clotting pathway. Patients with severe hemophilia B have functional FIX levels that are <1% of normal. If untreated, they suffer frequent hemorrhage into joints or muscles, either spontaneously or in response to mild trauma resulting in crippling arthropathy or premature death. The introduction of plasma derived FIX concentrates in the late 1960's has increased the median lifespan of patients in the developed world to 63 years. Restoration of hepatic production of functional FIX to >1% of normal levels can reduce or eliminate the need for prophylactic treatment with FIX concentrate, and if >5% can substantially reduce hemorrhage following all but the most severe trauma. However, chronic, repeated intravenous treatment is required for prophylaxis against spontaneous hemorrhage suggesting the need for alternative therapy. AAV8 mediated gene transfer of the FIX cDNA into liver cells has resulted in sustained increase of FIX levels (1-6%) with 6 of 10 subjects free of spontaneous hemorrhage at a median follow-up of 3.2 years. This study used self-complementary AAV2/8 with a liver specific promoter and the Factor IX cDNA that will reside episomally in the nucleus. The proposed study uses zinc finger nucleases to specifically insert AAV2/6 FIX cDNA in the liver albumin genome locus. The zinc finger nucleases induce a double strand break in the albumin gene, which is

A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy via Zinc Finger Nuclease (ZFN) mediated targeted integration of SB-FIX in Subjects with Severe Hemophilia B	
	repaired by homologous recombination with albumin sequences flanking the factor IX coding region, thus providing a long-term production of FIX in hemophilia B subjects by capturing the high level of albumin synthesis in the liver.
Objectives	**Primary:** Evaluate the safety and tolerability of SB-FIX. **Secondary:** 1. Change from baseline in FIX antigen and activity levels 2. Change from baseline in use of Factor IX replacement therapy 3. Change from baseline in frequency and severity of bleeding episodes 4. Immune response to FIX 5. Presence and shedding of AAV2/6 vector DNA, by PCR in plasma, saliva, urine, stool and semen **Exploratory:** Immune response to AAV2/6
Study Population	Male subjects, at least 12 years of age, with severe hemophilia B who are without inhibitors to FIX and have no hypersensitivity to recombinant FIX.
Number of Sites	Approximately 15 sites globally
Number of Subjects	Up to 16 subjects, 13 subjects ≥ 18 years old and potentially three 12-17 year old subjects. Two subjects ≥ 18 years old will be enrolled into each of the two dose cohorts. Enrollment within the ≥ 18 year old cohorts may be increased to 4 subjects if a dose-limiting toxicity (≥ Grade 3 AE related to study drug) occurs in one of the first 2 subjects or if the Safety Monitoring Committee (SMC) determines that it is necessary to expand the cohort. At the final dose, the SMC may expand a cohort by an additional 5 subjects to determine the acceptable dose. After completion of the dose escalation, then the remaining ≥ 18 year old subjects (up to 13 subjects) may be enrolled into the determined dose level as an expansion of that cohort. Once a dose demonstrating sufficient safety has been established and an increase in Factor IX level in at least two subjects ≥ 18 years old has occurred, then only a single cohort of three subjects 12-17 years old will be added at that dose.

A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy via Zinc Finger Nuclease (ZFN) mediated targeted integration of SB-FIX in Subjects with Severe Hemophilia B	
Inclusion & Exclusion Criteria	**Inclusion Criteria** 1. Signed informed consent 2. Male ≥18 years of age (adult cohort); Male 12-17 years of age (pediatric cohort) 3. Severe hemophilia B (native circulating FIX activity <1%, with or without cross reactive material) 4. FIX mutations confirmed by FIX genome sequencing 5. With 150 or more exposure days to FIX concentrates 6. Sexually active subject must agree to use double barrier contraceptive (one of them being a condom) or abstinence and all subjects must refrain from donating their sperm until at least 2 consecutive semen samples after SB-FIX are negative for AAV2/6 and for a minimum of 90 days after SB-FIX administration **Exclusion Criteria** 1. Presence of neutralizing antibodies to AAV2/6 2. History of hypersensitivity response or allergic reaction to FIX or FIX products 3. Currently receiving long acting FIX replacement therapy and unwilling to switch to short acting FIX infusions 4. FIX mutations known to be associated with FIX inhibitors, including those with a large gene deletion 5. Polymorphisms in the ZFN target region of the albumin locus 6. Presence of any liver mass on MRI or equivalent imaging technology, or elevated alpha-fetoprotein (AFP) 7. Any contraindication to the use of corticosteroids for immunosuppression 8. Currently receiving antiviral therapy for hepatitis B or C or with history of active hepatitis B (HBV DNA or HBS Ag positive) or hepatitis C (HCV RNA viral load) or HIV-1 (RNA viral load), or HIV 1/2 antibody positive. To be considered HCV-negative after an active HCV infection, viral assays in two samples collected at least six months apart must be negative 9. Chronic anemia, leukopenia, or thrombocytopenia 10. Past medical history of active tuberculosis or systemic fungal disease 11. Symptomatic cardiovascular disease as a co-morbid condition

A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy via Zinc Finger Nuclease (ZFN) mediated targeted integration of SB-FIX in Subjects with Severe Hemophilia B	
	12. Markers of hepatic inflammation or overt or occult cirrhosis as evidenced by one or more of the following: • Albumin ≤3.5 g/dL (35 g/L) • Total bilirubin >1.5 x ULN and direct bilirubin ≥0.5 mg/dL (8.55 µmol/L) • Alkaline phosphatase >2.0 x ULN • ALT or AST >2.0 x ULN 13. History of chronic renal disease or creatinine ≥ 1.5 mg/dL (133 µmol/L) 14. Systemic (iv or oral) immunomodulatory agent or steroid use (topical treatment is allowed, e.g., for asthma or eczema) within 3 months prior to Screening 15. History of chronic infection or other chronic disorder considered an unacceptable risk 16. History of malignancy except for treated basal cell or squamous cell carcinoma 17. History of alcohol or substance abuse 18. Previously received gene therapy product 19. Participation in prior investigational drug or medical device study within the previous 3 months 20. History of therapeutic non-adherence 21. Any other reason that, in the opinion of the Investigator or Medical Monitor, would render the subject unsuitable for participation in the study
Concomitant Medications	All medications including Factor IX short acting are permitted with the exception of those that are potentially hepatotoxic. Hepatotoxic agents such as diclofenac, amiodarone, chlorpromazine, fluconazole, isoniazid, rifampin, valproic acid, high doses of acetaminophen (4-8 gm/day) are not permitted.

<table>
<tr><td colspan="2">A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy via Zinc Finger Nuclease (ZFN) mediated targeted integration of SB-FIX in Subjects with Severe Hemophilia B</td></tr>
<tr><td>Dose and Rationale for Dose Selection</td><td>The doses to be evaluated were selected based on FIX activity in the NHP studies (Section 1.7). The configurations of ZFNs and donor rAAV2/6 vectors for these doses are illustrated in the table below. Current nonclinical data support the use of a 1:1:8 ZFN1:ZFN2:cDNA Donor ratio.
<table>
<tr><th>ZFN 1 (vg/kg)</th><th>ZFN 2 (vg/kg)</th><th>cDNA Donor (vg/kg)</th><th>Total rAAV Dose (vg/kg)</th></tr>
<tr><td>1.00E+12</td><td>1.00E+12</td><td>8.00E+12</td><td>1.00E+13</td></tr>
<tr><td>5.00E+12</td><td>5.00E+12</td><td>4.00E+13</td><td>5.00E+13</td></tr>
</table></td></tr>
<tr><td>Treatment Plan & Schedule</td><td>Up to 16 subjects, 13 subjects ≥ 18 years old and potentially three 12-17 year old subjects, who satisfy all inclusion/exclusion criteria will be enrolled into one of the following 2 treatment cohorts:
Total rAAV Dose (vg/kg) 1.00E+13
Total rAAV Dose (vg/kg) 5.00E+13

A single dose of each of the 3 components of SB-FIX (ZFN1, ZFN2, and cDNA Donor) will be added to 200 mL of diluent (refer to Study Pharmacy Manual) and adjusted to 0.25% human serum albumin. Total volumes will depend on subject’s cohort assignment and body weight (kg). The prepared investigational product will be administered via intravenous infusion at 100 mL/hour using a constant rate infusion pump while the subject is in the hospital or an acute care facility. Subjects will remain in the hospital or acute care facility for 24 hours after the end of the SB-FIX infusion for observation and will be discharged when all AEs, concomitant medications, and vital signs (temperature, pulse, respiratory rate, and blood pressure) are stable.

Within each cohort, treatment will be staggered so that each subsequent subject cannot be infused until the preceding subject has been observed for at least 4 weeks. Dose escalation to the next cohort cannot occur until at least 4 weeks after the last subject in the preceding cohort has been dosed, and the Safety Monitoring Committee has reviewed the safety data from the entire prior cohort.</td></tr>
</table>

A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy via Zinc Finger Nuclease (ZFN) mediated targeted integration of SB-FIX in Subjects with Severe Hemophilia B	
	After being discharged from the hospital or acute care facility, the subjects will be evaluated at the study center every two weeks for the first 12 weeks, every four weeks between Months 3 and 12, and every 3 months in Year 2 and Year 3. The liver function tests (AST, ALT, bilirubin, alkaline phosphatase, LDH, total protein, and albumin) of study subjects will be measured 2 times per week and FIX activity measured weekly for evaluation of AAV mediated immunogenicity during the first 12 weeks after SB-FIX infusion, every 4 weeks from Months 3 to 12, and every 3 months in Year 2 and Year 3. If there is a need to initiate immunosuppression because of transaminitis (Appendix 3), an oral dose of prednisone 60 mg/day (or equivalent) will be instituted. Tapering will begin when ALT level returns to baseline (based on 2 assessments in preceding week) and FIX activity levels have stabilized. During steroid treatment, liver function will be assessed twice a week until normalization of liver enzymes and FIX activity levels will be measured once a week until stabilization. If FIX activity of a subject reaches ≥ 5% post infusion (2 measurements at least one week apart), investigator will consult with Medical Monitor to discontinue prophylactic FIX treatment and agree an appropriate monitoring regimen. Once a dose demonstrating sufficient safety has been established and an increase in Factor IX level in at least two subjects ≧ 18 years old has occurred, then a single cohort of three 12-17 years old subjects will be added at that dose.
Dose Escalation	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 safety data for all subjects in the cohort has been reviewed by the SMC. If one of the first two subjects within a cohort develops a dose limiting toxicity (DLT) defined as a Grade 3 or higher AE (related to study drug), or if SMC determines that it is necessary to expand the cohort, 2 additional subjects may be enrolled and treated in that cohort. The SMC will be convened to decide if it is appropriate to continue expansion of that cohort, or dose de-escalate. During the study, if FIX activity level reaches above 50% of normal, further dose escalation will be halted until a discussion with the regulatory agencies has occurred and further dose escalation is warranted.

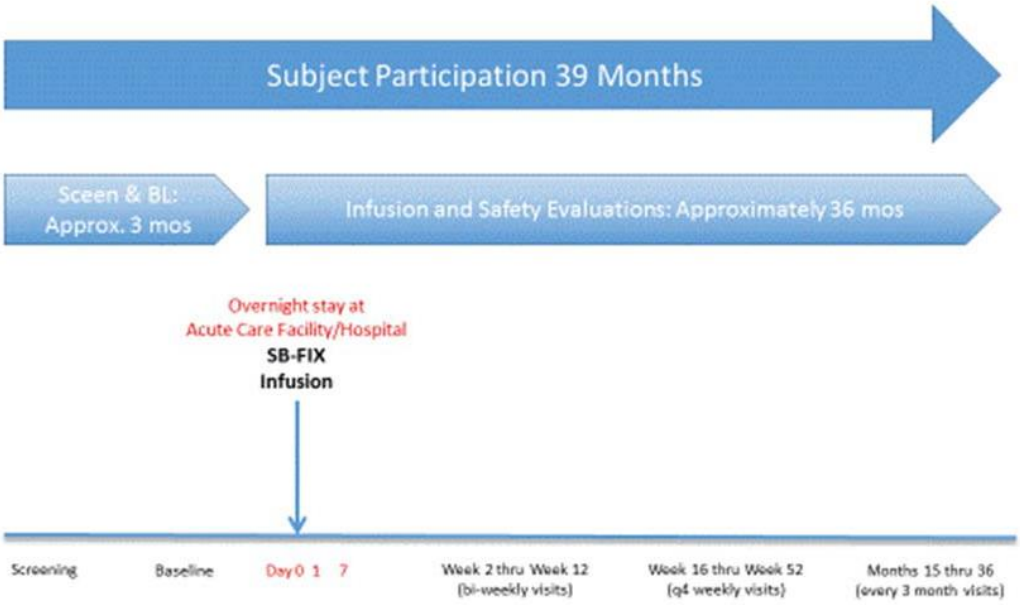
A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy via Zinc Finger Nuclease (ZFN) mediated targeted integration of SB-FIX in Subjects with Severe Hemophilia B	
Study Duration	The duration of study participation will be approximately 39 months for each subject divided into approximately 3 months for screening, 36 months for treatment and study follow-up. Accrual is planned for 20 months. Upon completion of this study, subjects will be invited to participate in a separate Long-Term Follow-Up (LTFU) Study to monitor the long term safety of the study treatment. To alleviate study burden, study subjects may participate in the LTFU study, provided they were followed up at least 12 months in this study.
Safety Monitoring Committee	An independent Safety Monitoring Committee (SMC) with appropriate medical and scientific expertise will be responsible to review accumulating safety data to ensure the safety of study subjects and provide recommendations as to the future of the study. The SMC will be convened after the completion of each cohort to determine if it is safe to proceed with the next dose cohort. The SMC may 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 earlier if the following occurs: • Any two Grade 2 AEs in the same system organ class that last more than 2 weeks with treatment or one Grade 3 or higher AE, if these AEs are not related to the primary hemophilia B disease unless they are associated with induction of FIX inhibitors • Serious adverse event not related to the primary hemophilia B disease unless it is associated with induction of FIX inhibitor • Death of a subject • Development of a malignancy • Development of a FIX inhibitor • Sponsor, in consultation with the SMC or Regulatory Agency, decides for any reason that subject safety may be compromised by continuing the study • The Sponsor decides to discontinue the development of the intervention to be used in this study. All data will then be evaluated to determine if changes should be made to the study or if accrual should be halted. In addition, no further dosing of patients will be performed until a substantial amendment application is approved by the Regulatory Agency.

A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy via Zinc Finger Nuclease (ZFN) mediated targeted integration of SB-FIX in Subjects with Severe Hemophilia B	
	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, studies SB-318-1502 in MPS I subjects and SB-913-1602 in MPS II subjects use similar ZFNs components as the present study in combination with a different donor cDNA (encoding human Factor 9). Given the similarities of the approaches, relevant data from 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. The SMC will no longer convene when no new subjects are enrolled or dosed in the study. Sangamo will continue to review subject safety data on an ongoing basis.
Safety Monitoring and Mitigation Plan	The liver function (AST, ALT, bilirubin, alkaline phosphatase, LDH, total protein, and albumin) of study subjects will be monitored closely throughout the study as indicated above in the Section Treatment Plan. Key potential anticipated risks are: 1. Development of transaminitis due to cell-mediated immunity to capsid and/or AAV gene product. Steroids, e.g., prednisone or equivalent may be administered to minimize the immune response to AAV vector 2. Development of inhibitors to the FIX expressed from the albumin locus. This is potentially problematic because the FIX production is continuous, and potentially could be cross-reactive to exogenous FIX preparations. Endogenous human FIX is not expected to be immunogenic in subjects who have not already developed inhibitors to exogenous FIX. If this occurs, standard of care for FIX inhibitors (which is generally effective for acquired hemophilia) will be instituted. 3. Reduction in albumin synthesis. This is not expected given the small fraction (<1%) of transduced cells with albumin locus disruption, and has not been observed in animal studies with levels of transduction and albumin locus disruption exceeding those expected in humans by several fold.

A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy via Zinc Finger Nuclease (ZFN) mediated targeted integration of SB-FIX in Subjects with Severe Hemophilia B	
Stopping Rules	The study treatment will be stopped if any of the following criteria are met and the SMC will be convened to determine the proper course of actions: • Any two Grade 2 AEs in the same system organ class that last more than 2 weeks with treatment or one Grade 3 or higher AE, if these AEs are not related to the primary hemophilia B disease unless they are associated with induction of FIX inhibitors • Serious adverse event not related to the primary hemophilia B disease unless it is associated with induction of FIX inhibitors • Death of a subject • Development of a malignancy • Development of a FIX inhibitor • Sponsor, in consultation with the SMC or Regulatory Agency, decides for any reason that subject safety may be compromised by continuing the study • Sponsor decides to discontinue the development of the investigational product The SMC will no longer convene when no new subjects are enrolled or dosed in the study. Sangamo will continue to review subject safety data on an ongoing basis.
Sample Size	This is a phase 1 study with up to 16 evaluable subjects. This study is exploratory and its sample size is not determined by statistical power considerations. In order to have an evaluable sample size, subjects who prematurely discontinue the study prior to 12 months of the study follow-up (i.e., were enrolled but not dosed, or lost to follow-up) may be replaced with another subject.

A Phase I, Open-Label, Ascending Dose Study to Assess the Safety and Tolerability of AAV2/6 Factor IX Gene Therapy via Zinc Finger Nuclease (ZFN) mediated targeted integration of SB-FIX in Subjects with Severe Hemophilia B	
Statistical Analyses and Study Endpoints	This is a Phase 1 exploratory study and thus, there will be limited statistical power to evaluate efficacy and related biological endpoints. Therefore, analyses will be primarily descriptive and exploratory in nature. The study endpoints are: **Primary:** Safety and tolerability will be assessed by the grading of AEs/SAEs and change in laboratory evaluations from baseline **Secondary:** 1. Changes in FIX antigen and FIX activity levels from baseline over time 2. Change from baseline in the number of FIX units infused per week 3. Change from baseline in number and severity of bleeding episodes 4. Changes in neutralizing antibodies to FIX from baseline over time 5. Presence and shedding of AAV2/6 vector DNA, by PCR in plasma, saliva, urine, stool, and semen over time **Exploratory:** Changes in serum antibodies to AAV2/6 from baseline over time

Schema of the Study Visits



ABBREVIATIONS

AAV	adeno associated virus
AE	adverse event/experience
ALT	alanine aminotransferase (SGPT)
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (SGOT)
CBC	complete blood count
CCOA	clinical certification of analysis
cDNA	complementary deoxyribonucleic acid
COP	colloid osmotic pressure
CRF	case report form
DNA	deoxyribonucleic acid
DSB	double strand break
EC	ethics committee
EDC	electronic data capture
F9	coagulation factor IX
FDA	Food and Drug Administration
FIX	Factor IX
FSHD	facioscapulohumeral muscular dystrophy
HBV	hepatitis B virus
HCV	hepatitis C virus
HDR	homology-directed repair
hF9	human Factor 9
hFIX	human Factor IX
HIV	human immunodeficiency virus
IV	intravenous
IRB	institutional review board
ITR	inverted terminal repeat
LTFU	long-term follow-up
MED	minimally effective dose
NAB	neutralizing antibody
NHEJ	non-homologous end-joining
NHP	non-human primates
NIH	National Institutes of Health
PCR	polymerase chain reaction
rAAV	recombinant adeno associated virus
RNA	ribonucleic acid
SAE	serious adverse event
SMCHD1	structural maintenance of chromosomes flexible hinge domain containing 1
SMC	Safety Monitoring Committee
SNP	Single nucleotide polymorphism
ZFN	zinc finger nucleases

1 INTRODUCTION

1.1 Hemophilia B

Hemophilia B is an X-linked recessive bleeding disorder caused by mutations in the gene encoding blood coagulation Factor IX (FIX). It is also known as Christmas disease and is the second most common form of hemophilia, after Hemophilia A or Factor VIII deficiency. It occurs in about one in 25,000 males with a prevalence of approximately 4,000 in the United States (http://www.hemophilia.org/About-Us/Fast-Facts). The disease manifestation varies depending upon the level of Factor IX clotting activity. The majority of subjects with hemophilia B have a severe form of the disease (<1% FIX activity). They are usually diagnosed during the first two years of life after developing spontaneous joint or deep muscle bleeding. Those with moderate disease (1-5% FIX activity) present with prolonged or delayed bleeding after relatively minor trauma and are diagnosed before age six. By comparison, mild hemophiliacs (>5-30% FIX activity) are diagnosed later in life and do not suffer from spontaneous bleeding but will develop excessive bleeding following surgery or tooth extraction. Finally, approximately 10% of female carriers have FIX activity below 30% and are at risk of excessive bleeding after major trauma or surgery.

The current treatment of hemophilia B has been FIX concentrates which were initially derived from donor plasma in the late 1960s. Subsequent improvements such as viral inactivation and donor screening led to more purified concentrates which culminated with the introduction of recombinant FIX in 1997. More recently, a recombinant FIX Fc fusion protein allowing for weekly or biweekly administration was approved for marketing in the United States. Increasing the levels of Factor IX to ~5% of normal (i.e. ~250 ng/mL) results in a profound improvement in symptoms and is sufficient to prevent spontaneous and life-threatening bleeding episodes. (Scriver, 2001; Lofqvist, 1997; Ljung, 1998). These therapeutic advances have increased the median life expectancy from 11 years prior to the introduction of plasma derived FIX to 63 years with the recombinant protein (Darby, 2007).

Current treatments for hemophilia B rely on chronic, repeated intravenous infusions of purified recombinant Factor IX and suffer from a number of drawbacks, including inhibitor formation. The current treatment strategy is prophylactic or on-demand rather than curative. An alternative approach to exogenous clotting factor delivery, based on continuous synthesis from a therapeutic transgene *in situ* (within the liver of the subject), offers the prospect of eliminating these concerns.

We propose treating hemophilia B via a novel strategy which places a corrective FIX transgene into the genome at the albumin locus, under the control of the subject's own endogenous albumin locus, resulting in liver-specific synthesis of Factor IX. Successful preclinical studies with this albumin ZFN/targeted Factor IX strategy in FIX deficient mice have been published

(Sharma 2015). AAV vectors encoding mouse-specific ZFNs targeting the albumin locus in the mouse genome and a human factor IX donor were injected into normal and hemophilia B mice.

Measurement of hFIX in normal mice showed expression at >3000 ng/mL (>50% normal FIX levels) that was stable for over a year. There was a dose response, with circulating FIX increasing from 100 ng/mL to >10,000 ng/mL with a 2 log increase in AAV vector dose.

Similarly, increases in FIX levels, with associated normalization of activated partial thromboplastin time (aPTT), were seen in Hemophilia B mice. See Figure 1 below.

Figure 1: Hepatic Gene Targeting of Mouse Albumin Locus

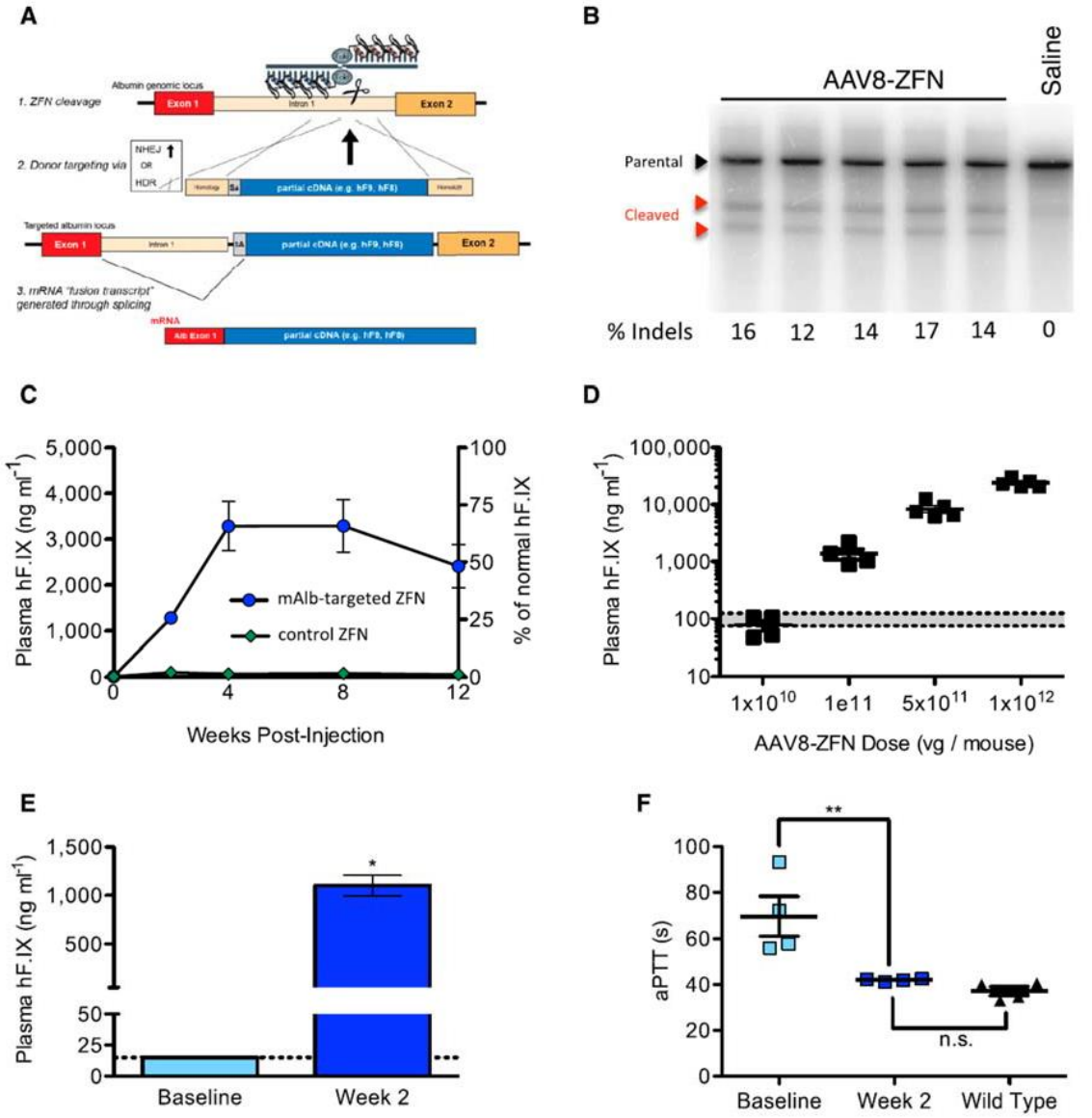


Figure 1. Hepatic gene targeting of the mouse albumin locus results in phenotypic correction of hemophilia B. (A) Schematic illustrating albumin targeting strategy. (B) Cel I nuclease assay from liver DNA measuring ZFN-induced indels within albumin intron 1. Lanes represent individual mice at day 7 after AAV8-ZFN treatment. (C) hFIX in mouse plasma after treatment with AAV8-hF9-donor and either AAV8-ZFN (blue circles) or AAV8-hF9-ZFN (green diamonds) with a target sequence not present in the mouse genome; n = 3 mice per group. (D) hFIX levels at week 2 after treatment are proportional to AAV dose (1:5 ZFN to donor). Gray bar: normal levels. Points represent individual mice. (E) hFIX levels in hemophilia B mice 2 weeks after treatment with AAV8-mAlb-ZFN and AAV8-hF9-donor (n = 4 mice per group). *$P = .029$, Fisher's exact test. (F) Clot formation in mice depicted in panel E, measured by aPTT prior to and 2 weeks after treatment. The aPTTs of wild-type mice are shown for comparison. **$P < .01$, 2-tailed Mann-Whitney test. HDR, homology directed repair; n.s., nonsignificant; SA, splice acceptor.

1.2 Prior Clinical Experience with AAV FIX Gene Therapy for Hemophilia

Hemophilia is an attractive target for gene therapy for several key reasons. First, there is a wide therapeutic window, almost 2 logs, since FIX activity levels as low as 1% to 2% of normal may be beneficial and levels of ~5% of normal are sufficient to prevent spontaneous bleeding.

Second, precise minute-to-minute regulation of FIX expression is not required unlike other proteins such as insulin. Therefore, gene therapy for hemophilia has been an intense area of investigation for the past several decades.

There have been several published AAV-mediated FIX cDNA gene transfer studies conducted in patients with severe hemophilia B reported to date, as well as four unpublished studies summarized below. The first study enrolled eight subjects with severe hemophilia B in an open-label, dose escalation design (Manno, 2003). Subjects were injected intramuscularly with an AAV2 human FIX cDNA vector at 2.0E+11 vg/kg (n=3), 6.0E+11 vg/kg (n=3), and 1.8E+12 vg/kg (n=2). The investigational product was well tolerated with no serious local or systemic toxicities. Gene transfer and expression were confirmed by Southern blot and immunohistochemical analyses from the muscle biopsies of the majority of subjects that were tested. However, the coagulopathy was unaffected since circulating levels of FIX were <2% of normal in all eight subjects with most levels <1% of normal.

In a subsequent follow-up study, these investigators treated seven subjects by infusing an AAV2 human FIX cDNA vector into the hepatic artery (Manno, 2006). The data demonstrated that AAV2 doses up to 2E+12 vg/kg were safe and well tolerated. Furthermore, the 2 subjects who received the highest dose of the vector achieved therapeutic circulating levels of FIX (3-10%). However, this effect was transient (~8 weeks) because of transduced hepatocyte necrosis due to a cell mediated immune response to the AAV2 capsid. The lack of efficacy in these studies was due to the poor liver tropism of AAV2 and the high incidence of anti-AAV2 antibodies and cell mediated immunity in these subjects.

Nathwani and colleagues conducted a phase 1/2 clinical study using an alternative AAV8 serotype in ten subjects with hemophilia B (Nathwani, 2014). Subjects received a single intravenous dose of a self-complementary rAAV2/8 vector expressing a codon-optimized human FIX cDNA. Study participants were enrolled sequentially in one of three cohorts (2E+11, 6E+11, or 2E+12 vg/kg). The vector was administered without immunosuppressive therapy, and participants were followed for 16 to 48 months. Results showed that rAAV-mediated expression of hFIX at 1 to 6% of normal levels (100-550 ng/mL) was observed in all participants over a period of 3.2 years. Four of the six high dose subjects discontinued FIX prophylaxis and remained free of spontaneous hemorrhage; in the other two, the interval between prophylactic injections was increased. This study demonstrated considerably improved efficacy compared to the previous studies by Manno et al.

Two participants, who received the high dose of vector, experienced a decrease in FIX expression levels. The first subject had a transient, asymptomatic elevation of serum alanine aminotransferase to 202 IU/L and seven days later was treated with 60 mg prednisolone over 12 weeks; this episode was associated with the detection of AAV8 capsid-specific T cells in the peripheral blood. The second subject had a slight increase in liver enzyme levels, was promptly treated (2 days) with 60 mg of prednisolone for 8 weeks and a smaller increase in AAV8 capsid specific T cells was observed. A total of four participants had elevated ALTs and received approximately 6-9 weeks of prednisolone starting at 60 mg then tapered over this period of time. The steroid therapy rapidly normalized aminotransferase levels, decreased AAV8 capsid specific CD8 T cell responses and stabilized hFIX levels in the range of 2 to 6% of normal values, a 50-70% reduction in FIX compared to the levels observed prior to the elevated liver enzymes.

More recently, a clinical study sponsored by uniQure (Miesbach, 2018) used an adeno-associated virus-5 (AAV5) vector with a liver-specific promoter driving expression of a codon-optimized wild-type human FIX gene. This open-label study included 10 adults with hemophilia B (FIX <2% of normal) and severe-bleeding phenotype. A single dose of 5E+12 or 2E+13 genome copies of AMT-060/kilogram was administered to 5 participants each. In the low-dose cohort, mean endogenous FIX activity increased to 4.4 IU/dL. Annualized FIX use was reduced by 81%, and the mean annualized spontaneous bleeding rate (ASBR) decreased from 9.8% to 4.6% (53%). In the higher-dose cohort, mean FIX activity increased to 6.9 IU/dL. Annualized FIX use decreased by 73%, and mean ASBR declined from 3.0 to 0.9 (70%). Limited, asymptomatic, and transient alanine aminotransferase elevations in three patients were treated with prednisolone. No decrease in FIX activity or capsid-specific T-cell responses were detected during transaminase elevations. A single infusion of AMT-060 had a positive safety profile and resulted in stable and clinically important increases in FIX activity, a marked reduction in spontaneous bleeds and FIX concentrate use, without detectable cellular immune responses against capsids. This trial was registered at www.clinicaltrials.gov as #NCT02396342; EudraCT #2013-005579-42.

Another study, sponsored by Spark Therapeutics (published in George, 2017) used a single- stranded AAV vector consisting of a bioengineered capsid, liver-specific promoter and factor IX Padua (factor IX–R338L) transgene at a dose of 5E+11 vector genomes per kilogram of body weight in 10 men with hemophilia B who had factor IX coagulant activity of 2% or less of the normal value. No serious adverse events occurred during or after vector infusion. Vector-derived factor IX coagulant activity was sustained in all the participants, with a mean steady-state factor IX coagulant activity of 33.7+/-18.5% (range, 14 to 81). On cumulative follow-up of 492 weeks among all the participants (range of follow-up in individual participants, 28 to 78 weeks), the annualized bleeding rate was significantly reduced (mean rate, 11.1 events per year [range, 0 to 48] before vector administration vs. 0.4 events per year [range, 0 to 4] after administration;

P = 0.02), as was factor use (mean dose, 2908 IU per kilogram [range, 0 to 8090] before vector administration vs. 49.3 IU per kilogram [range, 0 to 376] after administration; P = 0.004). A total of 8 of 10 participants did not use factor, and 9 of 10 did not have bleeds after vector

administration. An asymptomatic increase in liver enzyme levels developed in 2 participants and resolved with short-term prednisone treatment. The conclusion is that sustained therapeutic expression of factor IX coagulant activity after gene transfer was obtained in 10 participants with hemophilia who received the same vector dose. Transgene derived factor IX coagulant activity enabled the termination of baseline prophylaxis and the near elimination of bleeding and factor use (ClinicalTrials.gov number, NCT02484092).

Two more clinical studies were performed (sponsored by Baxalta/Shire and Dimension Therapeutics) using AAV8 and AAV5 serotypes, and a cDNA coding for FIX. Both studies

showed some degree of FIX expression and a potential for a capsid CD8 T cell response, but no precise results were published.

1.3 Rationale for Use of AAV2/6 Serotype Based on Preclinical Studies

AAV serotype 2/6 has a strong tropism for the liver and is capable of supporting high levels of F9 transgene expression following IV administration, with a similar biodistribution profile to that of AAV8 used in published clinical and preclinical studies (Nathwani, 2006; Jiang H, 2006).

Additional preclinical studies comparing AAV2/6 and AAV2/8 conducted by the Sponsor show a similar pattern of distribution for both vectors, a finding consistent with the results from the studies cited above.

1.4 Immunosuppression and Sustained FIX Expression

The immune system of Hemophilia B patients is presented with two antigens, one foreign, one endogenous (AAV capsid and wild type FIX) upon infusion of the gene therapy vector. Studies to date suggest that a cell mediated immune response is generated to AAV capsid proteins and not to FIX. Manno et al. and Nathwani et al. were both unable to detect a T cell response to FIX and the latter group also did not detect neutralizing antibodies (NAB) to FIX (Manno, 2006; Nathwani, 2014).

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, pre-existing NAB to AAV will affect transduction by forming immune complexes with the infused vector and thereby preventing hepatocyte transduction. Furthermore, following transduction, memory CD8 T cells may be reactivated and eliminate transduced hepatocytes expressing AAV protein- derived epitopes on their cell surface. Results from these clinical studies suggest that immunosuppression, for example with corticosteroids, may be necessary to achieve sustained FIX expression.

Subjects who are positive for neutralizing antibodies to AAV2/6 will not be enrolled in this study. Cell mediated immunity to the viral capsid post AAV infusion will be attenuated/abrogated with a short course of immunosuppression.

1.5 Clinical Experience with Zinc Finger Nucleases

Previous clinical experiences with Zinc Finger Nuclease were cell therapy using ZFNs for genome editing ex vivo.

Clinical safety data is now available from a related trial conducted by the Sponsor, Study SB- 913-1602, which is a ZFN-mediated *in vivo* genome editing Phase I study for MPS II using SB-913. SB-913 is a rAAV2/6-based gene transfer that comprises the highly similar ZFNs

components and differs from SB-FIX only in the donor cDNA (which encodes human factor 9). Study SB-913-1602 has enrolled 2 subjects as of 12 February 2018, who have received SB-913 at a dose of 5.00E+12 vg/kg. SB-913 infusion was generally well-tolerated, and no significant safety signals have been observed. Additional information on clinical experience with ZFNs can be located in the Investigator's Brochure.

1.6 SB-FIX: AAV2/6 Zinc Finger Nucleases Targeting the Human Albumin Locus and hFIX Donor Components

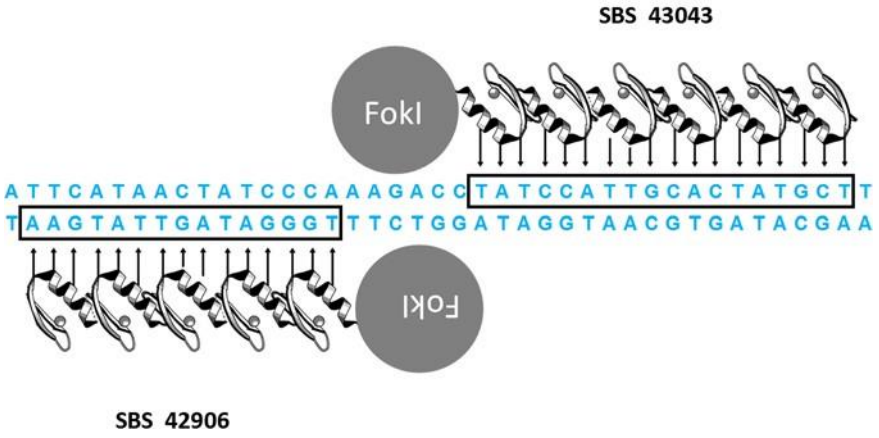
SB-FIX is composed of three AAV2/6 vectors that encode:

- Left ZFN (SB-42906) that targets bp 447-461 of the albumin locus, relative to the transcription initiation site (ZFN 1)
- Right ZFN (SB-43043) that targets bp 468-485 of the albumin locus, relative to the transcription initiation site (ZFN 2)
- Human FIX Donor cDNA with human albumin homology arms (SB-F9)

1.6.1 Zinc Finger Nucleases Targeting the Human Albumin Locus

To target the human albumin locus two individual ZFNs, SBS42906 (5-finger protein) and SBS43043 (6-finger protein) have been designed to bind adjacent 15 bp and 18 bp target sites, respectively, with high affinity and specificity. The strict requirement of both ZFNs being bound to a combined 33 bp recognition sequence in a specific spatial orientation on the DNA provides the functional specificity necessary to catalyze the formation of a double-strand break (DSB) at a single pre-determined site in the albumin locus. A schematic representation of this architecture is shown below in Figure 2. This is a graphical representation showing how the interaction of two ZFNs can facilitate the generation of a DSB targeted to a specific chromosomal location. In this example, the two ZFNs are each targeted to a specific sequence in an intronic region of the albumin gene (nucleotides 447–485 relative to the transcription start site) located on opposite strands of DNA. The FokI nuclease cleavage domain is attached to the carboxy-terminal end of each ZFP. Dimerization of the FokI cleavage domains is facilitated by the proper orientation and spacing of the two ZFP DNA binding sites, enabling generation of a DSB.

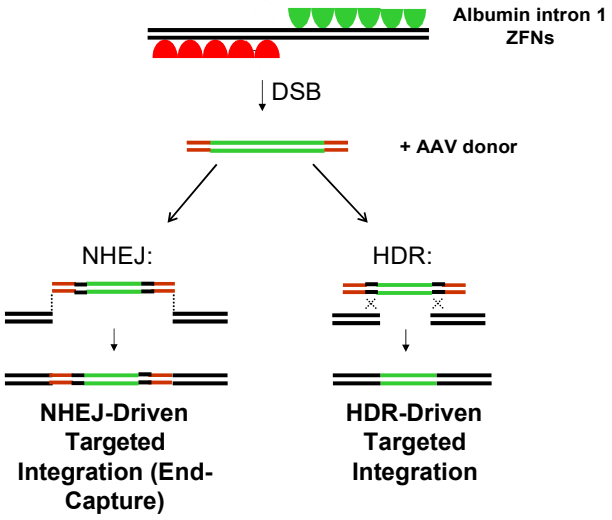
Figure 2: Schematic Representation of the Complexes between ZFNs SBS42906 and SBS43043 and Their DNA Target Sequences at the Albumin Locus



1.6.2 Exploiting ZFN-Driven Cleavage and DNA Repair to Insert F9 at the Albumin Locus

ZFN mediated targeted integration into the human albumin locus is a molecular process achieved by (1) creation of a DSB within the albumin locus in vivo in the genome of liver cells, and by (2) co-delivery of a DNA repair template encoding the hF9 transgene for insertion at the break during subsequent repair. Mechanistically, both the non-homologous end joining (NHEJ) and homology-directed repair (HDR) DNA repair pathways in human cells can mediate gene repair and consequent transgene integration. Examples of how each of these processes leads to integration and expression of the Factor IX transgene are provided in Figure 3.

Figure 3: ZFN-Induced DSBs Stimulate Targeted Integration of an AAV Donor via Either Non-Homologous End Joining (NHEJ) or Homology-Directed Repair (HDR)



Targeted integration by HDR requires the donor vector to encode sequences homologous to the break site.

All eukaryotic cells efficiently repair DSBs via the HDR or NHEJ pathways. These highly conserved pathways can be harnessed to generate defined genetic outcomes across a wide range of cell types and species. NHEJ repair, for example, rapidly and efficiently ligates the two broken ends, with the occasional gain or loss of genetic information (it can therefore be used to introduce small insertions and/or deletions at the site of the break). In the case of a rAAV donor, the whole rAAV genome can be ligated into the break site by the NHEJ pathway via the inverted terminal repeat (ITR) sequences at both ends of the AAV genome. For HDR, if a DNA repair template (often referred to as a donor DNA template) is provided in combination with the ZFNs, information encoded on this template (such as a therapeutic transgene) flanked by locus-specific homology arms can be used to repair the DSB, resulting in the targeted insertion of this transgene at the site of the break using the flanking arms of homology as a guide sequence.

1.6.3 Design of the Human Albumin-huF9 Transgene Donor (SB-F9)

The final hF9 donor construct was developed by 1) careful design of the albumin intron1 homology arms and 2) codon optimization of the hF9 coding sequence in order to achieve high levels of FIX expression from the human albumin locus.

To achieve maximal targeting of the huF9 transgene to the human albumin locus via the homology-directed repair pathway (see Figure 3), the huF9 transgene must be flanked by sequence homologous to site of ZFN cleavage site in intron 1. To avoid the inadvertent inclusion of sequences that might interfere with transgene expression (following integration into the albumin locus), the specific genomic features of the human albumin intron 1 locus were carefully

evaluated. The left (5') homology arm incorporates 280 bp of genomic DNA between the exon1 border and the human albumin ZFN cut site to avoid incorporating the Exon 1 splice donor

sequence in the left homology arm. For the right (3') homology arm, a smaller 100 bp of intronic sequence was used, which is based on the optimal mouse albumin donor that used a 100 bp arm to avoid incorporation of the albumin exon 2 splice acceptor site. These additional splicing signals when introduced by NHEJ-based targeted integration of the donor could cause mis- splicing and prevent efficient hFIX expression from the albumin locus.

1.7 Rationale for Dose Selection

Nonhuman primate (NHP) pharmacology/toxicology studies were used to establish a proposed Phase I clinical dose range for SB-FIX. In vitro data in hepatocyte preparations was not used because in vitro and in vivo AAV activity differ greatly (for example, AAV8 is highly hepatotropic in mice and NHPs in vivo, but almost inactive in hepatocyte preparations in vitro). Mouse data, while of great value in assessing the safety of extensive hepatic gene editing, was of limited value because the relationship between infused AAV dose and pharmacodynamic effects in liver has been much higher in mice using cDNA. Confirming this, surrogate SB-FIX, in doses ranging from 1E+13 to 1E+14 v/kg in mice, showed much higher levels of gene modification (30-48% indels) than seen in NHP studies at similar infused AAV doses (0.5-7% indels).

However, NHP data have generally been predictive of effective human doses with AAV8 cDNA (Nathwani, 2011a; Nathwani, 2011b; Mingozzi, 2007; Mingozzi, 2012; Jiang, 2006). For example, in the NHP studies of Nathwani (2011b), a self-complementary AAV2/8 vector encoding hF9 administered IV at a dose of 2E+12 vg/kg resulted in mean peak hFIX levels ~400% of normal, levels much higher than seen by other authors in NHP studies, and this dose did translate to a clinical dose of 2E+12 vg/kg yielding hFIX levels at 8-12% of normal. A similar approach was used for AAV5 encoding hydroxymethylbilane synthase (Gonzalez- Aseguinolaza, 2014).

Accordingly, dose-response data in NHP studies were used to support clinical dose selection. Surrogate NHP SB-FIX was generally safe and well-tolerated over the entire range of doses used in NHP studies. For efficacy, the minimally effective total AAV2/6 dose (MED) in immunosuppressed NHP was 1.2E+13 vg/kg, yielding hFIX plasma levels of 1% of normal (~50 ng/mL). This starting dose, due to the added donor AAV, is higher than starting doses typically used in cDNA AAV studies, but remains in the range of AAV doses that have been successfully administered in prior and ongoing clinical studies (see Section 9). The dose-response to SB-FIX thereafter is steep, with half-log increases in total AAV dose yielding approximately a log increase in circulating hFIX.

The use of NHP dose-ranging data to estimate appropriate dosing in humans rests on several assumptions as described in the investigator brochure:

- Human and NHP surrogate AAV/ZFN/donor activity are assumed to be similar.
- AAV2/6, a vector that has not been used in humans previously, is assumed to show the same relative NHP-to-human activity as other serotypes.
- Immunosuppressed NHP are assumed to show similar ZFN/donor activity as the non-immunosuppressed human subject. However, the potential for less than totalimmunosuppression in NHPs may argue for a potentially lower starting dose in humans.

Recognizing 1) caution regarding exact translation of doses in NHPs to humans; 2) a potentially steep dose-response curve; and 3) the need for a relatively high starting dose of SB-FIX compared to prior AAV cDNA studies, 4) since a related trial showing safety at the starting dose of 5.00E+12 vg/kg, the sponsor proposes a clinical starting dose of 15E+13 vg/kg SB-FIX (approximately the minimally effective dose in fully immunosuppressed NHPs). Subsequently the dose will escalate to 2E+13 vg/kg. By direct extrapolation from the NHP data, the clinical SB-FIX high dose escalation range is expected to modify ~0.1-0.35% of the target albumin loci, and yield mean peak hFIX levels up to ~290 ng/mL.

1.8 Risk Assessment of Albumin Expression in the Liver

The normal range of circulating albumin in the blood is 35-45 g/L (Minchiotti, 2013). Given the rate of albumin production by the liver (21-25 g/day) it can be estimated that conversion of ~0.01% of albumin alleles to Factor IX synthesis will yield therapeutically beneficial clotting factor levels (>3% of normal; 150 ng/mL) in plasma. The ZFN integration process itself should have no adverse consequences. At the individual cell level the targeted locus is completely dispensable, since albumin has no autocrine role. At the organismal level, heterozygous disruption of albumin yields no symptoms, while even homozygous disruption is tolerated (Watkins, 1994). Analbuminaemia (<1 g/L, range <1-21 g/L) has only been associated with mild edema and fatigue (Minchiotti, 2013; Prinsen and van der Velden, 2004; Nicholson, 2000). The relatively asymptomatic nature is partly due to transcriptional leakage, as well as compensation for decreased colloid osmotic pressure (COP) by the increase in small molecular weight proteins (Prinsen and van der Velden, 2004). Thus, the target of <1% albumin alleles converted to Factor IX expression would be expected to decrease production by <0.0001 g albumin per day, resulting with no impact on albumin production or accumulation below the normal range (compared to reported 5-8 g/L decrease in plasma albumin during pregnancy). Therefore, disrupting < 1% of the albumin alleles is predicted to have no measurable phenotype. Moreover, given the intronic location of the ZFN target site, ZFN cleavage and subsequent DNA repair (e.g., small insertion and deletions at the site of ZFN cleavage) will be functionally inert with respect to albumin expression.

2 STUDY OBJECTIVES

2.1 Primary Objective

Evaluate the safety and tolerability of SB-FIX.

2.2 Secondary Objectives

1. Change from baseline in FIX antigen and activity levels
2. Change from baseline in use of Factor IX replacement therapy
3. Change from baseline in frequency and severity of bleeding episodes
4. Immune response to FIX
5. Presence and shedding of AAV2/6 vector DNA by PCR in plasma, saliva, urine, stool and semen

2.3 Exploratory Objective

Immune response to AAV2/6

3 STUDY DESIGN

3.1 Overview

This is a Phase 1, open-label, ascending dose study. Subjects who satisfy all inclusion/exclusion criteria are eligible to participate in this study.

3.2 Number of Sites

Approximately 15 sites globally

3.3 Number of Subjects

Up to 16 evaluable subjects, 13 subjects ≥ 18 years old and potentially three 12-17 year old subjects. Two subjects ≥ 18 years old will be enrolled in each of two dose cohorts. Enrollment within the ≥ 18 years old cohorts may be increased to 4 subjects if a dose-limiting toxicity (≥ Grade 3 AE related to study drug) occurs in one of the first 2 subjects or if the Safety Monitoring Committee (SMC) determines that it is necessary to expand the cohort. At the final dose, the SMC may expand a cohort by 5 subjects to determine the acceptable dose. After completion of the dose escalation, then the remaining ≥ 18 year old subjects (up to 13 subjects) may be enrolled into the determined dose level as an expansion of that cohort.

In order to have an evaluable sample size, subjects who prematurely discontinue the study prior to 12 months of the study follow up (i.e., were enrolled but not dosed, or lost to follow-up) may be replaced with another subject.

Once a dose demonstrating sufficient safety has been established and an increase in factor IX level in at least two subjects ≥ 18 years old has occurred, then only a single cohort of three subjects 12-17 years old will be added at that dose.

3.4 Dose

The dose of the investigational product selected for this study is:

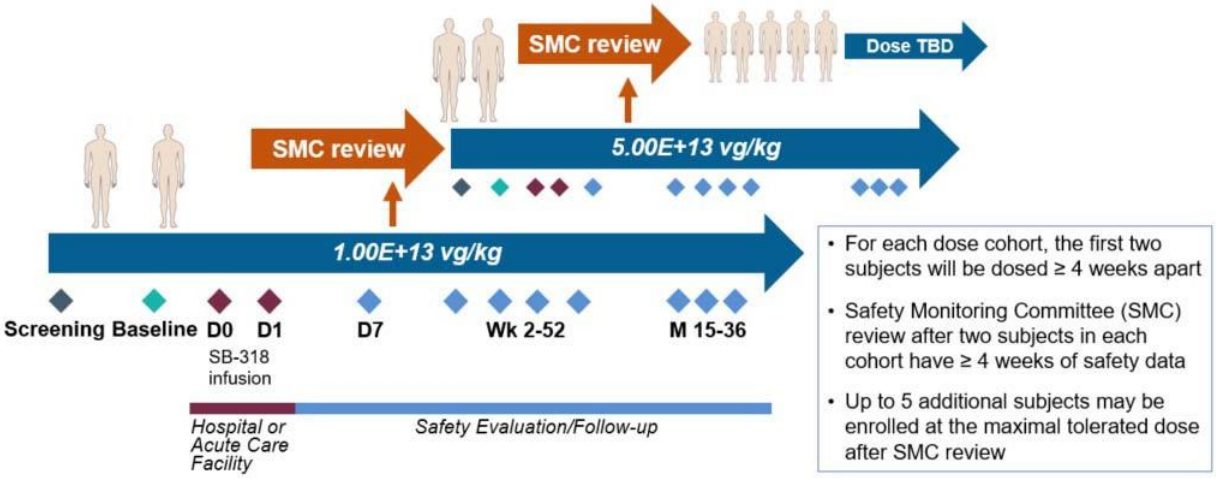
ZFN 1 (vg/kg)	ZFN 2 (vg/kg)	cDNA Donor (vg/kg)	Total rAAV Dose (vg/kg)
1.00E+12	1.00E+12	8.00E+12	1.00E+13
5.00E+12	5.00E+12	4.00E+13	5.00E+13

3.5 Study Duration

The duration of study participation will be approximately 39 months for each subject divided into approximately 3 months for screening, 36 months for treatment and study follow-up (Figure 4). Accrual is planned for 20 months.

Upon completion of the study, subjects will be invited to participate in a separate Long-Term Follow-Up (LTFU) study to monitor long-term safety of the study treatment. To alleviate study burden, study subjects may participate in the LTFU study, provided they were followed up at least 12 months in this study.

Figure 4: Study Overview



3.6 Study Schedule

Subjects will complete all screening procedures and will have eligibility confirmed before enrollment. Subjects who satisfy all inclusion/exclusion criteria will be enrolled into one of the 3 treatment cohorts.

A single dose of each of the 3 components of SB-FIX (ZFN1, ZFN2, and cDNA Donor) will be added to 200 mL diluent (refer to Study Pharmacy Manual) and adjusted to 0.25% human serum albumin, and then administered via intravenous infusion while the subject is in the hospital or acute care facility. Subjects will remain in the hospital or an acute care facility for 24 hours after the end of the SB-FIX infusion for observation, and will be discharged when all AEs, concomitant medications, and vital signs (temperature, pulse, respiratory rate, and blood pressure) are stable.

Within each cohort, treatment will be staggered so that each subsequent subject cannot be infused until the preceding subject has been observed for at least 4 weeks. Dose escalation to the next cohort cannot occur until at least 4 weeks after the last subject in the preceding cohort has been dosed, and safety data from the entire prior cohort has been reviewed by the Safety Monitoring Committee.

After being discharged from the hospital or acute care facility, the subjects will be evaluated at the study center every two weeks for the first 12 weeks, every four weeks between Months 3 and 12, and every 3 months during Year 2 and Year 3, or until enrollment into LTFU study. The liver function tests (AST, ALT, bilirubin, alkaline phosphatase, LDH, total protein, and albumin) will be performed 2 times a week for evaluation of AAV mediated immunogenicity during the first 12 weeks after SB-FIX infusion, and then every 4 weeks between Months 3 to 12, every 3 months in Year 2 and Year 3, or until enrollment into LTFU study.

If there is a need to initiate immunosuppression because of transaminitis (Appendix 3), an oral dose of prednisone 60 mg/day (or equivalent) will be instituted. Tapering will begin when ALT level returns to baseline (2 assessments in one week) and FIX activity levels have stabilized.

During prednisone (or equivalent) treatment, liver function will be assessed twice a week until normalization of liver enzymes and FIX activity levels will be measured once a week until stabilization.

If FIX activity of a subject reaches ≥ 5% post infusion (2 measurements at least one week apart), investigator will consult with Medical Monitor to discontinue prophylactic FIX treatment and agree an appropriate monitoring regimen.

At each study visit, laboratory blood tests, assessment of AEs, concomitant medications, and frequency of bleeding episodes and FIX usage will be performed (Appendix 1).

4 SUBJECT SELECTION

4.1 Inclusion Criteria

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

1. Signed informed consent
2. Male ≥18 years of age (adult cohort); Male 12-17 years of age (pediatric cohort)
3. Severe hemophilia B (native circulating FIX activity <1%, with or without cross reactive material)
4. FIX mutations confirmed by FIX genome sequencing
5. 150 or more exposure days to FIX concentrates
6. Sexually active subject must agree to use double barrier contraceptive (one of them being a condom) or abstinence and all subjects must refrain from donating their sperm until at least 2 consecutive semen samples after SB-FIX are negative for AAV2/6 and for a minimum of 90 days after SB-FIX administration

4.2 Exclusion Criteria

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

1. Presence of neutralizing antibodies to AAV2/6
2. History of hypersensitivity response or an allergic reaction to FIX or FIX products
3. Currently receiving long acting FIX replacement therapy and unwilling to switch to short acting FIX infusion
4. FIX mutations known to be associated with FIX inhibitors, including those with a large gene deletion
5. Polymorphisms in the ZFN target region of the albumin locus
6. Presence of any liver mass on MRI or equivalent imaging technology, or elevated alpha-fetoprotein (AFP)
7. Any contraindication to the use of corticosteroids for immunosuppression
8. Currently receiving antiviral therapy for hepatitis B or C or with history of active hepatitis B (HBV DNA or HB Ag positive) or hepatitis C (HCV RNA viral load) or HIV-1 (RNA viral load) or HIV1/2 antibody positive. To be considered HCV-negative after treatment of an active HCV infection, viral assays in two samples, collected at least six months apart, must be negative.
9. Chronic anemia, leukopenia, or thrombocytopenia
10. Past medical history of active tuberculosis or significant fungal disease
11. Symptomatic cardiovascular disease as a co-morbid condition
12. Markers of hepatic inflammation or overt or occult cirrhosis as evidenced by one or more

of the following:

a. Albumin ≤3.5 g/dL (35 g/L)
b. Total bilirubin >1.5 x ULN and direct bilirubin ≥0.5 mg/dL (8.55 µmol/L)
c. Alkaline phosphatase >2.0 x ULN
d. ALT or AST >2.0 x ULN

13. History of chronic renal disease or creatinine ≥ 1.5 mg/dL (133 µmol/L)
14. Systemic (iv or oral) immunomodulatory agent or steroid use (topical treatment is allowed, e.g., for asthma or eczema) within 3 months prior to Screening
15. History of chronic infection or other chronic disorder considered an unacceptable risk
16. History of malignancy except for treated basal cell or squamous cell carcinoma
17. History of alcohol or substance abuse
18. Previously received gene therapy product
19. Participation in prior investigational drug or medical device study within the previous 3 months
20. History of therapeutic non-adherence
21. Any other reason that, in the opinion of the Investigator or Medical Monitor, would render the subject unsuitable for participation in the study

4.3 Screen Failures

Individuals who do not meet the criteria for participation in this study may be rescreened with prior approval from Medical Monitor.

5 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 per local regulations. 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 Therapeutics will provide the 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 Therapeutics prior to submission to the IRB or EC equivalent to ensure that it meets standards for consent forms.

The IRB or EC equivalent must approve the consent form. A copy of the approved form must be submitted to Sangamo Therapeutics.

At the screening visit, the investigator or designated personnel will explain to each subject the nature of the study, its purpose, the procedures, the expected duration, alternative therapies available, and the benefits and risks of participation. Subjects will receive information and consent documents, with the opportunity to ask questions, and will be informed about their right to withdraw from the study at any time without any impact upon their future clinical care. After this explanation and before any study-specific procedures have been performed, the subject must voluntarily sign and date the informed consent form approved by the IRB or EC equivalent if the subject agrees to participate in the study.

The subject will receive a copy of the signed and dated written informed consent form and any other written information required for the study. Subjects will be re-consented at the time of any informed consent amendment, as applicable, and will be provided a copy of the revised consent form. When a subject is treated at a center different from the screening visit site, the details of the signed consent form will be reviewed, any questions will be answered, and the discussion documented in the medical record of the treating site.

The investigator must keep each subject's signed consent form on file for inspection by a regulatory authority at any time.

6 STUDY METHODOLGY

Prior to initiation of this study, this study site shall be approved by the local Institutional Review Board (IRB) or EC 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. A table of all study procedures is presented in the Schedule of Events (Appendix 1).

6.1 Screening Visits

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 evaluation may take up to approximately 3 months and may be performed across several visits during the screening period. Assessments must be completed and the results reviewed to judge and confirm eligibility. The following will be performed at the screening visits:

1. 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
2. A complete medical history including demographic information; access and review of concomitant medications. If the subject is not normally seen at the study center, it may be necessary to obtain medical records to confirm study eligibility.
3. Vital signs: Temperature, pulse, respiratory rate, and blood pressure
4. Review the inclusion and exclusion criteria

5. Assign a subject number
6. Physical exam, including height
    a. Physical exam includes assessments of skin, head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, endocrine metabolic, genitourinary, neurological, lymphatic and musculoskeletal systems.
7. Weight
8. 12-lead ECG
9. Chest X-ray
10. Urinalysis with microscopic exam
11. CBC with differential and platelet count
12. Coagulation screen: PT, INR, and PTT
13. Chemistry (Na, K, Ca, HCO_3, Cl, and phosphorus)
14. Metabolic panel (BUN, creatinine, glucose, uric acid)
15. Liver panel (total and direct bilirubin, alkaline phosphatase, ALT, AST, LDH, albumin, and total protein). Two liver panel tests should be performed at least one week apart during Screening. Note: direct bilirubin is performed at Screening only.
16. Neutralizing antibodies to AAV2/6
17. HBV DNA, Hepatitis B Surface Antigen, HCV RNA viral load, and HIV RNA viral load; HIV-1/2 antibody assay
18. FIX antigen and activity levels
19. FIX inhibitor level
20. SNP assay for the ZFN targeted region of the albumin locus
21. Assessment of concomitant medications
22. FIX genome sequencing (if not performed previously)
23. Liver MRI or equivalent imaging technology
24. Circulating alpha fetoprotein level

6.2 Subject Enrollment

Before subject enrollment, the study site must verify that the subject fulfills all eligibility criteria.

6.3 Baseline Assessments

Baseline assessments will be performed within 21 days before the SB-FIX infusion.

The following tests are performed at the baseline visit:

1. Assessment of AEs
2. Assessment of concomitant medications

3. Physical exam
4. Weight
5. Abdominal exam for hepatomegaly
6. Vital signs: Temperature, pulse, respiratory rate, and blood pressure
7. Neurologic cranial nerve exam and muscle strength testing of the upper extremities including shoulder, elbow, and hands
8. Chemistry (Na, K, Ca, HCO_3, Cl, and phosphorus)
9. Metabolic panel (BUN, creatinine, glucose, uric acid)
10. Liver panel (total bilirubin, alkaline phosphatase, ALT, AST, LDH, albumin, and total protein). LFT for baseline visit must be performed within 1 week of infusion
11. CBC with differential and platelet count
12. Coagulation screen (PT, INR, and PTT)
13. Total antibodies to AAV 2/6 (exploratory)
14. ZFN immunogenicity (exploratory)
15. PCR of SB-FIX vector genome in plasma, saliva, urine, stool, and semen
16. FIX antigen and FIX activity level
17. FIX inhibitor level
18. Assessment of bleeding episodes and FIX concentrates usage. Subjects will use a diary to record bleeding episodes, factor infusions, and concomitant medications starting at their baseline visit through their last visit.
19. ACTH stimulation (cosyntropin) test (prior to administration of prophylactic prednisone or equivalent)
20. Administration of prednisone (or equivalent) before the planned SB-FIX infusion if prophylaxis is indicated (refer to Appendix 3)
21. Exploratory samples for sEGFR and Gal3BP collected and stored for future analysis

6.4 Day 0 SB-FIX Infusion

Subjects will be hospitalized or admitted to an acute care facility for SB-FIX infusion and will remain in the hospital or acute care facility for 24 hours after the end of the infusion for observation, and will be discharged when all AEs, concomitant medications, and all vital signs (temperature, pulse, respiratory rate, and blood pressure) are stable.

The following evaluations will be performed prior to SB-FIX infusion:

1. AE assessment
2. Physical exam
3. Weight
4. Assessment of concomitant medication
5. Vital signs: temperature, pulse respiratory rate, and blood pressure within 15 (+/- 5) minutes of the start of the infusion, every 15 (+/- 5) minutes until stable, then 30 (+/- 5) minutes until 2 hours post-infusions, then every hour (+/- 10 min) for 3 hours, then every 2 (+/-10 min) hours for 4 hours and then every 4 (+/- 15 min) hours until discharge.
6. Chemistry, liver, and metabolic panel
7. CBC with differential and platelet count
8. Coagulation screen (PT, INR, and PTT)
9. Assessment of bleeding episodes and FIX concentrates usage
10. Administration of prednisone (or equivalent) if indicated (see Appendix 3)

SB-FIX will be infused via a peripheral vein catheter over a period of 2-8 hours depending on subject's cohort assignment and body weight.

6.5 Day 1

All subjects will remain in the hospital or acute care facility for 24 hours after the SB-FIX infusion for observation, and will be discharged when all AEs, concomitant medications, and all vital signs (temperature, pulse, respiratory rate, and blood pressure) are stable as determined by the investigator or designee.

The following evaluations will be performed:

1. AE assessment
2. Assessment of concomitant medications
3. Physical exam
4. Vital signs: temperature, pulse, respiratory rate, and blood pressure (see Day 0)
5. Chemistry, liver and metabolic panel
6. CBC with differential and platelet count
7. FIX antigen and activities
8. FIX inhibitor level
9. PCR of AAV2/6 vector genomes in plasma 12 hours after initiation of infusion

10. Assessment of bleeding episode and FIX concentrates usage
11. Administration of prednisone (or equivalent) if indicated (refer to Appendix 3)

Subjects will be followed for a total of 36 months after SB-FIX infusion according to the schedule in Appendix 1.

6.6 Day 7 (+/- 1 day)

The following evaluations will be performed:

1. AE assessment
2. Assessment of concomitant medications
3. Physical exam
4. Weight
5. Vital signs
6. Liver panel (to be performed 2 times a week). Local lab may be used for liver panel if clinically indicated and following consultation with the Medical Monitor.
7. FIX antigen and activity
8. PCR of vector genomes in plasma, saliva, urine, stool, and semen
9. Assessment in bleeding episode and FIX concentrates usage
10. Administration of prednisone (or equivalent) if indicated (refer to Appendix 3)

6.7 Weeks 2, 4, 6, 8, 10, and 12 (+/- 3 day)

The following evaluations will be performed at each visit unless stated otherwise:

1. AE assessment
2. Assessment of concomitant medications
3. Physical exam
4. Weight
5. Vital signs
6. Abdominal exam for hepatomegaly
7. Neurologic cranial nerve exam and muscle strength testing of the upper extremities including shoulder, elbow and hands (Week 12 only)
8. Chemistry, liver and metabolic panel (liver panel will be performed 2 times a week. Local lab may be used for liver panel if clinically indicated and following consultation with the Medical Monitor)
9. CBC with differential and platelet count (Weeks 4, 8, and 12)

10. Coagulation screen: PT, INR, and PTT (Weeks 4, 8, and 12)
11. FIX antigen (Weeks 4, 8, and 12)
12. FIX activity level (will be measured once a week)
13. FIX inhibitor level (Weeks 4, 8, and 12)
14. Total antibodies to AAV2/6 (Weeks 4, 8, and 12; exploratory test)
15. ZFN immunogenicity (weeks 4, 8, and 12; exploratory test)
16. PCR of vector genomes in plasma, saliva, urine, stool, and semen (Weeks 2, 4, 8 and 12 only)
17. Assessment of bleeding episodes and FIX concentrates usage
18. Liver MRI or equivalent imaging technology (Week 12 only)
19. Circulating alpha fetoprotein level (Week 12 only)
20. ACTH stimulation test (only performed if at the end of prednisone or equivalent taper)
21. Administration of prednisone (or equivalent) if indicated (see Appendix 3)

Any subject who has an elevated alpha fetoprotein and MRI mass suspicious (or equivalent) for hepatocellular carcinoma (HCC) or greater than 2 cm will undergo biopsy using surgical doses of Factor IX replacement. Histopathologic examination and genomic analysis (e.g., sequencing of the albumin locus and integration site analysis) will be performed to determine the origin and nature of the tumor. Detailed instruction on sample collection and tissue preparation for genomic analysis is provided in the Appendix 2.

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

The following assessments are performed at each visit unless stated otherwise.

1. AE assessment
2. Assessment of concomitant medications
3. Physical exam
4. Weight
5. Vital signs
6. Abdominal exam for hepatomegaly
7. Neurologic cranial nerve exam and muscle strength testing of the upper extremities including shoulder, elbow and hands (Weeks 24 and 52 only)
8. Chemistry, liver, and metabolic panel (Liver panel will be performed twice a week until termination of steroid treatment if on steroid treatment. Local lab may be used for liver panel if clinically indicated and following consultation with the Medical Monitor).
9. CBC with differential and platelet count (Weeks 28 and 52 only)

10. Coagulation screen (PT, INR, and PTT)
11. FIX antigen and activity level (FIX activity will be measured weekly if subject is receiving steroid treatment).
12. FIX inhibitor level
13. Total antibodies to AAV 2/6 (Weeks 24, 36, and 52 only; exploratory test)
14. ZFN immunogenicity (Weeks 24, 36, and 52 only; exploratory test)
15. PCR of vector genomes in plasma, saliva, urine, stool, and semen (unless two previous consecutive specimens have been negative)
16. Assessment of bleeding episodes and FIX concentrates usage
17. Liver MRI or equivalent imaging technology (Weeks 24 and 52 only)
18. Circulating alpha fetoprotein level (Weeks 24 and 52)
19. Administration of prednisone (or equivalent) if indicated (see Appendix 3)
20. ACTH stimulation test (only performed if at the end of prednisone [or equivalent] taper)

Any subject who has an elevated alpha fetoprotein and MRI mass suspicious for hepatocellular carcinoma (HCC) or greater than 2 cm will undergo biopsy using surgical doses of Factor IX replacement. Histopathologic examination and genomic analysis (e.g., sequencing of the albumin locus and integration site analysis) will be performed to determine the origin and nature of the tumor. Detailed instruction on sample collection and tissue preparation for genomic analysis is provided in the Appendix 2.

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

Subjects will be evaluated every 3 months in Year 2 and Year 3 after SB-FIX infusion. The following assessments are performed at each visits Months 15, 18, 21, 24, 27, 30, 33 and 36/End of Study (+/-1 months) unless stated otherwise.

1. AE assessment
2. Assessment of concomitant medications
3. Physical exam
4. Weight
5. Vital signs
6. Abdominal exam for hepatomegaly
7. Neurologic cranial nerve exam and muscle strength testing of the upper extremities including shoulder, elbow and hands (Months 18, 24, 30, and 36)
8. Urinalysis with microscopic exam (Month 36 only)
9. Chemistry, liver, and metabolic panel
10. CBC with differential and platelet count

11. Coagulation screen (PT, INR, and PTT)
12. FIX antigen and activity levels
13. FIX inhibitor level
14. Assessment of bleeding episodes and FIX concentrates usage
15. Liver MRI or equivalent imaging technology (Months 18, 24, 30, and 36)
16. Circulating alpha fetoprotein level (Months 18, 24, 30, and 36)
17. ACTH stimulation test (only performed if at the end of prednisone [or equivalent] taper)

An End of Study (EOS) visit will be conducted prior to subject's enrollment into the LTFU study.

At the EOS visit, subjects will be invited to participate in the LTFU Study. Study subjects may participate in the LTFU Study after 12 months of follow-up in the SB-FIX-1501 study, in which case an EOS visit may be conducted any time after Week 52 in combination with or before the next scheduled study visit.. Informed consent will be obtained prior to participating in the LTFU Study.

6.9.1 Liver Biopsy

A liver biopsy can be performed in two separate and non-exclusive occasions:

1- Prior to enrollment into the LTFU, subjects will be asked to provide a liver biopsy, at the discretion of the Principal Investigator and Sangamo Medical Monitor. This request is optional and does not preclude the patient from joining the LTFU study. The proposed mechanism of action of SB-FIX is to introduce the Factor IX transgene into a precise location in the albumin locus. To determine the level of insertion of the factor IX gene after SB-FIX injection, liver tissue will be obtained by liver biopsy, unless contraindicated by the Principal Investigator or physician, and analyzed by high-throughput sequencing of the albumin locus.

2- Any subject who has an elevated alpha fetoprotein and radiological hallmarks of hepatocellular carcinoma (HCC) on MRI will undergo liver biopsy with factor 9 replacement following the surgery dosing guidelines included in the drug label. Histopathologic examination and genomic analysis (e.g., sequencing of the albumin locus and integration site analysis) will be performed in an attempt to identify whether the transgene was inserted and its location. Detailed instruction on sample collection and tissue preparation for genomic analysis is provided in the Appendix 2.

6.10 Early Termination Visit (ETV)

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 Investigator to waive any procedures if it has been performed within the standard interval of scheduled study visits per protocol.

The following assessments and procedures will be performed at the ETV:

1. AE assessment
2. Assessment of concomitant medications
3. Physical exam
4. Weight
5. Vital signs
6. Abdominal exam for hepatomegaly
7. Neurologic cranial nerve exam and muscle strength testing of the upper extremities including shoulder, elbow and hands
8. Urinalysis with microscopic exam
9. Chemistry, liver, and metabolic panel
10. CBC with differential and platelet count
11. Coagulation screen (PT, INR, and PTT)
12. FIX antigen and activity levels
13. FIX inhibitor level
14. Assessment of bleeding episodes and FIX concentrates usage
15. ACTH stimulation test (only performed if at the end of prednisone [or equivalent] taper)
16. Liver MRI or equivalent imaging technology (if not performed within 6 months prior to the ETV)
17. Circulating alpha fetoprotein level
18. Vector genome in plasma, saliva, urine, stool, and semen by PCR

7 INVESTIGATIONAL PRODUCT AND OTHER STUDY MEDICATIONS

7.1 SB-FIX

The final investigational products SB-FIX include three AAV2/6 components in separate vials:

- Left ZFN (SB-42906) that targets bp 447-461 of the albumin locus, relative to the transcription initiation site (ZFN 1)
- Right ZFN (SB-43043) that targets bp 468-485 of the albumin locus, relative to the transcription initiation site (ZFN 2)
- Human FIX Donor cDNA with human albumin homology arms (SB-F9)

Each of the three AAV2/6 clinical components will be aliquoted to contain 5 mL per vial and frozen at ≤ -65°C. The lots will be tested for (identity, sterility, viability, potency, stability), and cryopreserved.

7.1.1 Inventory, Storage, and Handling of the Drug Product

The investigational products required for subject treatment will be shipped to the study center with dry ice and temperature monitoring device and required to be stored at ≤-65℃ (temperature monitored freezer) prior to administration.

The Clinical Certificate of Analysis (CCOA) will accompany each investigational product shipment. The vials will have a label affixed containing the following information: (manufacture facility, vector identity, lot number, concentration, volume, and storage conditions.

A detailed instruction of preparing the three AAV2/6 vectors for infusion will be provided to the study center. The investigational products should be prepared by a research pharmacy at or near the hospital or acute care facility. Frozen vials will be thawed as instructed in the pharmacy manual. The three AAV2/6 vectors will be added to 200 mL of diluent (refer to Study Pharmacy Manual) and adjusted to 0.25% human serum albumin. Total volumes will depend on subject's cohort assignment and body weight (kg). Once the investigational product is prepared, it should be transported at ambient temperature to the infusion location at the hospital or acute care facility. The investigational product will be infused at 100 mL/hour using a constant rate infusion pump.

The study center is required to maintain complete records of all study products received. Inventory will include the description of labeled product received during the course of this study, as well as a record of the labeled product that is dispensed. At the conclusion or termination of this study, destruction of all drug supplies must be coordinated with Sangamo Therapeutics.

Refer to the Study Reference Manual for additional details.

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

7.1.2 SB-FIX Administration

Side effects following SB-FIX cell infusions may include transient fever, chills, and/or nausea. It is recommended that the subject should be pre-medicated with acetaminophen 650 mg by mouth and diphenhydramine hydrochloride 25-50 mg by mouth or IV, prior to the infusion of SB-FIX. These medications may be repeated every 3-4 hours as needed. NSAIDs are not recommended because of the potential to cause platelet dysfunction but may be used as the discretion of the Principal Investigator.

SB-FIX will be shipped to the study site prior to the scheduled infusion. The Investigational Product, 3 components of SB-FIX (ZFN1, ZFN2, and cDNA Donor) will be thawed as instructed in the pharmacy manual, added to 200 ml of diluent, and adjusted to 0.25% human serum albumin. Total volumes will depend on subject's cohort assignment and body weight (kg). The prepared SB-FIX will be kept at room temperature prior to infusion. SB-FIX will be infused at 100 mL/hour through an intravenous catheter using an appropriate constant rate infusion pump while monitoring the subject's vital signs (pulse, blood pressure, respiration rate, and temperature). Detailed instructions for the thaw and infusion of the Investigational product are in the Study Pharmacy Manual.

7.1.3 Precautions

SB-FIX is an investigational product, and there is a possible risk of anaphylaxis. Emergency medical equipment will be available during the infusion in case the subject has an allergic response, or severe hypotensive crisis, or any other reaction to the infusion. Vital signs (temperature, pulse, blood pressure) will be taken before and after infusion, and then according to the study center procedures. In the unlikely event that the subject develops sepsis or systemic bacteremia following SB-FIX infusion, appropriate cultures and medical management should be initiated. If possible contamination of the SB-FIX product is suspected, an investigation can be conducted using archived samples that are stored at the manufacturing facility.

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 investigator will record all concomitant medications including those given in treatment of AEs on the concomitant medication page in the subject's case report form. Any medication taken by the subject from screening throughout the course of the study, including over-the-counter medicinal products, dietary supplements, and herbal medications, should be recorded on this form. A short course of prednisone (or equivalent) may be instituted either as prophylaxis or post AAV exposure if an immune reaction to the AAV capsid develops (See Appendix 3). Any treatment with prednisone (or equivalent) and pre-treatment with acetaminophen and diphenhydramine hydrochloride should be recorded on the concomitant medications page.

All medications including Factor IX short acting are permitted with the exception of those that are potentially hepatotoxic. Hepatotoxic agents such as diclofenac, amiodarone, chlorpromazine, fluconazole, isoniazid, rifampin, valproic acid, high doses of acetaminophen (4-8 gm/day) are not permitted.

8 SAFETY AND POTENTIAL RISKS

8.1 SB-FIX

The three individual recombinant AAV (rAAV) vectors encoding the individual albumin ZFNs and the human FIX Donor cDNA 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-FIX rAAV2/6 vectors are pseudotyped vectors with both inverted terminal repeats (ITRs) being derived from AAV2 ITRs and the virus being packaged in the presence of the AAV2 rep gene and AAV6 cap gene. Virus 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 demonstrating that rAAV2/6 effectively delivered the hFIX cDNA cassette to liver hepatocytes, resulting in expression of hFIX in the systemic circulation.

SB-FIX has never been administered to man. Clinical safety data is now available from a related trial conducted by the Sponsor, Study SB-913-1602, which is a ZFN-mediated *in vivo* genome editing Phase I study for MPS II using SB-913. SB-913 is a rAAV2/6-based gene transfer that comprises the highly similar ZFNs components and differs from SB-FIX only in the donor cDNA (which encodes human factor 9). Study SB-913-1602 has enrolled 2 subjects as of 12- Feb-2018, who have received SB-913 at a dose of 5.00E+12 vg/kg. SB-913 infusion was generally well-tolerated, and no significant safety signals have been observed. Additional information on clinical experience with ZFNs can be located in the Investigator's Brochure.

The immune system of patients is this study will be exposed to two antigens upon infusion of the gene therapy vector, one foreign (AAV capsid) and the other endogenous (FIX). Clinical studies

to date suggest an immune response will be generated to AAV capsid proteins but whether an immune response will develop against FIX in this proposed study remains to be determined.

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. Results from these clinical studies suggest that immunosuppression, for example with corticosteroids, may be necessary to achieve sustained expression of the gene encoding FIX.

Subjects who are positive for neutralizing antibodies to AAV2/6 at screening will not be enrolled in this study. Cell mediated immunity to the viral capsid will be attenuated/abrogated with a short course of immunosuppression (refer to Appendix 3). If any subjects develop increased LFTs or FIX activity decrease by >10% while on prednisone (or equivalent) treatment, the dose of prednisone (or equivalent) may be adjusted after consultation with the Medical Monitor.

There is no specific risk associated with the 12 to 17 year old subjects, who could be considered as adults on the physiological levels (including liver size and growth). However, as conservative approach, these paediatric subjects will be included only after their adult counterparts have shown no safety concerns and will be enrolled only after the SMC reviews the relevant adult safety data.

8.1.1 Potential Off-Target Effect

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, 2011). This assay allows for evaluation of all potential integration sites within the genome. The integration site assay was run using the SB-FIX ZFNs (SBS42906 and SBS43043). This yielded a ranked list of 49 candidate cleavage sites. As expected, the top ranked locus in the human genome is 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-FIX ZFNs, revealed significant modification at albumin (28.9% on-target activity) and only low levels of modification (0.64%) at one of the 47 potential off-target sites monitored in this study. This off-target site was mapped to exon 38 (out of 48 exons) of the structural maintenance of chromosomes flexible hinge domain containing 1 (SMCHD1) gene. SMCHD1 has been linked to chromosome X-inactivation, tumor suppression, DNA damage repair and facioscapulohumeral muscular dystrophy (FSHD).

A mouse knockout of the murine homolog of SMCHD1 has been generated (Blewitt, 2008). While male knockout (by genetrap/gt) mice (*Smchd1* gt/gt) develop normally, female knockout mice exhibit embryonic lethality, due to problems with X chromosome inactivation and

misregulation of CpG methylation (Blewitt, 2008). 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. Given we would expect the levels of on-target modification in patients to be significantly lower than the 28.9% observed in vitro, we would also expect the level of SMCHD1 modification to be much lower than 0.64% in vivo. Furthermore, it is unclear whether X-inactivation would have any impact on liver hepatocytes, which are often polyploid.

In a study describing the potential role of SMCHD1 in tumor suppression, male knockout mice showed normal embryonic development but increased lethality after birth (Leong, 2013). Surviving mice appeared normal and showed no predisposition or susceptibility to tumor formation. If these male knockout mice were crossed into a premalignant Eu-Myc transgenic mouse model, then some hematopoetic cancers were detected, but only in homozygotes (Leong, 2013).

It has also 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, 2014). No evidence for decreased cell survival or spontaneous activation of apoptosis (cleaved PARP-1) or DNA damage markers (KAP-1 phosphorylation) was seen in cells during the effort to develop and characterize the SB-FIX ZFNs.

SMCHD1 mutations have also been associated with facioscapulohumeral muscular dystrophy (FSHD), which is an autosomal dominant muscular dystrophy affecting facial, shoulder girdle, upper arm and other muscle tissues (Larsen, 2015). FSHD type 1 is linked to the contraction of macrosatellite D4Z4 repeats and misregulation of the DUX4 transcript in myoblasts (Statland and Tawil 2014). The far less common FSHD type 2 (about 5% of all cases) has been linked to mutations in SMCHD1 (Lemmers, 2012). However, SB-FIX 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.

8.1.2 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 into the cellular DNA where they may affect genes controlling cell proliferation. AAV vectors do not integrate but the use of ZFN nucleases and a donor will result in permanent modification of the albumin genome. The mouse and NHP studies showed no increase in tumor by gross and histopathologic examination (see section 4.4 of Clinical Investigator Brochure). Although there is no adequate animal model to address the tumorigenic potential, the available toxicological data do not suggest show any tumor formation.

8.2 Prednisone (Or Equivalent Corticosteroid)

Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Prednisone is a synthetic corticosteroid and is a prodrug that is methylated in the liver to produce the active moiety.

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

- Osteoporosis
- Loss of blood supply to bones (aseptic necrosis) which may cause severe bone pain, fractures (especially of the hip and shoulder) and may require surgical correction
- Hypertension
- 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
- Diabetes
- Adrenal insufficiency
- Irritation of stomach and esophagus with possible ulcer type symptoms and, rarely bleeding
- Emotional disturbances

9 SAFETY MONITORING AND ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event (AE)

An 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 this 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 from investigational product, including those occurring as a result of an overdose, abuse, withdrawal phenomena, sensitivity, or toxicity to investigational product
- 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 treatment.

The term AE also applies to laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g., that required unscheduled diagnostic procedures or treatment measures, or resulted in withdrawal from the study).

9.1.2 Adverse Reaction (AR)

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 AE 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.

9.1.3 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).

9.1.4 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

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., an AE in which the subject was at risk of death at the time of the event; it does not refer to an event which 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 Sangamo, a SAE includes any event suggesting significant risk to human subjects.

9.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

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.

9.2 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.

9.3 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 and relationship to the investigational drug. The principal investigator may delegate these duties to sub-investigators and 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 case report form (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 causing no or minimal interference with usual social & functional activities
- Grade 2, Moderate: Symptoms causing greater than minimal interference with usual social & functional activities
- Grade 3, Severe: Symptoms causing inability to perform usual social & functional activities
- Grade 4, Potentially Life-threatening: Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
- Grade 5: For any AE where the outcome 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.

All Grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as AEs if it is not associated with a diagnosis already reported on the case report form. A Grade 1 or 2 clinical laboratory abnormality should be reported as an AE only if it is considered clinically significant by the investigator.

In the event of death, the cause of death should be recorded as the AE and reported as an 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 Investigator should make every effort to obtain and send death certificates and autopsy reports to Sangamo Therapeutics Inc.

9.4 Serious Adverse Event Reporting Period

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

All SAEs, whether or not unexpected or considered to be associated with the administration of SB-FIX, must be reported immediately to Sangamo or its designees, and must be submitted to Sangamo or its designees on an SAE Report form within 24 hours of the Principal Investigator’s discovery of the event.

SAEs must be recorded on the SAE Report Form through the electronic data capture (EDC) system. The paper SAE Report Form is intended as a back-up option when the eCRF system is not functioning or is inaccessible. Please refer to the study reference manual for SAE reporting guidelines.

Follow-up reports are submitted in a timely fashion as information becomes available. Follow-up SAE reports should include the same event terminology as initially reported.

All SAEs must be followed with appropriate medical management until resolved or stabilized.

The Principal Investigator is responsible for promptly notifying the IRB/EC 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 regulatory authority) 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 regulatory authority.

9.5 SUSAR Reporting Obligations

Sangamo or its designee will submit SUSAR reports to appropriate regulatory authorities (including competent authorities in all member states concerned), IRB/EC or equivalent, and 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 eight (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 Sangamo or its designee within 24 hours. Sangamo or its designee will inform the regulatory authorities, IRB/EC or equivalent, 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 Investigators will notify the IRB/EC 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 Sangamo or its designee.

9.6 Pregnancies of a Partner Reporting

Pregnancies of a partner should be recorded using the Pregnancy Initial Report Form. Pregnancies should be followed until final outcome is known. All follow-up for a pregnancy should be submitted on a Pregnancy Follow-up Report Form.

10 TREATMENT SCHEDULE, DOSE ESCALATION & STOPPING RULES

10.1 Schedule for Subject Treatment

Within each cohort, treatment will be staggered so that each subsequent subject cannot be infused until the preceding subject has been observed for at least 4 weeks. Dose escalation to the next cohort cannot occur until at least 4 weeks after the last subject in the preceding cohort has been dosed, and safety data from the entire prior cohort has been reviewed by the Safety Monitoring Committee. Participating sites will be informed about the current cohort as described in the cohort management plan.

10.2 Dose Escalation Rules

If one of the first two subjects within a cohort develops a dose limiting toxicity (DLT) defined as a Grade 3 or higher AE (related to study drug) or if the SMC determines that it is necessary to expand the cohort, 2 additional subjects may be enrolled and treated in that cohort. DLT grading will follow the same grading criteria in Section 9.3. The Safety Monitoring Committee (SMC) will be convened to decide if it is appropriate to continue expansion of that cohort, or dose de-escalate.

During the study, if FIX activity reaches above 50% of normal, further dose escalation will be halted until a discussion with the regulatory agencies has occurred and further dose escalation is warranted.

10.3 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 has been infused with SB-FIX infusion. Safety data including adverse events, 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 two Grade 2 AEs in the same system organ class that last more than 2 weeks with treatment or one Grade 3 or higher AE, if these AEs are not related to the primary hemophilia B disease unless they are associated with induction of FIX inhibitors
- Serious adverse event not related to the primary hemophilia B disease unless it is associated with induction of FIX inhibitors
- Death of a subject
- Development of a malignancy

- Development of a FIX inhibitor
- Sponsor, in consultation with the SMC or Regulatory Agency, decides for any reason that subject safety may be compromised by continuing the study
- Sponsor decides to discontinue the development of the intervention to be used in this study.

If the study is paused because a stopping criteria is met, then the study can resume only after the regulatory agencies have approved (including the application for a substantial amendment if required). The SMC will no longer convene when no new subjects are enrolled or dosed in the study. Sangamo will review subject safety data on an ongoing basis.

11 SUBJECT WITHDRAWAL/DISCONTINUATION, AND SAFETY MONITORING COMMITTEE

11.1 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 the sponsor or primary care provider if he or she thinks the study is no longer in the best interest of the subject.
- Subject judged by the 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 or EC equivalent, Office for Human Research (OHR), regulatory agencies, investigator, or Sangamo Therapeutics.

Subjects will be strongly encouraged to continue with follow-up safety evaluations. If a subject discontinues from the study a conference between the investigator and medical monitor will take place to ensure that all subjects will comply with the follow-up safety evaluations of the protocol. If 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.

11.2 Safety Monitoring and Mitigation Plan

The liver function (AST, ALT, bilirubin, alkaline phosphatase, and albumin) of study subjects will be monitored closely throughout the study as indicated above in the Section Treatment Plan.

Key potential anticipated risks are:

1. Development of transaminitis due to cell-mediated immunity to capsid and/or AAV gene product. Steroids, e.g., prednisone (oral or intravenous) may be administered to minimize the immune response to AAV vector (Appendix 3).
2. Development of inhibitors to the FIX expressed from the albumin locus. This is potentially

problematic because the FIX production is continuous, and potentially couldbe cross-reactive to exogenous FIX preparations. Endogenous human FIX is not expected to be immunogenic in subjects who have not already developed inhibitors to exogenous FIX. If this occurs, standard of care for FIX inhibitors (which is generally effective for acquired hemophilia) will be instituted.

3. Reduction in albumin synthesis. This is not expected given the small fraction (<1%) of transduced cells with albumin locus disruption and has not been observed in animal studies with levels of transduction and albumin locus disruption exceeding those expected in humans by several fold.

11.3 Safety Monitoring Committee

An independent Safety Monitoring Committee (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 determine if it is safe to proceed with the next dose cohort. The SMC may be convened at any time if there are excessive or unexpected toxicities associated with the conduct of the protocol.

The study treatment will be stopped if the following criteria are met, and the SMC will convene to determine the proper course of action:

- Any two Grade 2 AEs in the same system organ class that last more than 2 weeks with treatment or one Grade 3 or higher AE, if these AEs are not related to the primary hemophilia B disease unless they are associated with induction of FIX inhibitors
- Serious adverse event not related to the primary hemophilia B disease unless it is associated with induction of FIX inhibitors
- Death of a subject
- Development of a malignancy
- Development of a FIX inhibitor
- Sponsor, in consultation with the SMC or Regulatory Agency, decides for any reason that subject safety may be compromised by continuing the study
- Sponsor decides to discontinue the development of the intervention to be used in this study.

All data will then be evaluated to determine if changes should be made to the study or if accrual should be halted. In addition, no further dosing of patients will be performed until a substantial amendment application is approved by the Regulatory Agency.

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, studies SB-318-1502 in MPS I subjects and SB-913-1602 in MPS II subjects use similar ZFNs

components as the present study in combination with a different donor cDNA (encoding human Factor 9). Given the similarities of the approaches, relevant data from 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.

The SMC will no longer convene when no new subjects are enrolled or dosed in the study. Sangamo will review subject safety data on an ongoing basis.

12 STATISTICAL ANALYSIS AND DATA ANALYSIS

This is an exploratory Phase 1 study and thus, there will be limited statistical power to evaluate efficacy and related biological endpoints. Therefore, analyses will be primarily descriptive and exploratory in nature.

12.1 Sample Size

This study will enroll up to 16 evaluable subjects. Subjects who do not complete at least 12 months of the study may be replaced. The selection of 2 subjects per cohort was not based on statistical calculations since this is a Phase I safety study to evaluate safety and tolerability. Once a dose demonstrating sufficient safety has been established and an increase in Factor IX level in at least two subjects ≧ 18 years old has occurred, then only a single cohort of three subjects 12- 17 years old will be added.

12.2 Statistical Methods/Data Analysis

All tables, listings, and data summaries will be performed in SAS version 9.2 or later.

12.3 Safety Population

All subjects enrolled in this study who receive any portion of the SB-FIX infusion will be included in the safety population.

12.4 Demographics

Demographic and baseline characteristics will be summarized by treatment cohorts.

12.5 Endpoints and Analysis

This is a Phase 1 exploratory study and thus, there will be limited statistical power to evaluate efficacy and related biological endpoints. Therefore, analyses will be primarily descriptive and exploratory in nature. The study endpoints are described in Section 12.5.1, Section 12.5.2, and Section 12.5.3.

12.5.1 Primary Endpoint

Safety and tolerability will be assessed by the grading of AE/SAE and change in laboratory evaluations from baseline.

12.5.2 Secondary Endpoints

Secondary endpoints include:

1. Changes in FIX antigen and activity levels from baseline over time
2. Change from baseline in the number of FIX units infused per week
3. Change from baseline in number and severity of bleeding episodes
4. Changes in neutralizing antibody to FIX from baseline over time
5. Presence and shedding in AAV2/6 vector DNA, by PCR in plasma, saliva, urine, stool and semen over time

12.5.3 Exploratory Endpoint

The exploratory endpoint is changes in serum total antibodies to AAV2/6 from baseline over time.

The analyses of these endpoints will be descriptive and exploratory in nature. Continuous variables will be summarized by means, standard deviations, medians and ranges for all enrolled subjects. Categorical variables will be summarized with counts and percentages per category for all enrolled subjects. Change from the preceding year values may be calculated for selected clinical and laboratory parameters. Shift-tables (change-from-baseline relative to the normal range) may be constructed for selected laboratory parameters.

13 INVESTIGATOR OBLIGATIONS

The investigator will ensure that the study is conducted in compliance with the protocol, the Declaration of Helsinki and according to ICH Guidelines for Good Clinical Practice (E6) and all regulatory and institutional requirements, including those for subject privacy, informed consent, Institutional Review Board or Ethics Committee approval and record retention.

13.1 Institutional Review Board and BioSafety Committee

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

13.2 Protocol Amendments

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

13.3 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 his/her 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 regulatory authorities, other national or local health authorities, Sangamo Therapeutics, and the associated IRB/EC.

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/EC equivalent prior to the release of such information. Identifiable subject data may not be used for purposes of promoting the investigational product.

13.4 Reporting Obligations

Sangamo Therapeutics, Inc. is required to notify any governing regulatory agencies the status of the trial according to applicable regulations. Status reports must be filed by the Principal Investigator with their IRB or EC equivalent as required per reporting requirements.

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

14 ADMINISTRATIVE CONSIDERATIONS

14.1 Study Documentation

The 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 the Sponsor or the regulatory agencies at any time and should consist of the following elements:

a. Subject files containing the completed medical records, supporting source documentation, electronic case report forms and the IRB or EC equivalent approved Informed Consents signed by subjects.

b. Study files containing all versions of the IRB or EC equivalent approved protocol with all amendments, IRB or EC equivalent approved informed consent forms, copies of all pre-study documentation, Form FDA 1572 (as required) and all relevant correspondence to and from the IRB or EC equivalent and the Sponsor.
c. The investigator should maintain a list of appropriately qualified persons who are delegated to perform significant study-related studies. In addition, the 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 case report forms.

14.2 Record Retention

The investigator shall retain records 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 investigator shall retain these records until 2 years after the investigation is discontinued and the FDA or applicable regulatory authorities are notified. Study records shall be kept for at least 25 years or the maximum period by applicable policy or regulation (whichever is greater). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Sangamo Therapeutics. It is the responsibility of Sangamo Therapeutics to inform the investigator as to when these documents no longer need to be retained.

14.3 Case Report Forms

The investigator is responsible for the quality of the data recorded on the case report form. 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 case report forms (CRFs) provided by Sangamo Therapeutics. All forms must be legible and complete. The investigator must review all entries for completeness and correctness. When changes or corrections are made on any case report form, 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 investigator agrees to complete and sign case report forms in a timely fashion, after completion of each subject, and make them available to the Sangamo Therapeutics study monitor for full inspection. In addition, all data queries should be resolved promptly.

14.4 Termination of the Study

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

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

14.5 Study Monitoring

Sangamo Therapeutics, as sponsor of this study, is responsible for ensuring the proper conduct of the study as regards protocol adherence and validity of the data recorded on the case report forms presented to the regulatory authorities. Sangamo Therapeutics has therefore assigned a clinical monitor and a medical monitor to this study. Their duties are to aid the investigator and, at the same time, Sangamo Therapeutics in the maintenance of complete, legible, well-organized, and easily retrievable data. In addition, a Sangamo Therapeutics 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 Therapeutics (or designees) at appropriate intervals to assure satisfactory consenting process, data recording, and protocol adherence. In order to perform their roles well, the Sangamo Therapeutics monitors must be given direct access to primary subject data (source documents) that support data entered onto the case report forms. The 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 to keep abreast of subject status and to answer questions.

Regulatory authorities, the IRB or EC equivalent, and/or the sponsor's clinical quality assurance group may request access to all source documents, case report forms, and other study documentation for on-site audit, or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

The 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
- AEs as described in Section 9.1 of this protocol

Entries in the subject notes must contain the signature or initials of the person making the entries. The clinical study monitor will perform source data verification at each monitoring visit.

14.6 Publication Statement

The results of this clinical trial may be used by Sangamo Therapeutics 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 by an investigator.

All proposed publications, papers, abstracts, or other written materials related to the study, or an outline of any proposed oral presentations, shall be submitted to Sangamo Therapeutics for approval at least 45 days prior to (1) submission of such written materials for publication or (2) any proposed oral disclosure to a third party. 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 the event that Sangamo Therapeutics determines that an enabling description of patentable subject matter is contained in such written material or outline, it shall notify the clinical site(s) within 1 month after receipt by Sangamo Therapeutics and Sangamo Therapeutics will have an additional 90 days for review.

In the event of publication using multi-center data, the number of subjects enrolled by each investigator will usually determine the order of participation, unless otherwise agreed upon by the investigators and Sangamo Therapeutics.

14.7 Study Funding

The costs necessary to perform the study will be agreed to by the 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 investigator and Sangamo Therapeutics.

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APPENDIX 1. SCHEDULE OF EVENTS

Procedure	Screening	Baseline (w/in 21 days before SB-FIX infusion)	Hospitalization or Acute Care Facility		Day 7 (+/-1 day)	Weeks 2, 4, 6, 8, 10, 12 (+/- 3 day)	Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (+/- 1 wk)	Months 15, 18, 21,24, 27, 30, 33, 36/EOS* (+/- 1 M)	Early Termination Visit
			Day 0	Day 1					
Informed consent	X								
Medical History, Inclusion/Exclusion Criteria	X								
Physical Exam [(a)]	X	X	X	X	X	X	X	X	X
Weight	X	X	X		X	X	X	X	X
Abdominal Exam for hepatomegaly		X				X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Neurologic cranial nerve exam and muscle strength testing of the upper extremities		X				X (WK 12 only)	X (Wks 24 and 52)	X (Months 18, 24, 30, and 36)	X
12-lead ECG	X								
Chest X-ray	X								
Urinalysis with microscopic exam	X							X (Month 36 only)	X
CBC w differential and platelet count	X	X	X	X		X (WKs 4, 8, 12)	X (WK 28,52)	X	X
Serum Chemistry, Metabolic Panel	X	X	X	X		X	X	X	X

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Procedure	Screening	Baseline (w/in 21 days before SB-FIX infusion)	Hospitalization or Acute Care Facility		Day 7 (+/-1 day)	Weeks 2, 4, 6, 8, 10, 12 (+/- 3 day)	Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (+/- 1 wk)	Months 15, 18, 21,24, 27, 30, 33, 36/EOS* (+/- 1 M)	Early Termination Visit
			Day 0	Day 1					
Liver Panel[(b)]	XX	X	X	X	X (2 x/wk)	X (2x /wk)	X (2 x/wk if using steroid)	X	X
Direct bilirubin	X								
Neutralizing antibodies to AAV 2/6	X								
Total antibodies to AAV2/6 (exploratory)		X				X (WKs 4, 8, 12)	X (WKs 24, 36, 52)		
Coagulation screen (PT, INR, and PTT)	X	X	X			X (WKs 4, 8, 12)	X	X	X
FIX activity	X	X		X	X	X (weekly)	X (Weekly if using steroid)	X	X
FIX antigen	X	X		X	X	X (WKs 4, 8 ,12)	X	X	X
FIX inhibitor level	X	X		X		X (WKs 4, 8, 12)	X	X	X
HBV DNA, HBsAg, HCV RNA viral load, and HIV RNA viral load and HIV-1/2 antibody assay	X								
SNP assay	X								
Concomitant medication review[(c)]	X	X	X	X	X	X	X	X	X

APPENDIX 1. SCHEDULE OF EVENTS

Procedure	Screening	Baseline (w/in 21 days before SB-FIX infusion)	Hospitalization or Acute Care Facility		Day 7 (+/-1 day)	Weeks 2, 4, 6, 8, 10, 12 (+/- 3 day)	Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (+/- 1 wk)	Months 15, 18, 21,24, 27, 30, 33, 36/EOS* (+/- 1 M)	Early Termination Visit
			Day 0	Day 1					
AE assessment[(c)]		X	X	X	X	X	X	X	X
ZFN immunogenicity (exploratory)		X				X (WKs 4, 8, 12)	X (Wk 24, 36, 52)		
Assessment of bleeding episodes and FIX concentrates usage		X	X	X	X	X	X	X	X
ACTH stimulation test[(d)]		X				X	X	X	X
Prednisone administration (or equivalent) if indicated		X	X	X	X	X	X		
SB-FIX infusion			X						
Vector genome in plasma, saliva, urine, stool and semen by PCR[(e)]		X		X	X	X (WKs 2, 4, 8, 12)	X		X
FIX genome sequencing [(f)]	X								
Liver MRI [(g)]	X					X (WK 12 only)	X (WKs 24 and 52)	X (Mos 18, 24, 30, and 36)	X
Circulating alpha fetoprotein level [(g)]	X					X (WK 12 only)	X (WKs 24 and 52)	X (Mos 18, 24, 30, and 36)	X

APPENDIX 1. SCHEDULE OF EVENTS									
	Screening	Baseline (w/in 21 days before SB-FIX infusion)	Hospitalization or Acute Care Facility		Day 7 (+/-1 day)	Weeks 2, 4, 6, 8, 10, 12 (+/- 3 day)	Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (+/- 1 wk)	Months 15, 18, 21,24, 27, 30, 33, 36/EOS* (+/- 1 M)	Early Termination Visit
Procedure			Day 0	Day 1					
Exploratory samples[h]		X							
Liver Biopsy [i]								X (EOS only)	

* Study subjects may participate in the LTFU Study after 12 months of follow-up in the SB-FIX-1501 study, in which case an EOS visit may be conducted any time after Week 52 in combination with or before the next scheduled study visit.

a. Height will be measured at Screening Visit only.
b. At Screening, liver panel will be performed two times at least one week apart. Liver panel will be tested twice per week for the first 12 weeks after the SB-FIX infusion. LFT for the baseline visit must be performed within 1 week of infusion.
c. Subjects will use a diary to record bleeding episodes, factor infusions, and concomitant medications starting at their baseline visit through their last visit.
d. ACTH stimulation test will be performed at Baseline for all subjects, and the test will be performed again only at the end of steroid taper. ACTH test will be performed at the early termination visit if subject is on a steroid regimen at the time of their visit.
e. Vector genomes in plasma, saliva, urine, stool, and semen by PCR (unless two previous consecutive specimens have been negative). On Day 1, the only vector genome analysis performed is in plasma (12 hours after infusion).
f. Only for subjects with no FIX sequencing previously
g. Any subject who has an elevated alpha fetoprotein and MRI mass suspicious for hepatocellular carcinoma (HCC) or greater than 2 cm will undergo biopsy using surgical doses of Factor IX replacement. A MRI of the liver can be replaced by an abdomen CT-scan (or any equivalent imaging technology) – with vascular phases specific for a search of a liver mass – in case the subject has a contraindication to MRI (for example history of hip replacement).
h. Blood samples for sEGFR and Gal3BP will be collected and stored for future analysis.
i. At the end of EOS visit, subjects may be asked to provide a liver biopsy, at the discretion of the Principal Investigator and Sangamo Medical Monitor.

APPENDIX 2. BIOPSY SAMPLE COLLECTION

A liver biopsy can be performed in two separate and non-exclusive occasions:

1- Prior to enrollment into the LTFU, subjects will be asked to provide a liver biopsy, at the discretion of the Principal Investigator and Sangamo Medical Monitor. This request is optional and does not preclude the patient from joining the LTFU study. The proposed mechanism of action of SB-FIX is to introduce the Factor IX transgene into a precise location in the albumin locus. To determine the level of insertion of the factor IX gene after SB-FIX injection, liver tissue will be obtained by liver biopsy, unless contraindicated by the Principal Investigator or physician, and analyzed by high-throughput sequencing of the albumin locus.

2- 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 alpha fetoprotein and MRI mass suspicious for hepatocellular carcinoma (HCC) or greater than 2 cm will undergo biopsy using surgical doses of FIX replacement. Histopathologic examination and genomic analysis (e.g., sequencing of the albumin locus and integration site analysis) will be performed in an attempt to identify the origin and nature of the tumor.

Liver Biopsy Sample Collection and Tissue Preparation

Liver biopsy will be obtained prior to enrollment into the LTFU at the discretion of the Principal Investigator and Sangamo Medical Monitor, and/or if a liver mass is detected during the study. A liver biopsy sample will be collected in 10% neutral buffered formalin and processed for histopathological evaluation by the site. A second liver biopsy sample will be flash frozen in liquid nitrogen. Samples may be stored in a -80ºC freezer before shipment. Details of the histopathological evaluation, including the weight of liver tissue obtained from each biopsy sample, will be summarized in a report and sent to the sponsor.

The efficiency of SB-FIX in targeting insertion of Factor IX 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-FIX.

APPENDIX 3. IMMUNOSUPPRESSION REGIMEN

Steroid prophylaxis will not be instituted at the initiation of this study. Subject's LFTs will be monitored twice a week and FIX activity will be monitored once a week for the first 12 weeks after SB-FIX infusion. The same monitoring schedule of LFTs and FIX activity will continue after Week 12 if the subject is receiving steroid treatment.

If a subject experiences an increase in ALT >2 times of the baseline value, oral prednisone at a dose of 60 mg/day will be instituted, followed by a rapid tapering targeted at 50% per week as provided in the table below.

	WK 1	**WK 2**	**WK3**	**WK 4**
Prednisone	60 mg/day	30 mg/day	15 mg/day	5 mg/day

Prednisone may be replaced by an equivalent product from the corticosteroids class, for example methylprednisolone or prednisolone, oral or intravenous, at the discretion (for type of corticosteroid and possible dose adjustment based on weight) of the investigator.

Tapering will only proceed when ALT value has stabilized (three consecutive values under the ULN with no increase of ALT) or FIX levels have stabilized or increased during the preceding week. If a subject's LFTs again increase, or FIX levels decrease > 10% while on prednisone, the dose of prednisone may be adjusted (increased) after consultation with the Medical Monitor.

A short course of steroid (prophylaxis or post-exposure at a defined time point after SB-FIX infusion) will be initiated for the remaining untreated subjects if ALT elevation >2 times of baseline is observed in two subjects, or ALT elevation > 5 times of baseline is observed in one subject. The SMC will be consulted in determining the timing of the initiation of the steroid treatment based on the timing of ALT increases or FIX decreases from the previously treated subjects.

An ACTH stimulation (cosyntropin) test will be performed at the end of the taper to ensure that the hypothalamic-pituitary-adrenal axis has not been suppressed.

If a subject develops transaminitis during or after the prophylactic course of prednisone treatment, Medical Monitor should be consulted to determine an appropriate course of treatment.

Twice weekly LFT's and weekly FIX activity measurements should continue until the subject's prednisone course has been terminated.