Sangamo Therapeutics, Inc
SB-FIX-1501

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

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Statistical Analysis Plan

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List of Abbreviations

AAV	Adeno Associated Virus
AE	Adverse Event/Experience
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (SGPT)
AST	Aspartate Aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
CBC	Complete Blood Count
COA	Certification of Analysis
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
ELISA	Enzyme Linked Immunoassay
FDA	Food and Drug Administration
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	Homologous Recombination
IV	Intravenous
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NAB	Neutralizing Antibody
NHEJ	Non-homologous End-joining
NHP	Non-human Primates
NIH	National Institutes of Health
PCR	Polymerase chain reaction
PI	Principal Investigator
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SNP	Single Nucleotide Polymorphism
SOC	System Organ Class
WHO	World Health Organization
ZFN	Zinc Finger Nucleases

1. Introduction

Hemophilia B is an X-linked recessive bleeding disorder caused by mutations in the gene encoding blood coagulation Factor IX (FIX). FIX is a serine protease that is critical for the intrinsic clotting pathway. 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.

In this study, it's proposed 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). Adeno Associated Virus (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 aPTT, were seen in Hemophilia B mice.

The purpose of the Statistical Analysis Plan (SAP) is to describe the analyses and data presentations for Sangamo's protocol SB-FIX-1501 (Amendment 8, 20March2020). This SAP outlines the types of analyses that will address the study objectives and explains in detail how the data will be handled and analyzed. It contains the definitions of analysis sets and statistical methods for the analysis of endpoints. Since this is an exploratory Phase I study, all analyses will be descriptive and exploratory in nature. No hypotheses testing will be carried out.

2. Objectives

2.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of SB-FIX.

2.2. Secondary Objectives

The secondary objectives of this study are to evaluate:

- Change from baseline in FIX antigen and activity levels
- Change from baseline in use of Factor IX replacement therapy
- Change from baseline in frequency and severity of bleeding episodes
- Immune response to FIX

- Presence and shedding of AAV2/6 vector DNA by PCR in plasma, saliva, urine, stool and semen

2.3. Exploratory Objectives

The exploratory endpoint will not be analyzed in data listing and table. It will be discussed in a separate document.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase I, open-label, ascending dose study of 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. The duration of study participation will be approximately 39 months for each subject, including 3 months for screening, 36 months for treatment and study follow-up. Accrual is planned for 20 months.

Up to 16 subjects will be enrolled. Among them, 13 subjects will be aged at 18 years or older and potentially three subjects will be between 12-17 year old. Two subjects $\geqslant$ 18 years old will be enrolled in each of two dose cohorts.

Subjects who satisfy all inclusion/exclusion criteria will be enrolled into one of the following two treatment cohorts:

Cohort 1: Total rAAV Dose (vg/kg) 1.00E+13

Cohort 2: 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 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.

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 (Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), bilirubin, alkaline phosphatase (ALP), LDH, total protein, and albumin) will be performed 2 times per 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, and every 3 months in Year 2 and Year 3, or until enrollment into LTFU study.

3.2. Study Endpoints

3.2.1. Primary Endpoint

- Grading of adverse event (AE) and serious adverse event (SAE)
- Change from baseline in laboratory evaluations

3.2.2. Secondary Endpoints

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

3.3. Treatments

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

- Left ZFN (SB-42906)
- Right ZFN (SB-43043)
- Human FIX Donor cDNA with human albumin homology arms (SB-F9)

3.4. Dose Modifications

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

4. General Statistical Considerations

Study day will be calculated as event/assessment date - date of SB-FIX infusion. Thus, the date of SB-FIX infusion is considered as Day 0. The relative study day for assessment will be derived as the assessment date subtracted from the date at Day 0.

Baseline is defined as the last non-missing assessment prior to the SB-FIX infusion. Measurements that are obtained after infusion will be considered as post-baseline values. Change from baseline is defined as post-baseline assessment minus baseline assessment.

Summary tables will be provided when there is more than one enrolled subject in a cohort. Otherwise, data will be presented in the form of a listing.

Continuous variables will be summarized using the following descriptive statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum and maximum,

where appropriate. Categorical variables will be summarized using the frequency count (n) and percentage (%) of subjects for each category, where appropriate.

No imputation will be performed for missing data unless otherwise specified.

Data will be displayed in all listings sorted by treatment cohort and subject identifier.

All analyses will be conducted using SAS® Version 9.3 or higher. The Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 will be used for coding adverse events. Prior or concomitant medication data will be coded using the World Health Organization (WHO) Drug Dictionary Global B3 March 2020.

4.1. 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.

4.2. Analysis Set

4.2.1. Enrolled Set

The enrolled set will include subjects who enrolled in this study.

4.2.2. Safety Set

The Safety set will include all subjects who enrolled in this study and receive any portion of the SB-FIX infusion.

Unless specified otherwise, all collected data used for table summaries will be based on Safety set, and corresponding listings will be provided for enrolled set. Any percentage will be calculated based on number of subjects for the Safety set if not otherwise specified.

5. Subject Disposition

5.1. Disposition

A disposition table of subjects will be presented, which will include the number and percentage of subjects for the following categories: subjects in Enrolled set and Safety set, subjects who completed the study, and subjects who early terminated from the study. The disposition will be summarized by treatment cohort. The percentages will be based on the number of subjects in each treatment cohort and overall. The reasons for early termination of the study will also be summarized in the table.

Subject disposition and analysis set assignment data will be presented in a listing.

5.2. Protocol Deviations

Protocol deviation data will be presented in the table and listing. All COVID-19-related protocol deviations will be summarized in the table and flagged in the listing.

6. Demographics and Baseline Characteristics

6.1. Demographics

The demographics will be summarized by treatment cohort and overall. The following variables will be included:

- Age (Years)
- Race (White, African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight and Height at baseline prior to dosing

Age will be derived as (Date of inform consent – date of birth + 1)/365.25.

The demographics data will be listed as well.

6.2. Medical History

The number and percentage of subjects with any medical history will be summarized by treatment cohort and for each body system code. Body system codes are recorded on the eCRF. Percentages will be calculated based on number of subjects for the Safety set.

Subject medical history data including specific details will be presented in a listing.

7. Treatments and Medications

7.1. Concomitant Medications

The concomitant medication is defined as any medication (including those given in treatment of AEs) taken by the subject from screening throughout the course of the study.

Concomitant medications will be coded using the WHO Drug Dictionary. The dictionary will be updated throughout the life of the project to allow for the most recent version of the dictionary to be used. The medication names will be coded according to the Anatomical Therapeutic Chemical (ATC) class level 4 and preferred terms provided in the dictionary.

Concomitant medications will be summarized by providing the number and percentage of subjects by ATC class and preferred term for each treatment cohort and overall. ATC classes will be sorted in decreasing order of frequency based on the total number of subjects who take each medication in the total column, while preferred terms within each drug class will be presented alphabetically. In addition, the total number of medications and the number and percentage of subjects receiving at least 1 concomitant medication will

also be presented. If a subject has multiple medications for a given preferred term the subject will only be counted once.

All concomitant medications will be presented in a listing.

7.2. Study Treatments

The prepared investigational product will be intravenously infused at 100 mL /hour using a constant rate infusion pump on Day 0 while the subjects are in the hospital or an acute care facility. As it's a single infusion study, compliance or modification data is not applicable.

All infusion data including specific details will be presented in a listing.

8. Endpoint Analysis

8.1. Primary Analysis

The primary analysis in this study aims to assess the safety and tolerability of SB-FIX infusion by the grading of adverse event, serious adverse event and change from baseline in laboratory evaluations.

8.1.1. Adverse events

A treatment-emergent adverse event (TEAE) is defined as any event which occurs on or after the date of infusion, or an event that occurs prior to start of infusion and has frequency, intensity, or the character of the condition that worsens after administration of study treatment.

To identify TEAE, if the AE end date is partial, it will be imputed as follows (where UK and UKN indicate unknown or missing day and month respectively):

Partial end dates

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

If the AE end date is on or after infusion date (after any imputation) or completely missing, the AE onset date will be compared with infusion date. In the event that only a partial start date (month/year) is available, it will be handled as follows:

Partial onset dates

- UK-MMM-YYYY: If the month and year are different from the month and year of the infusion date, assume 01-MMM-YYYY. If the month and year are the same as the infusion month and year, and the end date (after any imputation) is on or after the infusion date, then assume the infusion date. If the month and year are the same as the infusion month, and year and the end date (after any imputation) is prior to the infusion date, then assume the end date for the onset date.

- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of infusion, assume 01-JAN-YYYY of the collected year. If the year is the same as the infusion year, and the end date (after any imputation) is on or after the infusion date, then assume the infusion date. If the year is the same as the infusion year, and the end date (after any imputation) is prior to the infusion date, then assume the end date for the onset date.

If the AE end date is complete and the partial AE start date imputed by the rules above is after the AE end date, then the start date will be imputed by the AE end date.

All AEs will be coded according to the most recent version of the MedDRA. Severity will be categorized by toxicity grade according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

AEs not listed in the CTCAE 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.

Relationship of Adverse Events to Study Drug

The relationship of AEs to study drug has two categories: Related and Not related. 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 AE reaction will be categorized as Not Related. No imputation will be done for missing relationship.

Severity of Adverse Events

All AEs will be summarized by maximum severity (CTCAE Grade 1, 2, 3, 4 and 5). If a subject reports multiple occurrence of a specific event within a specific analysis period, the subject will be counted only once by the maximum severity. No imputation will be done for missing severity.

The incidence of AEs will be summarized in tables with count and percentage of subjects with AEs by system organ class (SOC) and preferred term. Unless otherwise specified, at each level of SOC or preferred term, a subject with multiple events will only be counted once per SOC or preferred term. Percentages of subjects with AEs will be calculated out of

the number of subjects in each summary cohort of the Safety set. Tables will be sorted by SOC in decreasing order on total frequency in overall group and preferred term in alphabet order.

The following categories of AE will be summarized:

- TEAEs
- Severity (CTCAE Grade 1, 2, 3, 4 and 5) of TEAEs
- Relationship of TEAEs to study treatment
- Grade 2 or greater TEAEs
- SAEs
- Grade 2 or greater SAEs
- AEs leading to death
- AEs leading to study discontinuation

All AEs will be presented in data listings. TEAEs and SAEs will be flagged in the listings.

8.1.2. Laboratory Evaluations

The laboratory assessments include serum chemistry and metabolic panel, liver panel, CBC w diff and Platelet, and urinalysis with microscopic exam. The lab assessments will be evaluated over time on the study except urinalysis. Urinalysis assessments will only be collected at screening. All summaries will be based on the SI units, and missing values will not be imputed. Summary statistics of the observed values and change from baseline will be provided at the scheduled visits for serum chemistry and metabolic panel, liver panel, and CBC w diff and Platelet parameters by treatment cohort. The number and percentage of subjects with shift on extreme post-baseline values in low/normal/high from baseline will be presented in a shift table for liver panel parameters. Extreme laboratory value is the lowest or highest category a patient has post-baseline for the laboratory parameter. If a patient has a value below the normal range and a value above the normal range, the value furthest from the normal range will be chosen.

The coagulation level (by PT, PTT, and INR) is assessed over time. The level of PT, PTT and INR will be summarized by treatment cohort and by visit for baseline, post-baseline and change from baseline values. Corresponding listing will be provided. The mean and standard error by cohort will be plotted for each coagulation parameter by timepoint and treatment cohort.

All laboratory data will also be presented in listings for each summary section with abnormal values flagged.

8.2. Secondary Analysis

The secondary analysis in this study aims to estimate effect of SB-FIX infusion on bleeding episodes and AAV2/6 SB-FIX recombinant related assessments.

8.2.1. FIX antigen and FIX activity levels

The FIX antigen and FIX activity levels are assessed over time during the study. The level of FIX antigen and FIX activity will be summarized by treatment cohort and by visit for baseline, post-baseline and change from baseline values. Corresponding listing will be provided. The mean and standard error by cohort will be plotted for each parameter by timepoint and treatment cohort.

8.2.2. Bleeding episodes and Factor replacements

The bleeding episodes and FIX concentrates usage is recorded in diary over time during the study. The subjects will report the bleeding episodes at each visit. The severity has three levels: mild, moderate and severe. The related information of each bleeding episode will be presented in a listing. The number of bleeding episodes and Factor replacements usage after three weeks post treatment will be summarized by subject. In addition, the corresponding annualized frequency will be calculated at subject level too. Factor replacements include Benefix, Ixinity, and Mononine. The annualized bleeding episodes will be derived as

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Annualize Number of Bleeding Episodes>=3 Weeks =(Number of Bleeding
Episodes>=3 Weeks)/(Post Dose Days at Last Visit -21 Days)*365.25
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and the number of Factor replacement exposed will be annualized in same approach.

8.2.3. Neutralizing Antibodies to FIX

FIX inhibitor level reflects the immunogenicity response to FIX. It is collected over time during the study. The level of FIX inhibitor will be summarized by treatment cohort and by visit for baseline, post-baseline and change from baseline values. Corresponding listing will be provided. The mean and standard error by cohort will be plotted by timepoint and treatment cohort.

8.2.4. Presence and shedding of AAV2/6 vector DNA

Presence and shedding of AAV2/6 vector DNA, by PCR in plasma, saliva, urine, stool and semen over time is conducted in lab section over time till week 52. The level of vector genome from each type of sample will be summarized by visit. Corresponding listing will be provided. The mean and standard error by cohort will be plotted for AAV shedding in blood and in serum by timepoint and treatment cohort.

8.2.5. Vital Signs

The vital sign data collected after infusion until 2 hours post-infusion will be pooled for each subject and the mean of pooled data will be summarized by cohort as one timepoint,

ie 2 hour post-infusion timepoint. The data collected at Baseline, and post-infusion will be summarized by timepoint for each cohort. Change from baseline will be summarized too. The vital sign data will be listed.

9. Other Analysis

9.1. Neurological cranial nerve exam and muscle strength testing

The neurological cranial nerve exam and muscle strength testing will be conducted from baseline over time. The neurological cranial nerve exam includes oculomotor nerve, trochlear nerve and abduces nerve assessment, facial nerve assessment, accessory nerve assessment, hypoglossal assessment and muscle strength assessment. Each assessment has outcome categorized into normal, abnormal non-clinically significant and abnormal clinically significant. The muscle strength testing includes scapular assessment, shoulder abduction, elbow flexion, and hand extension. The test result has: no contraction, visible/palpable muscle contraction but no movement, movement with gravity eliminated, movement against gravity only, movement against gravity with some resistance, and movement against gravity with full resistance. The number and percentage of subjects in each exam and test will be summarized by visit. Corresponding listing will be displayed.

9.2. Circulating alpha fetoprotein

The test for circulating alpha fetoprotein will be conducted over time. The circulating alpha fetoprotein data will be summarized in table and presented in a listing.

9.3. Other assessments

The other assessments including physical exams, 12-lead ECG, chest X-ray, SNP assay, liver imaging findings, etc will be provided in separate listings.

10. Safety Monitoring Committee

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 SOC that last more than 2 weeks with treatment or one Grade 3 or greater 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.

Data analyses for SMC review will be presented in a separate document.

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. References

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