Sangamo Therapeutics, Inc.

Statistical Analysis Plan
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Protocol Number: SB-728mR-1401

A Phase 1/2, Open-label Study to Assess the Safety and Tolerability of Repeat Doses of Autologous T-Cells Genetically Modified at the CCR5 Gene by Zinc Finger Nucleases in HIV-Infected Subjects Following Cyclophosphamide Conditioning

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List of Abbreviations

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
CCR5	Chemokine (C-C motif) Receptor 5
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CRF	Case Report Form
CSR	Clinical Study Report
CTC	Common Terminology Criteria
CTX	Cyclophosphamide
eCRF	Electronic Case Report Form
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PBMC	Peripheral Blood Mononuclear Cell
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SB-728mR-T	SB-728mR modified T-cells
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
WBC	White Blood Cell Count

1 Introduction

This document describes the planned statistical analyses for Protocol SB-728mR-1401, A phase 1/2, open-Label Study to Assess the Safety and Tolerability of Repeat Doses of Autologous T-Cells Genetically Modified at the CCR5 Gene by Zinc Finger Nucleases in HIV-Infected Subjects Following Cyclophosphamide Conditioning. This document supplements the study protocol Amendment 2 which should be referred to for further details regarding the study objectives and design and is developed prior to database lock. This SAP provides additional details concerning the statistical analyses outlined in the protocol. Any deviations from this statistical analysis plan will be described in the Clinical Study Report.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of repeat doses of SB-728mR-T following CTX conditioning.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate:

- Effect of repeat doses of SB-728mR-T on engraftment following CTX conditioning
- Long-term persistence of SB-728mR-T in peripheral blood as measured by pentamer PCR
- Change in CD4+ T-cell counts in peripheral blood after repeat treatments with SB-728mR-T
- Effect of SB-728mR-T on plasma HIV-1 RNA levels following HAART interruption
- Change in HIV reservoirs as part of exploratory research

3 Study Design

This is a Phase 1/2, open-label, multi-center study. Subjects who satisfy all inclusion/exclusion criteria are eligible to participate in this study. Subjects will be enrolled sequentially into two treatment cohorts, Cohort 1 and Cohort 2. The first 3 subjects will be enrolled and treated in Cohort 1. The next 3 subjects will be enrolled and treated in Cohort 2. Depending upon the outcome in Cohort 1 and Cohort 2, the remaining 6 subjects will be enrolled and treated in either Cohort 1 or Cohort 2.

Cohorts 1 and 2 data will be collected as subject visits occur per the study protocol. The first time point at which a regimen decision for the final 6 subjects can be made is two weeks after the third infusion of the first and second patients in Cohort 2, and, if the decision is to use the Cohort 2 regimen, at least 2 weeks after the first infusion of the third subject in Cohort 2, and after all safety issues that require a pause in enrollment to that point have been resolved. The staggering of patients in Cohort 1 will ensure that more data than this will be available for Cohort 1 subjects.

General considerations to determine cohort selection for the last 6 subjects will be:

- Safety considerations: evaluation of severity and duration of AEs and SAEs and laboratory data in cohort 1 and cohort 2 subjects and resolution of any safety issues requiring a pause in enrollment
- Efficacy considerations: primarily, evaluation of the change in CD4 and CD8 count, and level of engraftment of CCR5 modified T-cells as measured by pentamer duplication. These parameters peak 7 days after infusion. Secondarily, any viral load changes which have occurred during treatment interruptions in subjects from Cohort 1.

Sangamo will perform the analyses and assessment at the time point described above.

3.1 Dosing Schedule

Eligible subjects will be enrolled sequentially into two treatment cohorts:

- Cohort 1: Subjects will receive intravenous CTX 1.0 g/m2 on Day -2 followed by 2 infusions of SB-728mR-T on Day 0 and Week 2
- Cohort 2: Subjects will receive intravenous CTX 1.0 g/m2 on Day -2 followed by 3 infusions of SB-728mR-T on Day 0, Week 2, and Week 4

Subjects will undergo an apheresis to collect PBMC for the production of SB-728mR-T cells. The manufactured SB-728mR-T cells will be divided into 2 to 3 doses (total dose: up to ~4.0 x 10^{10} cells) depending on cohort assignment. All subjects will receive a dose of CTX 1.0 g/m2 on Day -2, and the first and second doses of SB-728mR-T on Day 0 and Week 2, respectively. The third dose of SB-728mR-T will be administered on Week 4 for Cohort 2 subjects only. Treatment of at least the first 4 subjects will be staggered so that each subsequent subject will not be treated until at least 2 weeks after the preceding subject. Subjects who are aviremic and have CD4 cell counts ≥500 cells/µL will undergo a minimum 16 weeks TI beginning 4 weeks after the last infusion of SB-728mR-T. TI may be extended beyond 16 weeks for subjects whose HIV RNA levels ≤ 10,000 copies/mL and CD4 count ≥ 500 cells/µL at the end of the 16-week TI. Subjects will be followed for 12 months following the first SB-728mR-T infusion in the Study Period and an additional 24 months in the long-term follow-up (LTFU) period.

3.2 Schedule of Procedures

A detailed schedule of events is provided in the protocol Appendix I.

3.3 Sample Size Consideration

This is a phase 1/2 study in which up to 12 subjects will be treated to evaluate safety and tolerability of repeat infusions of SB-728mR-T following CTX conditioning. In order to have an evaluable sample size, subjects who prematurely discontinue the study prior to the conclusion of the TI may be replaced with another subject.

There will be limited statistical power to evaluate safety, efficacy, and related biological endpoints. Therefore, analyses will be primarily descriptive and exploratory in nature.

4 Statistical Methods

4.1 Analysis Conventions

This section details general conventions to be used for the statistical analyses.

- Separate summary will be provided for each cohort.
- Summary statistics will consist of number and percent in each category for discreet variables, and sample size, mean, median, standard deviation and range for continuous variables.
- All listings will be sorted by cohort and subject number. Within each subject, data points will be listed chronologically.
- SAS Version 9.4 will be the statistical software for all statistical analyses, data summaries, listings, and graphs.

4.2 Missing Data

When necessary for analysis, dates without a specific day of the month (e.g., JAN2020) will be assigned the 15th day of the month and dates without a specific day or month (e.g., 2020) will be assigned the 15th day of June. If the incomplete date is a start date and the above imputation inappropriately results in a date on or before the first infusion of SB-728mR-T, the incomplete date will be assigned to the day following the first infusion of SB-728mR-T. If an imputation results in an imputed start date after the stop date, the start date will be set to the day prior to the stop date.

4.3 Analysis Populations

For the purpose of statistical analysis, the study has Safety population defined.

The Safety Population include all subjects enrolled in study who receive any portion of the SB-728mR-T.

4.4 Subject Disposition

Subject disposition will be summarized by cohort and for overall based on all enrolled subjects. The number of Enrolled Subjects, Number of Subjects Treated with at least 1 dose of SB-728mR-T, Number of Subjects Treated with 2 doses of SB-728mR-T, Number of Subjects Treated with 3 doses of SB-728mR-T, the number and percent of subjects in safety population, the number and percent of subjects who complete study, who are early terminated from study and reason for early termination will be presented.

4.5 Demographic and Baseline Information

4.5.1 Demographic and Baseline Characteristics

Patient demographic and baseline characteristics will be summarized by treatment cohorts and all cohorts combined. Age at Informed Consent, Sex, Childbearing potential (for female subjects only), ethnicity, race, height (cm), weight (kg), Time from HIV Diagnosis or Suspected Infection (month), Time from First Antiretroviral Treatment (month) and CCR5 Delta 32 (heterozygous vs wild type) will be included.

Time from HIV Diagnosis or Suspected Infection (month) will be calculated as (date of first infusion of SB-728mR-T – date of HIV Diagnosis or Suspected Infection + 1) / 30.4375. Time from First Antiretroviral Treatment (month) will be calculated as (date of first infusion of SB-728mR-T – date of First Antiretroviral Treatment + 1) / 30.4375. In case of partial date, date will be imputed following the rule defined in section 4.2.

4.5.2 Medical History

Listing for Medical history will be provided. No summary table will be provided.

4.6 Concomitant Medication and Current HIV Treatments

Concomitant medications and current HIV treatments are coded using WHODDE B2 format, March 1, 2014 release. All concomitant medications reported on the concomitant medication eCRF and all current HIV treatments collected on Current HIV Treatment and Interruption Summary eCRF will be included in listing. No summary table will be provided.

4.7 Safety Evaluation

The primary objective of this study is to evaluate the safety and tolerability of repeat doses of SB-728mR-T following CTX conditioning. Safety assessment will occur on subjects who received SB-728mR-T. Safety evaluation will be based on the Safety population.

4.7.1 Treatment Exposure

Subjects will receive 1.0 g/m2 of IV CTX 2 days prior to the first infusion of SB-728mR-T. Two days after receiving CTX, subjects will receive either two or three SB-728mR-T infusions (Cohorts 1 and 2 respectively), each dose separated by 14 days. Dose administration information collected in eCRF for both CTX and SB-728mR-T will be included in listing.

4.7.2 Adverse Events

All adverse events will be collected during the study period. In LTFU, only the adverse events which are serious, unexpected and considered to be related to treatment of SB-728mR-T will be recorded in eCRF. A treatment-emergent adverse event (TEAE) is an adverse event with an onset on or after the first infusion of SB-728mR-T infusion, or an adverse event present at first infusion of SB-728mR-T but worsens. Only treatment-emergent adverse events will be summarized. All adverse events will be included in subject listings.

All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. The incident of TEAEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT). Severity will be categorized by toxicity grade according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004, Clarification 1.0, August 2009 with the exception of the following: nausea or vomiting will be a Grade 3 non-hematological AE if IV fluids are required for more than 24 hours. AEs not listed in the DAIDS Clinical Trial Toxicity Criteria with the exception of noninfective cystitis will be evaluated by using the criteria specified in protocol section 10.3. Noninfective cystitis will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. The relationship of the AE to the

investigational drug will be determined by the principal investigator. Incidence of TEAEs will be provided for the following:

- All TEAEs
- TEAEs by Severity
- TEAEs with grade ≥ 3
- TEAEs related to Study Drug (SB-728mR-T)
- TEAEs related to CTX
- Serious TEAEs
- TEAEs with action of study drug dose interrupted
- TEAEs with action of study drug discontinued

If a subject experience the same AE more than once with different severity, the event with the maximum grade will be tabulated in "by severity" tables. If a subject has different AEs of different severity under the same SOC, the subject is only counted in the worst severity under that SOC. If a subject experiences multiple AEs under the same preferred term (system organ class), the subject will be counted only once for that preferred term (system organ class). If a subject experiences multiple occurrences of the same AE with different relationship to study medication categories, the subject will be counted once under the related category under that SOC.

The TEAE tables will be sorted in alphabetical order by SOCs and within each SOC, preferred terms are sorted in a descending order by frequency based on overall column.

All AEs will be included in listings. All deaths will be listed with cause of death from death report eCRFs. The information from eCRF about reportable clinical condition and malignancy in LTFU will be also listed in listing.

4.7.3 Clinical Laboratory Evaluations

Clinical laboratory results (chemistry, hematology, immunology (CD4 and CD8 T-cell counts) and HIV-1 RNA Viral Load), long-term persistence of SB-728mR-T in peripheral blood as measured by pentamer PCR will be evaluated throughout the study. Hepatitis B, Hepatitis C, and CCR5 SNP Cel-I assay will be collected at screening only. Serum Pregnancy will be test at screening and urine pregnancy tests will be collected at baseline and prior to SB-728mR-T infusions.

Descriptive statistics for the actual value and change from baseline value will be summarized by visit for below selected lab parameters.

- Hematology: WBC count with differential, Absolute Neutrophil Count (ANC), red blood cell (RBC) count, hematocrit, hemoglobin, platelets
- Chemistry: Alanine Aminotransferase, Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Bicarbonate, Bilirubin, Calcium, Chloride, Creatinine, Phosphate, Potassium, Protein, Sodium, Urea Nitrogen
- Immunology: CCR5 Modified CD4 Cells (in 10^9/L, calculated as (pentamer/10^6 PBMC)*4*(lymphocyte count + monocyte count)) , Pentamer Assay, CD3 (absolute count and

percentage), CD4 (absolute count and percentage), CD8 (absolute count and percentage), CD4/CD8 ratio.

- Viral Load: HIV-1 RNA

Baseline will use the value collected at baseline visit (one week prior to CTX administration per protocol), if that value is missing, the last value prior to date of CTX dosing will be used. If in the same visit, the lab test result is collected in both central lab and local lab, the central lab result will be used for summary.

A line plot by cohort will be generated to show the change of median CD4 (based on absolute count), CD8 (based on absolute count), CCR5 modified CD4 T Cells and HIV-1 RNA values over visits. For each subject, a line plot will be generated to show the HIV-1 RNA level change over time. For HIV-1 RNA level, y axis will be in log-scale.

Laboratory values will be converted to a set of standard units prior to analysis. If the result contains "<", the result will be imputed to half of the boundary value (e.g. if the original result is "<20", it will be imputed to 10 in analysis). For HIV-1 RNA, the original unit is "copies/mL", it will be converted to "log copies/mL" when summary the statistics. If no HIV-1 RNA is detected, it will be summarized as 0.

All laboratory parameters will be included in subject listings, with abnormal values flagged.

4.7.4 Vital Signs, Physical Examination and Electrocardiogram data

Vital Signs (excluding height and weight at the Baseline visit), Physical Exam and Electrocardiogram data will be collected at the site in the source documentation only. No table and listing will be generated.

5 Alterations to the Clinical Study Protocol

The following change is made from statistical section of protocol:

- Analysis population is changed from "Intent-to-treat" to Safety population, as the definition is based on number of subjects who received any infusion.

6 Appendix

Appendix 1: Tables, Listings, and Figures Specifications

Table, listing, and figure shells to support the clinical study report will be specified in an additional document.