Sangamo Therapeutics, Inc.

Statistical Analysis Plan
Version Final, 23 Nov 2020

Protocol Number: SB-728-1101

A Phase 1, Open-label Study to Assess the Effect of Escalating Doses of Cyclophosphamide on the Engraftment of SB-728-T in Aviremic HIV-Infected Subjects on HAART

Statistical Analysis Plan Approvals

For protocol: SB-728-1101

Prepared by:

_____ DATE: _____
YINPU CHEN

VP, BIOSTATISTICS, Q2

Reviewed and Approved by:

_____ DATE: _____
MICHAEL CHEN

SENIOR DIRECTOR, BIOMETRICS, SANGAMO

_____ DATE: _____
BERNARD SOUBERBIELLE

VP, TRANSLATIONAL MEDICINE, SANGAMO

_____ DATE: _____
MAOZHEN TIAN

SENIOR MANAGER, STATISTICAL PROGRAMMING, SANGAMO

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List of Abbreviations

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
CCR5	Chemokine (C-C motif) Receptor 5
CD3	Cluster of Differentiation 3
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CRF	Case Report Form
CSR	Clinical Study Report
CTX	Cyclophosphamide
eCRF	Electronic Case Report Form
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SB-728-T	SB-728 T-cells
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
WBC	White Blood Cell Count
WHODDE	WHO Drug Dictionary

1 Introduction

This document describes the planned statistical analyses for Protocol SB-728-1101, A phase 1, Open-Label Study to Assess the Effect of Escalating Doses of Cyclophosphamide on the Engraftment of SB-728-T in Aviremic HIV-Infected Subjects on HAART. This document supplements the study protocol Amendment 9 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 escalating doses of cyclophosphamide administered up to 3 days prior to SB-728T infusion.

2.2 Secondary Objectives

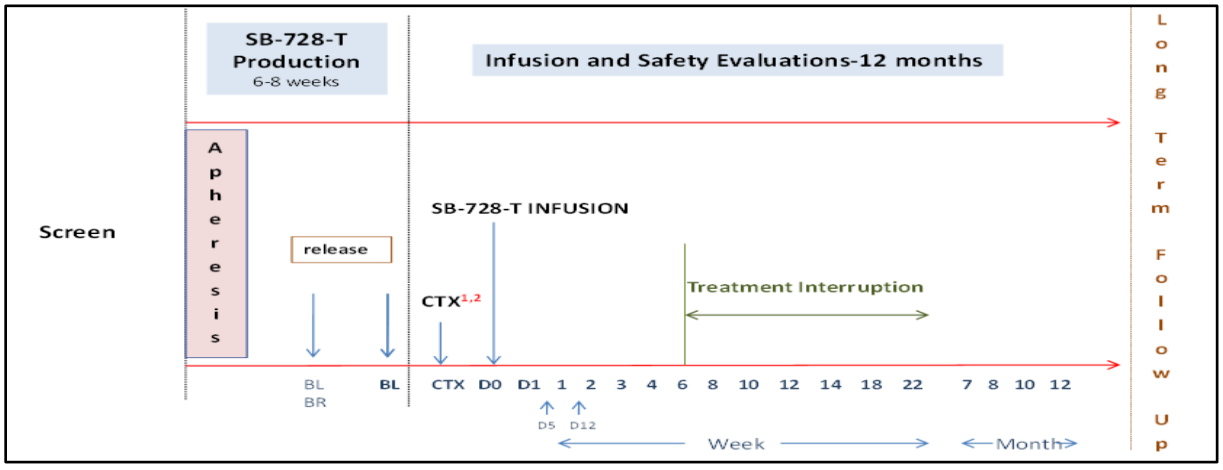
The secondary objectives of this study are to evaluate:

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

3 Study Design

This is a Phase 1, open-label, dose-escalation, multi-center study. Subjects who satisfy all inclusion/exclusion criteria are eligible to participate in this study. Up to 40 aviremic HIV-infected subjects on stable HAAT will be enrolled and treated in 5 dose cohorts (3 – 6 subjects/cohorts).

The study will be approximately 15 months for each subject divided into approximately 3 months for screening, leukapheresis, and SB-728-T production, followed by 12 months for treatment and study follow-up.



3.1 Dosing Schedule

Eligible subjects will be enrolled sequentially into 5 dose cohorts.

- Cohort 1: Intravenous cyclophosphamide 200 mg
- Cohort 2: Intravenous cyclophosphamide 0.5g/m2
- Cohort 3: Intravenous cyclophosphamide 1.0 g/m2
- Cohort 4: Intravenous cyclophosphamide 2.0 g/m2
- Cohort 5: Intravenous cyclophosphamide 1.5 g/m2

Within each cohort, treatment will be staggered so that each subsequent subject cannot be infused with cyclophosphamide until at least 2 weeks after the preceding subject. Up to 3 days after receiving cyclophosphamide, subjects will be infused with 0.5 to 4.0 x 10^{10} SB-728-T cells. Subjects who are aviremic and have CD4 cell counts ≥500 cells/µL will undergo a minimum 16 week TI beginning 6 weeks after infusion of SB-728-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 after the infusion.

The decision to dose escalate to the next cohort will be made by a Safety Monitoring Committee (SMC). Safety data through Week 4 from all subjects within a cohort will be reviewed by the SMC. If one subject within a cohort develops a dose limiting toxicity (DLT) defined as a Grade 3 non-hematological AE excluding alopecia or Grade 4 hematological AE (all deemed related to cyclophosphamide), 3 additional subjects will be enrolled and treated in that cohort. Dose escalation to the next cohort may proceed if there is no more than one DLT in a cohort of 6 subjects.

If no DLT develops in 3 subjects in Cohort 5 (1.5 g/m^2), additional subjects may be enrolled into that cohort. And upon evaluation of data from Cohort 5 (1.5 g/m^2), the sponsor may elect to enroll additional subjects into Cohort 3 (1.0 g/m^2).

Subjects will complete all screening procedures then undergo a 10 L leukapheresis to collect peripheral blood mononuclear cells for the manufacturing of SB-728-T (approximately 2 months). Subjects will then receive IV cyclophosphamide up to 3 days prior to the infusion of SB-728-T on Day 0 for optimal engraftment. Subjects in Cohorts 4 and 5 will have additional testing on Day 5 and Day 12. Subjects will be seen weekly on Weeks 1 through 4. Subjects will then begin a minimum 16-week TI beginning on Week 6. Subjects will be evaluated at weeks 8, 10, 12, 14, 18 and 22 during the TI. After completion of the 16-week TI or during TI extension, subjects will be seen at Month 7, Month 8, Month 10, and Month 12.

Upon the sponsor's request, additional blood collection and /or an optional leukapheresis may be performed during the study.

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 study in which three to six evaluable subjects in each cohort will be treated to evaluate safety of each cyclophosphamide dose level. A cohort can be expanded if there is no DLT in 3 subjects

treated or no more than 1 DTL in 6 subjects treated in that cohort. In order to have an evaluable sample size, subjects who prematurely discontinue the study prior to the conclusion of the TI will be replaced with another subject. Safety will be evaluated after each cohort before treating the next dose cohort. The table below provides the probability of failing to observe an AE in a sample size of three or six evaluable subjects, for various underlying true AE rates. Thus, only AEs that occur at least 60% of the time are likely to be detected in a cohort of three subjects.

	Probability of Failing to Observe an Adverse Event	
True Adverse Event Rate	N=3	N=6
5%	86%	74%
10%	73%	53%
20%	51%	26%
30%	34%	12%
40%	22%	5%
50%	13%	2%
60%	6%	<1%
70%	3%	<1%

The table below shows the exact 95% confidence intervals for possible number of observed safety outcomes in three or six subjects. For example, if no AEs are observed in a group of six evaluable subjects, we can be 95% confident that the true AE rate is less than 46%.

	Exact 95% Confidence Interval	
# Observed Adverse Events	N=3	N=6
0	(0.0%, 70.1%)	(0.0%, 45.9%)
1	(8.4%, 90.6%)	(0.4%, 64.1%)
2	(9.4%, 99.2%)	(4.3%, 77.7%)
3	(29.2%, 100.0%)	(11.8%, 88.2%)
4	–	(22.3%, 95.7%)
5	–	(35.9%, 99.6%)
6	–	(54.1%, 100.0%)

4 Statistical Methods

4.1 Analysis Conventions

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

- Tables and listings will summarize all safety, laboratory, and outcome measures by cohort.
- Summary statistics will consist of count and percentages per category for discrete variables, and means, medians, standard deviations and ranges for continuous variables.
- Summary tabulations will occur within each cohort and among all cohorts combined.
- All tables, listings, and data summaries will be performed in SAS version 9.4.

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-728-T, the incomplete date will be assigned to the day following the first infusion of SB-728-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

Safety Population will be defined for this study. The Safety Population include all subjects enrolled in study who receive any portion of the SB-728-T infusion. Subjects will be analyzed according to the treatment they actually received.

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 the subjects treated with SB-728-T infusion. Number and percent of subjects in Safety population, number and percent of subjects who complete the study, number and percent of subjects who early terminated from study and reason for early termination will be presented.

Listings for disposition and subject eligibility data will be also provided.

4.5 Demographic and Baseline Information

4.5.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment cohorts and all cohorts combined. Age at informed Consent, Sex, Childbearing potential, Ethnicity, Race, Height (cm), Weight (kg), Time from HIV Diagnosis (month), CCR5 Delta 32 will be included. Calculations for derived data are as follow:

- Age at Informed Consent (Years) will be calculated as the number of years between year of birth and year of informed consent date.
- Time from HIV Diagnosis (month) will be calculated as (date of infusion of SB-728-T – date of HIV Diagnosis + 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, Procedures, HIV Treatment and Leukapheresis

Concomitant medications and HIV treatments are coded using WHODDE format, March 1st, 2012 version. All information collected in concomitant medications eCRF, Current HIV treatment eCRF, Procedure

eCRF, Structure Treatment Interruption Start eCRF, Structure Treatment Interruption Stop eCRF, Leukapheresis eCRF will be included in listing. No summary table will be provided.

4.7 Safety Evaluation

Safety assessment will occur on subjects received SB-728-T. Safety evaluation will be based on safety population.

4.7.1 Treatment Exposure

Subjects will receive intravenous cyclophosphamide followed by $0.5 - 4.0 \times 10^{10}$ SB-728-T cells. Data for Cyclophosphamide and SB-728-T cells administration will be included in listing.

4.7.2 Adverse Events

All adverse events will be collected during both the treatment and follow-up periods. A treatment-emergent adverse event (TEAE) is an adverse event with an onset on or after the infusion of SB-728-T, or an adverse event present at the infusion of SB-728-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 15.0. The incident of TEAEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT). The relationship of the AE to the investigational drug will be determined by the principal investigator. 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. Adverse events not listed in the DAIDS Clinical Trial Toxicity Criteria will be evaluated by using the following criteria, Noninfective cystitis will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03:

- 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.

Incidence of TEAEs will be provided for the following:

- All TEAEs
- TEAEs by Severity
- TEAEs with grade $\geqslant$ 3
- TEAEs related to Study Drug
- TEAEs related to Cyclophosphamide
- 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 experience the same AE multiple times, the subject will be counted only once in the specific preferred term (system organ class). If 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. If a subject has different AEs of different relationship to study medication under the same SOC, the subject is only counted in the related category under that SOC.

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

All AEs will be included in listings. All deaths will be listed with cause of death from death report eCRF.

4.7.3 Clinical Laboratory Evaluations

For all cohorts, clinical laboratory results (chemistry, hematology, Immunology (CD3+/CD4+/CD8+ T-cells percent and absolute), and Viral Load), long-term persistence of SB-728-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 test will be collected at Screen and urine pregnancy test will be at Baseline.

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, red blood cell (RBC) count, hematocrit, hemoglobin, Platelet Count.
- Chemistry: ALT, 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, if that value is missing, the last value prior to date of infusion will be used.

Line plots 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 Viral Load values over visits. For each subject, a line plot will be generated to show the Viral Load level change over time. HIV-1 RNA viral load level will be plotted in log-scale (base 10).

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 Viral Load, the original unit is “copies/mL”, it will be converted to “log copies/mL” when summarize the statistics. If no Viral Load is detected, it will be summarized as 0.

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

4.7.4 Physical Examination and Electrocardiogram data

Electrocardiogram data reported on Electrocardiogram eCRF will also be included in listings. Physical Examination results will be collected on Physical Exam eCRF and included in listings.

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.

Statistical Analysis Plan Approvals

For protocol: SB-728-1101

Prepared by:

DATE: 16 Dec. 2020

YINPU CHEN

VP, BIOSTATISTICS, Q2

Reviewed and Approved by:

DocuSigned by:

12/17/2020 | 15:37 PST

Signer Name: Michael Chen
Signing Reason: I approve this document
Signing Time: 12/17/2020 | 15:37 PST
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DATE: _____

MICHAEL CHEN

SENIOR DIRECTOR, BIOMETRICS, SANGAMO

DocuSigned by:

12/21/2020 | 11:54 PST

Signer Name: Bernard Souberbielle
Signing Reason: I approve this document
Signing Time: 12/21/2020 | 11:54 PST
F303C044A8CD4EC2A31137EEA405E5EA

DATE: _____

BERNARD SOUBERBIELLE

VP, TRANSLATIONAL MEDICINE, SANGAMO

DocuSigned by:

12/17/2020 | 06:57 PST

Signer Name: Maozhen Tian
Signing Reason: I approve this document
Signing Time: 12/17/2020 | 06:57 PST
0A4B0B22EC0424098D7CE80AC1A7B40...

DATE: _____

MAOZHEN TIAN

SENIOR MANAGER, STATISTICAL PROGRAMMING, SANGAMO