# Clinical Study Protocol

## 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

**Protocol Number:** SB-728mR-1401

**BB-IND:** 16082

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**Confidentiality Statement**

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# Sangamo BioSciences, Inc.

## Clinical Approval Signature Page

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**Protocol Title:** **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**

**Amendment 2:** **October 10, 2014**

_____ _____
Winson Tang, M.D Date
Vice President, Clinical Research

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Dale Ando, M.D. Date
Vice President Therapeutic Development and CMO

| Protocol SB-728mR-1401 Synopsis | |
|---|---|
| **Title** | 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 (CTX) Conditioning |
| **Sponsor** | Sangamo BioSciences, Inc. |
| **Investigational Products** | SB-728mR-T (autologous T-cells modified at the CCR5 gene by ZFNs via messenger ribonucleic acid (mRNA) electroporation) |
| **Objectives** | **Primary:**<br>To evaluate the safety and tolerability of repeat doses of SB-728mR-T following CTX conditioning.<br>**Secondary:**<br>1. Evaluate the effect of repeat doses of SB-728mR-T on engraftment following CTX conditioning<br>2. Evaluate long-term persistence of SB-728mR-T in peripheral blood as measured by pentamer PCR<br>3. Evaluate change in CD4+ T-cell counts in peripheral blood after repeat treatments with SB-728mR-T<br>4. Evaluate the effect of SB-728mR-T on plasma HIV-1 RNA levels following HAART interruption<br>5. Evaluate the change in HIV reservoirs as part of exploratory research |
| **Study Population** | Up to 12 aviremic HIV-infected subjects on HAART may be enrolled and treated in two dose cohorts. |
| **Main Inclusion Criteria** | 1. HIV diagnosed men and women ≥ 18 years of age on HAART with undetectable viral loads for the preceding 2 months and peripheral blood CD4+ T-cell counts ≥500 cells/μL at screening.<br>2. Aviremic subjects who initiated antiretroviral therapy within (≤) 1 year of HIV diagnosis or suspected infection<br>3. Aviremic subjects on HAART with low innate immune system activation as determined by percentage of activated CD14+/CD16+ monocytes ≤ 60%. |
| **Study Design** | Phase 1/2, open-label, multi-center study. |
| **Treatment Plan** | Up to 12 subjects will be enrolled and treated in two dose cohorts:<br>Cohort 1: Subjects will receive intravenous CTX 1.0 g/m$^2$ on Day -2 followed by 2 infusions of SB-728mR-T on Day 0 and Week 2<br>Cohort 2: Subjects will receive intravenous CTX 1.0 g/m$^2$ on Day -2 followed by 3 infusions of SB-728mR-T on Day 0, Week 2, and Week 4<br>Enrollment of Cohort 1 and Cohort 2 will be sequential. 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. |

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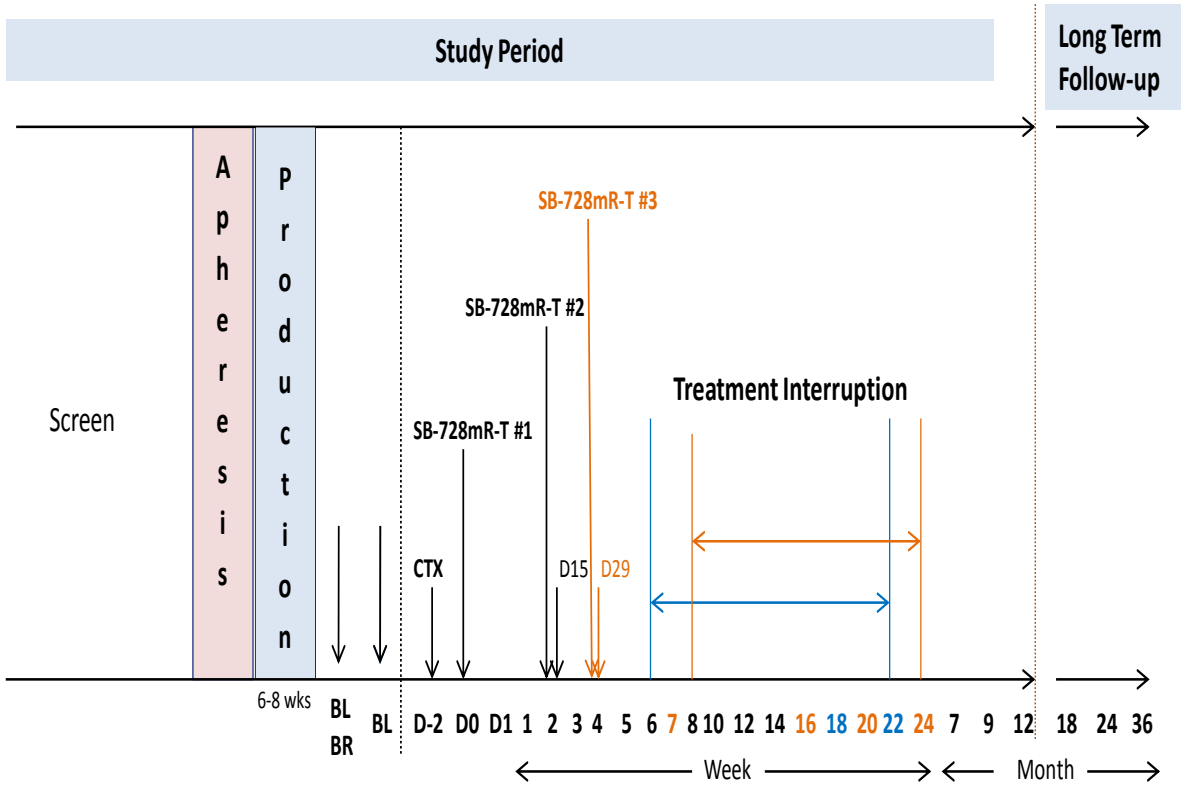
| | Treatment of at least the first 4 subjects will be staggered so that each subsequent subject will not be treated until at least 2 weeks after the preceding subject.<br>Enrolled subjects will undergo a 10L leukapheresis to collect peripheral blood mononuclear cells for the manufacturing of SB-728mR-T. The final product will be split into 2 or 3 doses and frozen until infusion.<br>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. CTX will not be administered to a subject until the subject's SB-728mR-T product lot is released and the number of cells manufactured meets the minimum dose requirement.<br>Subjects with aviremia and CD4 cell counts ≥500 cells/μL will have their anti-retroviral treatment stopped 4 weeks after the last dose of SB-728mR-T. HAART will be discontinued for a period of at least 16 weeks.<br>During the 16-week treatment interruption (TI), HAART will be reinstituted in subjects whose CD4 cell counts drop to <500 cells/μL and/or whose HIV-RNA increases to >100,000 copies/mL on three consecutive measurements tested every 2 weeks.<br>At the end of the 16-week treatment interruption:<br>• HAART will be reinstituted in subjects with HIV RNA levels >10,000 copies/mL and/or CD4 <500 cells/μL.<br>• Subjects with HIV RNA levels ≤10,000 copies/mL and CD4 count ≥ 500 cells/μL may elect to remain off HAART and undergo extended TI (subjects with HIV RNA levels below limit of detection will remain off HAART).<br>During extended TI, HIV-1 RNA and CD4 counts will be measured monthly. HAART will be reinstituted in subjects when one or both of the following criteria are met:<br>• HIV RNA levels > 10,000 copies/mL, confirmed by two additional consecutive monthly measurements<br>• CD4 count < 500 cells/μL, confirmed by an additional consecutive monthly measurement |
| **Study Duration** | The duration of study participation will be approximately 40 months.<br>Study Period: Approximately 16 months, including 4 months for screening, leukapheresis, and SB-728mR-T production, and 12 months follow-up following the first SB-728mR-T treatment.<br>Long-term Follow-up (LTFU) Period: An additional 24 months following the Study Period for long-term safety. |
| **Sample Size and Analyses** | This is a phase 1/2 study in which up to twelve evaluable subjects in two cohorts will be treated to evaluate safety and tolerability of repeat infusions of SB-728mR-T following CTX conditioning.<br>There will be limited statistical power to evaluate safety, efficacy, and related biological endpoints. Therefore, analyses will be primarily descriptive and exploratory in nature. |

**TABLE OF CONTENTS**

# Schema of the Study Visits




**Black** font indicates both Cohort 1 and Cohort 2
**Blue** font indicates Cohort 1: IV CTX 1.0 g/m$^2$ followed by two SB-728mR-T infusions 14 days apart
**Orange** font indicates Cohort 2: IV CTX 1.0 g/m$^2$ followed by three SB-728mR-T infusions 14 days apart

**ABBREVIATIONS**

| | |
|---|---|
| AE | adverse event/experience |
| AIDS | acquired immunodeficiency syndrome |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase (SGPT) |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase (SGOT) |
| CBC | complete blood count |
| CCR2 | chemokine (C-C motif) receptor 2 |
| CCR5 | chemokine (C-C motif) receptor 5 |
| CD4 | cluster of differentiation 4 |
| C of A | Certificate of Analysis |
| CRF | case report form |
| CTX | cyclophosphamide |
| CXCR4 | chemokine (C-X-C motif) receptor 4 |
| DMSO | dimethyl sulfoxide |
| DNA | deoxyribonucleic acid |
| FDA | Food and Drug Administration |
| HAART | highly active antiretroviral therapy |
| HBsAg | hepatitis B surface antigen |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| IFN | interferon |
| IV | intravenous |
| IRB | institutional review board |
| mRNA | messenger ribonucleic acid |
| LTFU | long-term follow-up |
| NNRTI | non-nucleoside reverse transcriptase inhibitors |
| NRTI | nucleoside reverse transcriptase inhibitors |
| NIH | National Institutes of Health |
| PBMC | peripheral blood mononuclear cell |
| PCR | polymerase chain reaction |
| PI | Principal Investigator |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SB-728-T | SB-728 modified T-cells |
| SB-728mR-T | SB-728mR modified T-cells |
| TI | Treatment Interruption |
| VL | viral load |
| ZFN | zinc finger nucleases |

# 1. INTRODUCTION

The advent of potent anti-retroviral agents has changed HIV infection from a nearly universal fatal disease to a chronic viral infection. However, in response to selection pressures associated with the use of antiretrovirals, the virus is developing resistance to many of these drugs. Thus, there is a need for new therapeutic approaches that can eradicate HIV such as T-cell immunotherapy. The objectives of T cell immunotherapy are to augment HIV-specific T-cells and to reverse or decrease the progressive destruction of CD4+ T-cells that leads to clinical AIDS. However, these CD4+ T-cells remain susceptible to infection with HIV. Sangamo BioSciences, Inc. (Sangamo) has developed a process to modify autologous T-cells *ex vivo* at the CCR5 gene by zinc finger nucleases (ZFNs). Since CCR5 is an important co-receptor for HIV entry, it is hypothesized that disruption of CCR5 in T-cells with zinc finger nucleases will offer a survival advantage to these cells.

The **first generation** of Sangamo's autologous T cell agent, called **SB-728-T,** used a replication deficient recombinant Ad5/F35 adenoviral vector ancillary product to deliver the CCR5 modifying ZFNs to autologous T cells. SB-728-T has been evaluated in four separate clinical studies to date, three of which were conducted under Sangamo's BB-IND 14129.

The **new** investigational product **SB-728mR-T** is a second generation refinement of SB-728-T, a CCR5 gene modified autologous T cell product. The rationale for developing this second generation product is multifaceted. The availability of an improved gene delivery system of mRNA electroporation that can effectively modify the CCR5 gene with high efficiency, with no need for adenoviral gene transfer and thus avoiding the potential for associated immunogenicity, is of key importance. The prevalence of preexisting antibodies to adenovirus has been reported to be more than 50%. Indeed, the prevalence of adenoviral antibodies detected in the conduct of the SB-728-T program in the HIV subjects has been 40%. In addition, expression of the ZFNs encoded by the mRNA is transient, and there is minimal toxicity to the T cells during manufacturing.

SB-728mR-T consists of enriched autologous T-cells that have been transduced *ex vivo* with SB-728mR-T resulting in disruption of the CCR5 gene. SB-728mR is an mRNA encoding the CCR5 specific ZFNs (SBS8196z and SBS8267) which through electroporation delivers these nucleases to transduced cells. The two ZFNs of the SB-728mR bind to a specific DNA sequences encoding the first transmembrane domain of the CCR5 gene, just upstream from the naturally occurring CCR5 delta 32 mutation. Binding of the CCR5-specific ZFNs to CCR5 gene induces a double stranded break which is repaired by the cell leading to random sequence insertions or deletions in up to 30% of cells transduced with SB-728mR. These insertions and deletions disrupt CCR5 protein expression.

Additional information can be found in the Clinical Investigator's Brochure for SB-728mR-T.

## 1.1 Clinical Experience with SB-728mR-T

This is the first study in which SB-728mR-T will be administered to humans. Side effects for SB-728mR-T in man are unknown but are expected to be the same or similar to the first generation autologous T cell agent, SB-728-T.

## 1.2 Clinical Experience with the First Generation SB-728-T

Single doses of SB-728-T have been administered to 70 HIV subjects in four Phase 1/2 clinical studies, one of which was sponsored by UPenn and the remaining three by Sangamo. In general, the infusions of SB-728-T have been safe and well tolerated with the most common AEs being

complaints consistent with a leukocyte transfusion reaction such as fever, chills, headaches, myalgia, and arthralgia. These symptoms were mild to moderate in severity, short lived, reversible, and readily managed with fluids and acetaminophen. Garlic-like body odor was reported in the majority of subjects and is related to the metabolism of DMSO used as a cryopreservative for the T-cells. There has been only one related SAE reported to date and that occurred in the University of Pennsylvania study (Tebas et al. 2014). The subject developed fever, chills, joint and back pain within 12 hours of infusion.

The cumulative experience with SB-728-T administered to 70 HIV subjects over 4 years suggests that infusion of SB-728-T was associated with increases in total lymphocyte and CD4 count. Circulating CCR5 modified cells peaks around 2 weeks post T-cell infusion, and declined thereafter with an estimated mean half-life of 48 weeks. The CCR5 modified cells traffic to the lymphoid tissues of the rectal mucosa. The CCR5 modified cells are long lived and persist in the circulation, the longest time period tested to date being 42 months. A total of 35 subjects across 4 studies initiated an Analytical Treatment Interruption (TI). Of these, 24 subjects completed either the 12- or 16-week TI. Eight subjects are still currently undergoing the 16-week TI. Nine of the 24 subjects (38%) have >1-log drop in HIV-RNA from peak levels. Three subjects have had at least one VL that was below the level of detection. One subject has had viral control without HAART with HIV-RNA levels below the limit of detection (occasional blips) for a period of 31 weeks.

### 1.3 Cyclophosphamide to Enhance SB-728mR-T Engraftment

CTX is a nitrogen mustard alkylating agent that attaches an alkyl group to the guanine base of DNA. It has beneficial immunomodulatory effects that may be exploited for adaptive immunotherapy. Several mechanisms have been suggested including; 1) T-cell growth factors such as type 1 IFN, 2) dendritic cell expansion and activation with antigen driven T cell proliferation, 3) improved homing to lymphoid organs, 4) homeostatic proliferation and 5) elimination of regulatory T-cells.

Lymphodepletive treatment to enhance engraftment of adoptively transferred T-cells has been pioneered in the treatment of cancer. The T cell populations used in these studies consisted of antigen specific or chimeric T cell receptor-transduced autologous cells. Recently, clinical success was reported with the use of CTX lymphodepletion prior to the adoptive transfer of tumor infiltrating lymphocytes and chimeric antigen receptor CD19 (CART19) transduced autologous T-cells (Dudley et al., 2005; Dudley and Rosenberg, 2003; Porter et al., 2011). The data suggest that nonmyeloablative lymphodepletion prior to adoptive transfer of T-cells results in greatly enhanced *in vivo* expansion. Furthermore, the expanded cells retain their immunologic function.

In an ongoing Sangamo sponsored clinical trial (SB-728-1101), escalating doses of CTX were administered to 18 HIV subjects in five dose cohorts: 0.2 g (n=3), 0.5 g/m$^2$ (n=6), 1.0 g/m$^2$ (n=3), 2.0 g/m$^2$ (n=3), and 1.5 g/m$^2$ (n=3) prior to SB-728-T infusion. Data in the first 4 cohorts to date suggests that SB-728-T infusions were safe and well tolerated. However, increasing doses of CTX were associated with a number of toxicities. These included nausea and vomiting, alopecia, and neutropenia. In addition, the severity of the AEs increased with more Grade 3 and 4 AEs in Cohort 4 (2 g/m$^2$) with all of the AEs attributed to CTX. There were five Grade 3 (severe) AEs [neutropenia (2), alopecia (2) and nausea (1)] and one Grade 4 AE (neutropenia) in Cohort 4. By comparison, there were only two Grade 3 AEs (MRSA cellulitis/abscess of left arm

and superficial left cephalic vein thrombosis) in Cohort 1 and one Grade 3 AE (decrease serum phosphorus) in Cohort 2 and all of them were unrelated to CTX or SB-728-T. One subject in Cohort 4 developed two dose limiting toxicities, Grade 3 nausea and Grade 4 neutropenia.

Subjects in Cohorts 1-5 received between 0.8 to 3.6 $x10^{10}$ of SB-728-T cells. There were dose related increases in total CD4 and CCR5-modified CD4 T cells with increasing doses of CTX between 200 mg and 1 $g/m^2$. However, dose escalation to 1.5 and 2.0 $g/m^2$ of CTX resulted in declines in total CD4 and CCR5-modified CD4 T cells to levels that were similar to that seen with 0.5 $g/m^2$ dose cohort. Sixteen of the 18 subjects underwent a 16-week TI beginning 6 weeks after SB-728-T administration. There was an approximate 1-log decrease in HIV-RNA in one subject in the 0.2 g and 0.5 $g/m^2$ dose cohorts and an approximate 3-log decrease in one subject in the 1.0 $g/m^2$ dose cohort. The TIs are still ongoing for two subjects each in Cohorts 3 (1.0 $g/m^2$) and 4 (2.0 $g/m^2$) and for all 3 subjects in Cohort 5 (1.5 $g/m^2$).

Due to the enhanced engraftment and safety profile in the 1.0 $g/m^2$ CTX group as compared to the other four cohorts, a CTX dose of 1.0 $g/m^2$ has been selected for this study.

Additional information on the safety of CTX is discussed in **Section 9.2**.

### 1.4 HAART Treatment Interruption

HAART TI was initially advocated to enhance antiviral immune response in acute HIV infection (Paton, 2008) and in the setting of virologic failure and multidrug resistance (Lawrence et al., 2003). However, studies conducted to date have failed to demonstrate a clinical benefit in either setting. In subjects with successfully treated chronic HIV infection, TI is associated with inferior clinical outcomes (Oxenius et al, 2002). However, TI has been successfully deployed as an analytical method to assess the effectiveness of different immunologic/immune-modulatory interventions, especially during vaccine trials. The kinetics of viral rebound are well characterized, typically occurring within 2 to 4 weeks following discontinuation of drug, and viral replication is routinely re-suppressed with resumption of therapy. Data from UPenn study suggests that TI can be safely performed in the currently proposed study (**Section 9.3**).

A variety of *in-vitro* studies may be used to assess HIV-1 specific immune responses following the infusion of CCR5 disrupted CD4 cells. However, the correlation of *in vitro* testing to immune protection *in vivo* is largely unknown (van Lunzen et al, 2007). By comparison, plasma HIV RNA level is an excellent biomarker for assessing the antiviral activity of a test agent in patients with chronic HIV infection. Therefore, sustained suppression of plasma HIV-1 RNA after the discontinuation of HAART and or the protection of CD4 cell loss associated with ongoing viral replication would be the most stringent test of an immunologic intervention such as SB-728mR-T.

In the current study, only subjects with aviremia and CD4 cell counts ≥500 cells/μL at the initiation of the TI will have their HAART interrupted. In addition, subjects will be monitored closely during the TI period. A set of criteria to reinstitute HAART based on CD4 count and VL data during TI, at the end of the TI, and during extended TI is described in **Section 8.3**.

Subjects may have HAART reinstituted at any time at the discretion of the subject and/or PI.

### 1.5 Rationale for Proposed SB-728mR-T Dose Schedule

We postulate that the anti-viral effect of SB-728-T may depend upon the number of bi-allelic modified T-cells in which both CCR5 alleles have been disrupted. There was a strong correlation

between declines in VL with the estimated number of bi-allelic modified cells during the treatment interruption. This suggests that strategies to increase the engraftment of modified cells may be beneficial. One potential strategy to increase T-cell engraftment is through repeated administration of SB-728mR-T. Studies in a murine tumor model by Kircher et al. suggest that a fractionated administration schedule improves bio-distribution of CD8 T cells. Unfortunately, the experimental design (magnetic resonance imaging) did not allow for quantization of engraftment in that study. Clinical studies to date have been inconclusive (Kircher 2003). Repeat infusion (at least 6 weeks after the first dose) of T cells expressing a CD19 chimeric antigen receptor coupled to both the CD28 and ζ-endodomains increased engraftment after the second dose in one subject but not in two other subjects (Savoldo 2011). In a study with CD8 T cells transduced with a chimeric receptor gene (CD4/CD3-ζ), Walker et al. showed that six infusions (each infusion separated by 56 days) did not increase engraftment (Walker 2000). However, when CD4/CD3-ζ modified CD4 and CD8 T cells were administered simultaneously (3 infusions, each separated by 14 days), engraftment increased slightly. However, the increased survival of the modified cells may be due to HIV-specific CD4 T cell help. Therefore, the optimal schedule of dosing (fractionated schedule versus single dose) remains to be determined. The current change in manufacturing from an adenoviral vector to mRNA electroporation will allow for repeat dosing of SB-728mR-T. The expectation is that with repeat dosing, we will increase engraftment, potentially to levels that will control HIV.

### 1.6 Risk Benefit Analysis

SB-728-T infusions in the four studies conducted to date have been well tolerated with chills/rigors, nausea and low grade fevers the most common AEs. The highest dose that has been administered to an individual subject was $3.6 \times 10^{10}$ cells. Similarly, CTX has been safely administered to HIV patients in study SB-728-1101. Data from this dose escalation study suggest that a non-myeloablative dose 1.0 g/m$^2$ provides for maximal engraftment with the least toxicity. The AEs at this dose were readily managed by routine medical interventions such as antiemetics and adequate hydration. Collectively, these data suggest that the potential benefit of expanding HIV-1 resistant CCR5 modified T-cells may be greater than the potential adverse effects of low dose CTX.

### 1.7 Study Hypothesis

The objectives of T-cell immunotherapy in people infected with HIV are to augment HIV-specific T-cells and to reverse or decrease the progressive destruction of T-cells that leads to clinical AIDS. SB-728-T has been safely administered to over 70 HIV-infected subjects in four clinical trials conducted to date. The level of engraftment has varied from negligible to ~10% of the T-cells in the vascular compartment. Preliminary analyses of VL during TI in these studies suggest that an anti-HIV effect may correlate with the level of SB-728-T engraftment. Concurrently, non-myeloablative lymphodepletion with CTX has been demonstrated to enhance engraftment of adoptively transferred T-cells through a variety of mechanisms. The current study is being undertaken to increase SB-728mR-T engraftment through the administration of repeat doses of SB-728mR-T following CTX conditioning.

## 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:

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

# 3. STUDY DESIGN

## 3.1 Overview

This is a Phase 1/2, open-label, multi-center study. Subjects who satisfy all inclusion/exclusion criteria (**Section 4**) 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.

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/$m^2$ 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 week 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.
Additional research blood collection and/or an optional leukapheresis may be performed during the study upon sponsor request.

### 3.2 Number of Subjects
Up to 12 aviremic HIV-infected subjects on HAART will be enrolled and treated in 2 dose cohorts.

### 3.3 Study Duration
The duration of study participation will be approximately 40 months, including 16 months for the Study Period (approximately 4 months for screening, leukapheresis, and SB-728mR-T production, and 12 months following the first SB-728mR-T infusion) and an additional 24 months of LTFU.

### 3.4 Visit Schedule
Subjects will complete all screening procedures and enrolled subjects will undergo a 10 L leukapheresis to collect peripheral blood mononuclear cells for the manufacturing of SB-728mR-T (approximately 2 months). Subjects will then receive 1.0 g/m$^2$ of IV CTX 2 days prior to the first infusion of SB-728mR-T. The first SB-728mR-T infusion will occur on Day 0. Subsequent SB-728mR-T infusions will be given 14 days apart. Subjects will be seen one day after each SB-728mR-T infusion and weekly on Weeks 1 through 6 (Cohort 1) and Week 8 (Cohort 2). Subjects will then begin a minimum 16-week TI beginning 4 weeks after the last SB-728mR-T infusion (Week 6 for Cohort 1 and Week 8 for Cohort 2). During the TI, subjects will be evaluated every 2 weeks for the first 8 weeks and monthly for the following 8 weeks. After completion of the 16-week TI (**Section 9.3**), subjects may extend the TI if they meet the protocol-specified requirements for TI extension. During extended TI, HIV-1 RNA and CD4 counts will be tested monthly. All subjects will be seen at Month 7, Month 9, Month 12, Month 18, Month 24, and Month 36.

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

### 3.5 Study Procedures
Subjects will have periodic blood tests to assess safety labs, plasma HIV-1 RNA levels and CD4+ T-cell counts; physical exams; AE assessment; and review of medications (**Appendix I**).

## 4. SUBJECT SELECTION
### 4.1 Inclusion Criteria
1. Written informed consent signed and dated by study subject.
2. Male or female, 18 years of age or older.
3. Documented HIV diagnosis.
4. Adequate venous access and no other contraindications for leukapheresis.
5. Absolute neutrophil count (ANC) ≥ 2500/mm$^3$.
6. Hemoglobin level ≥ 13 g/dL (males); ≥ 12 g/dL (females).
7. Platelet count ≥ 200,000/mm$^3$.

8. Serum creatinine ≤ 1.5 mg/dL.
9. AST and ALT ≤ 2.5 times the upper limit of normal.
10. Must be willing to comply with study-mandated evaluations; including only changing antiretroviral regimen when indicated by the study doctor during the study period.
11. Female of childbearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test at the baseline visit prior to infusion.

    *A female subject is considered to be of childbearing potential if she is postmenarcheal, has an intact uterus and at least 1 ovary, and is less than 2 years postmenopausal.*
12. Have no polymorphisms in the CCR5 ZFN target region as determined by Cel 1 SNP assay.
13. Aviremic subjects who initiated antiretroviral therapy within (≤) 1 year of HIV diagnosis or suspected infection. The general classes of antiviral agents that a subject must be taking in order to be enrolled into the study include: non-nucleoside reverse transcriptase inhibitors (NNRTI); nucleoside reverse transcriptase inhibitors (NRTI); protease inhibitors; integrase inhibitors; and fusion inhibitors. HAART regimens must be in accordance with the Department of Health and Human Services (DHHS) document, "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents". Should a newly-approved product become available that is not captured in the current guideline, clinicians and sponsor will determine subject eligibility.
14. Aviremic subjects on HAART with low innate immune system activation as determined by percentage of activated CD14+/CD16+ monocytes ≤ 60%.
15. Have had undetectable VLs for at least 2 months prior to screening. Subjects who had intermittent isolated episodes of detectable low-level viremia <500 copies RNA/mL; blips) will remain eligible.
16. HIV-1 RNA below the limit of detection
17. CD4+ T-cell count ≥500 cells/μL.
18. Willing to discontinue current antiretroviral therapy during the TI.

## 4.2 Exclusion Criteria

1. Acute or chronic hepatitis B or hepatitis C infection.
2. Active or recent (in prior 6 months) AIDS defining complication.
3. CXCR4 tropic or dual tropic HIV virus.
4. Any cancer or malignancy within the past 5 years, with the exception of successfully treated basal cell or squamous cell carcinoma of the skin or low grade (0 or 1) anal or cervical dysplasia.
5. Current diagnosis of NYHA grade 3 or 4 CHF, uncontrolled angina or uncontrolled arrhythmias.
6. History or any features on physical examination indicative of a bleeding diathesis.
7. Previous treatment with any HIV experimental vaccine within 6 months prior to screening, or any previous gene therapy using an integrating vector.

NOTE: Subjects treated with placebo in an HIV vaccine or gene therapy study will not be excluded if documentation that they received placebo or sham gene therapy is provided.

8. Use of chronic corticosteroids, hydroxyurea, or immunomodulating agents (e.g., interleukin-2, interferon-alpha or gamma, granulocyte colony stimulating factors, etc.) within 30 days prior to screening.

   NOTE: Use of inhaled or topical steroids is not exclusionary.

9. Breast-feeding, pregnant or unwilling to use acceptable methods of birth control for 6 months following the last infusion of SB-728mR-T cells.

   NOTE: The following are acceptable methods of birth control:

   a. Condoms (male or female) with or without a spermicidal agent
   b. Intrauterine device (IUD)
   c. Diaphragm or cervical cap with spermicide
   d. Hormonal-based contraception

   *Subjects who become pregnant after SB-728mR-T infusion must inform the investigator of their pregnancy and agree to provide follow-up information at time of delivery*.

10. Use of Aspirin, dipyridamole, warfarin or any other medication that is likely to affect platelet function or other aspects of blood coagulation during the 2 week period prior to leukapheresis.
11. Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements.
12. Serious illness requiring systemic treatment and/or hospitalization within 30 days prior to study entry.
13. Elevations of baseline serum bilirubin and amylase ≥3 times the upper limit of normal.

    NOTE: Asymptomatic elevations due to HAART medications are not exclusionary, when, in the opinion of the investigator, the abnormalities are not attributable to intrinsic hepatic disease.

14. Recent vaccination or intercurrent illness (within 5 weeks prior to SB-728mR-T infusion).

    NOTE: it is recommended that subjects should have completed their routine vaccinations (hepatitis A or B, pneumococcus, influenza and tetanus diphtheria booster) at least 30 days prior to screening for the study.

15. Have an allergy or hypersensitivity to study product excipients (human serum albumin, DMSO and Dextran 40).
16. Currently participating in another clinical trial or participation in such a trial within 30 days prior to screening visit.
17. Subjects who are currently taking maraviroc or have received maraviroc within 6 months prior to screening.
18. Any other condition that, in the opinion of the clinical investigator or sponsor, might compromise any aspect of this trial.

# 5. INFORMED CONSENT

Prior to entering the study, 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 involved in study participation. Subjects will be given an information and consent document, will have the opportunity to ask questions, and will be informed of their right to withdraw from the study at any time without prejudice. After this explanation and before any study-specific procedures have been performed, the subject must voluntarily sign and date the informed consent document.

The subject will receive a copy of the signed and dated written informed consent form and any other written information required to be provided to the subject. Subjects will be re-consented at the time of any informed consent amendment, as applicable, and will be provided a copy of the consent form.

# 6. STUDY METHODOLOGY

Prior to initiation of this study, the study site must have the protocol and subject informed consent form approved by the IRB. Subjects must be willing to participate in all study procedures in this protocol. The following sections describe all study procedures. See **Section 7** for details of evaluations. 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 I**).

## 6.1 Screening Visit Procedures

The objective of the screening visit is to identify subjects who meet the stated inclusion and exclusion criteria and who are willing and able to participate in the study. The following screening information and procedures must be completed and results reviewed for eligibility. The following will be performed at the screening visit:

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. Assign a subject number
3. Review the inclusion and exclusion criteria
4. 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.
5. Complete Physical Exam, including vital signs
6. 12-lead ECG
7. Hepatitis B surface antigen (HBsAG) and hepatitis C antibody (HCV)
8. Serum pregnancy test (female of childbearing potential)
9. Urinalysis for presence of glucose, protein, bilirubin, blood, pH, and specific gravity
10. CBC
11. Serum chemistry: electrolytes (Na, K, $CO_2$, Cl), creatinine, BUN, glucose, uric acid, total bilirubin, ALP, ALT (or SGPT), AST (or SGOT), LDH, albumin, calcium, and total protein, phosphorus.

12. CD4+ T-cell counts
13. HIV-1 RNA
14. CCR5 SNP Cel-I assay (not required if prior results available)
15. HIV-1 Co-receptor Tropism
16. Innate immune system activation evaluation (not required if prior results available)
17. Research blood

## 6.2 Subject Enrollment Procedures

Prior to the first leukapheresis, the study site must verify that the subject meets all inclusion and none of the exclusion criteria. A subject is considered enrolled after they meet all the entry criteria and have undergone the first leukapheresis.

## 6.3 Pre- Leukapheresis and Leukapheresis

Subjects who meet all the eligibility criteria will be scheduled for leukapheresis. Sangamo BioSciences should be contacted by the study center prior to scheduling leukapheresis and Sangamo will ensure availability of manufacturing facility.

### 6.3.1 Pre-Leukapheresis:

The following blood tests must be drawn approximately 1 week prior to the leukapheresis procedure and results sent to the Apheresis unit and Sangamo.

1. CBC
2. Electrolytes (Na, K, $C0_2$, Cl)
3. Calcium
4. Liver function tests (albumin, total protein, alkaline phosphatase, AST, ALT, total bilirubin)

### 6.3.2 Leukapheresis:

From a single 10L volume leukapheresis, at least 10 x $10^9$ white blood cells will be harvested to manufacture SB-728mR-T. The leukapheresis procedure will be conducted according to the facilities guideline. The cells from the leukapheresis product will be genetically modified and expanded using anti-CD3/CD28 beads. The cell product is expected to be ready for release to the study center approximately 6-8 weeks later. If the product from the first leukapheresis does not meet cell release criteria or there are insufficient cells for the intended dose, a second leukapheresis may be scheduled. The second leukapheresis will be at least three weeks after the first leukapheresis. AEs documented during leukapheresis will be entered onto the CRFs.

## 6.4 Baseline Assessments

### 6.4.1 Baseline for Research Blood Collection:

The following blood tests will be drawn between the leukapheresis procedure and CTX administration:

1. CBC
2. CD4+ T-cell count
3. Research blood

### 6.4.2 Baseline:

Baseline assessments will be performed approximately one week prior to CTX administration, and the subject should be evaluated. The following tests are performed at the baseline visit:

1. Assessment of AEs
2. Review concomitant medications
3. Urine pregnancy test (for females of child bearing potential only)
4. Chemistry
5. CBC
6. Urinalysis
7. CD4+ T-cell count
8. HIV-1 RNA
9. Height and Weight
10. Research blood (may be performed on the day of CTX infusion and prior to CTX infusion)

The following may be performed up to 4 weeks prior to the first SB-728mR-T infusion

11. Pentamer
12. SB-728mR immunogenicity

## 6.5 Study Treatment and Follow-up

After baseline tests are reviewed, the study center and Sangamo BioSciences will schedule SB-728mR-T dosing. Refer to the Study Reference Manual for details. All subjects will be followed for a total of 36 months after the first SB-728mR-T infusion according to the schedule in Appendix I.

### 6.5.1 Cyclophosphamide Administration (Day -2)

CTX should be administered 2 days prior to SB-728mR-T infusion. All subjects will remain at the study site after CTX administration until vital signs are satisfactory and stable. Subject may be released from the study site at investigator's discretion. Subjects will be monitored, as needed, post CTX administration.

1. AE assessment
2. Assessment of concomitant medications
3. Vital signs: temperature, pulse, and blood pressure (pre and post CTX administration)

Pre-CTX administration:

4. Chemistry
5. CBC
6. Urinalysis
7. CD4+ T-cell count
8. Volume status of subject will be assessed to ensure subject is euvolemic
9. Euvolemic subjects will be infused IV with 1L of IV fluids over approximately 1-2 hours.

10. Antiemetic administration: Subjects may be prescribed with an antiemetic (IV, oral or suppository) before, during, and after CTX infusion to prevent and treat nausea and vomiting. Recommended antiemetic regimen: Palonosetron (Aloxi) 0.25 mg IV and Aprepitant (Emend) 125 mg by mouth (PO) 60 minutes before CTX. Other antiemetics may be given at the discretion of the investigator and with sponsor consultation if possible.

CTX Administration:

1. CTX 1.0 g/m$^2$ administration

Post-CTX Administration:

2. 1L of IV fluids infused over approximately 1-2 hrs after CTX administration
3. Subjects should consume at least 4L of fluids over the 24 hrs after receiving CTX.
4. Recommended antiemetic regimen: Aprepitant (Emend) 80 mg PO daily (QD) for the following 6 days. Other antiemetics may be given at the discretion of the investigator and with sponsor consultation if possible.

Post CTX administration, if neutrophil count drops to $\leq$ 750/mm$^3$, administration of Filgrastim is recommended. Filgrastim can be discontinued when neutrophil count is $\geq$ 1000/mm$^3$ (**Section 8.2**).

### 6.5.2 SB-728mR-T Infusions: Day 0 and Week 2 (+/- 1 day); and Week 4 (Cohort 2 only) (+/- 1 day)

SB-728mR-T should be infused 2 days after completion of the CTX administration (**Section 8.1**). All subjects will remain at the study site for approximately 2 hours after SB-728mR-T infusion and vital signs are satisfactory and stable.

1. AE assessment
2. Assessment of concomitant medications
3. Vital signs: temperature, pulse, and blood pressure (pre and post SB-728mR-T infusion, and as needed)

Pre-SB-728mR-T Infusion:

4. Chemistry (Day 0)
5. CBC
6. Urine pregnancy test (for females of child bearing potential only)
7. Urinalysis (Day 0) and (Week 4: Cohort 2)
8. CD4+ T-cell count
9. HIV-1 RNA (Weeks 2 and 4)
10. Pentamer (Week 2) and (Week 4: Cohort 2)
11. Research blood (Day 0 and Week 2)

SB-728mR-T Infusions Day 0 and Week 2 (Cohort 1); Day 0, Week 2 and Week 4 (Cohort 2):

12. SB-728mR-T infusion

Each SB-728mR-T infusion will occur 14 days apart.

### 6.5.3 Day 1 / Day 15, and Day 29 (Cohort 2 only) (one day post SB-728mR-T infusions)

1. AE assessment
2. CBC
3. Urinalysis (Day 1)
4. CD4+ T-cell count
5. Pentamer
6. Research blood (Day 1 only)

### 6.5.4 Weekly Visits Post SB-728mR-T Infusion (+/- 2 day)

**Cohort 1: Week 1, Week 3, Week 4, and Week 5**
**Cohort 2: Week 1, Week 3, Week 5, Week 6, and Week 7**

1. AE assessment
2. Review of concomitant medications
3. Chemistry (Weeks 1 and 3) and (Week 5: Cohort 2 only)
4. CBC
5. Urinalysis (Week 1) and (Week 4: Cohort 1 only)
6. CD4+ T-cell count
7. HIV-1 RNA
8. Pentamer

### 6.5.5 16-Week HAART Treatment Interruption

**Cohort 1 (Week 6-Week 22): Weeks 6, 8, 10, 12, 14, 18, and 22**
**Cohort 2 (Week 8-Week 24): 8, 10, 12, 14, 16, 20, and 24**

All subjects with aviremia and CD4 cell counts ≥500 cells/μL will undergo a minimum 16-week TI. Subjects will be seen every other week (+/- 3 days) for the first 8 weeks and then every month (+/- 1 week) for the remaining 8 weeks of the TI. (**Section 8.3**)

Subjects will discontinue HAART under the supervision of the principal investigator. NNRTIs such as Rescriptor, Sustiva, Intelence, and Viramune have been reported to have a longer half life than NRTIs. Therefore, to avoid suboptimal drug exposure which may promote drug resistance, subjects on a NNRTI containing regimen should discontinue the NNRTI seven days before stopping their other antiretrovirals (Taylor et al., 2007). The time of medication interruption is noted in medication records and CRFs. The TI begins for an individual subject on the day that all antiretrovirals agents have been discontinued.

The following procedures will be performed at each visit during the TI:

1. Begin TI (discontinue all HAART) (Week 6: Cohort 1) (Week 8: Cohort 2)
2. AE assessment
3. Assessment of concomitant medications
4. Vital signs (temperature, pulse, blood pressure, and weight) (Weeks 6 and 22: Cohort 1) (Week 8 and 24: Cohort 2)
5. Chemistry (Weeks 8, 12, 22: Cohort 1), (Weeks 8, 12 24: Cohort 2)
6. CBC
7. CD4+ T-cell (during the initial 16 week TI, test will be repeated every 2 weeks for 3 consecutive measurements for values <500 cells/μL)

8. HIV-1 RNA (during the initial 16 week TI, test will be repeated every 2 weeks for 3 consecutive measurements for values >100,000 copies/mL)
9. HIV-1 coreceptor tropism and resistance testing will be performed once if HIV RNA exceeds 1,000 copies/mL
10. Pentamer
11. SB-728mR-T immunogenicity (Week 12 only)
12. Research blood (Weeks 6, 12, and 22: Cohort 1) and (Weeks 8, 14, and 24: Cohort 2)

At the end of the 16-week TI at Week 22 (Cohort 1) and Week 24 (Cohort 2):

- HAART will be reinstituted in subjects with HIV RNA levels >10,000 copies/mL and/or CD4 <500 cells/μL.
- Subjects with HIV RNA levels ≤ 10,000 copies/mL and CD4 count ≥ 500 cells/μL may elect to remain off HAART and undergo extended TI beyond 16-weeks (subjects with a VL that is below the limit of detection will remain off HAART). (**Section 8.3**)

During extended TI, HIV-1 RNA and CD4 counts will be measured monthly. HAART will be reinstituted when one or both of the following criteria are met:

- HIV RNA levels > 10,000 copies/mL, confirmed by two additional consecutive monthly measurements (for a total of 3 measurements)
- CD4 count < 500 cells/μL, confirmed by an additional consecutive monthly measurement (for a total of 2 measurements)

Subjects will not be put back on HAART until all results are available.

Subjects may have HAART reinstituted at any time at the discretion of the subject and/or PI.

### 6.5.6 Month 7, Month 9 and Month 12 (+/- 1 week)

1. AE assessment
2. Assessment of concomitant medications
3. Complete Physical Exam, including vital signs (Month 12 only)
4. Chemistry
5. CBC
6. Urinalysis (Months 7 and 12 only)
7. CD4+ T-cell count

   (For subjects in extended TI, test will be repeated monthly. HAART will be reinstituted if CD4 count <500 cells/μL for a total of 2 consecutive measurements)
8. HIV-1 RNA

   (For subjects in extended TI, test will be repeated monthly. HAART will be reinstituted if HIV-1 RNA levels > 10,000 copies/mL for a total of 3 consecutive measurements)
9. Pentamer
10. SB-728mR-T immunogenicity (Months 7 and 12 only)
11. Research blood

### 6.5.7 Long-term Follow-up (LTFU): Month 18 and Month 24 (+/- 1 month) and Month 36 (=/- 3 months)

1. Complete Physical Exam, including vital signs (Months 24 and 36 only)
2. Clinical condition assessment
3. Assessment of concomitant medications (Months 24 and 36 only)
4. Chemistry
5. CBC
6. CD4 T-cell count

   (For subjects in extended TI, test will be repeated monthly. HAART will be reinstituted if CD4 count <500 cells/μL for a total of 2 consecutive measurements)
7. HIV-1 RNA

   (For subjects in extended TI, test will be repeated monthly. HAART will be reinstituted if HIV-1 RNA levels > 10,000 copies/mL for a total of 3 consecutive measurements)
8. Pentamer

There are no disallowed medications (experimental or licensed) for subjects in the long-term follow-up portion of the study.

**The following additional study procedures may be performed upon request of sponsor:**

1. Additional Research Blood collection of 80 mL one or two times. The second blood collection of 80 mL will be performed only when insufficient cells are obtained from the first collection. If any subject agrees to undergo optional leukapheresis in the study, this research blood collection of 80 mL will not be performed.
   a. Blood collection for CBC with differential and CD4+ T-cell counts
   b. 80 mL blood collection
2. Optional leukapheresis

Subject who agrees to an optional leukapheresis will undergo the following additional study procedures:

- **Pre-Leukapheresis Visit:** ≤ 7 days prior to the leukapheresis procedure, the following blood tests will be performed and results sent to the apheresis facility and Sangamo:
  a. CBC
  b. Electrolytes (Na, K, $C0_2$, Cl)
  c. Calcium
  d. Liver function tests (albumin, total protein, alkaline phosphatase, AST, ALT, total bilirubin)
  e. CD4+ T-cell counts (The test will be performed only if the leukapheresis center cannot collect this blood sample)
- **Leukapheresis Procedure Visit:** The following will be performed:

a. CBC and CD4+ T-cell counts (prior to the leukapheresis). If the leukapheresis center cannot collect the blood sample, this blood collection should be done at the pre-leukapheresis visit.

b. a 10L volume leukapheresis procedure will be conducted according to the apheresis facility guidelines.

## 7. INSTRUCTIONS FOR EVALUATIONS

- Complete Physical Exam: a complete physical examination must include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdomen; examination of the lower extremities for edema; and a breast exam for females. The complete physical exam will also include vital signs (temperature, pulse, blood pressure) (weight and height at Screen and Baseline Visits).
- CBC: Hemoglobin, hematocrit, platelet count, red cell count, and white cell count with differential count and absolute neutrophil count.
- Chemistry: Bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, total protein, albumin, calcium, and phosphorous.
- Hepatitis B: subjects must have documentation of a negative HBsAg test at screening.
- Hepatitis C: subjects must have documentation of a negative HCV antibody test at screening. If the HCV antibody is positive, the subject may return for a HCV RNA test. If the HCV RNA test is negative, the subject may undergo leukapheresis.
- HIV-1 Co-receptor Tropism and Resistance Testing: the HIV-1 co-receptor tropism assay measures whether a patient has CCR5, CXCR4 or dual tropic virus. The tropism assay looks at the surface receptors on HIV to determine the dominant co-receptor. Resistance testing will be performed using a highly accurate HIV drug resistance test that provides the complete picture of resistance and combines actual phenotype and genotype drug resistance data. The report will include drug resistance information for all of the approved NRTIs, NNRTIs, protease inhibitors, and integrase inhibitors.

## 8. INVESTIGATIONAL PRODUCT AND OTHER STUDY MEDICATIONS

### 8.1 SB-728mR-T

SB-728mR-T is autologous T-cells modified at the CCR5 gene by ZFNs that are delivered by mRNA electroporation. Autologous T lymphocytes are transduced *ex vivo* with SB-728mR. The final T-cell product, SB-728mR-T, is generated using 2 major elements: 1) SB-728mR electroporation used for gene delivery of CCR5 specific zinc finger nucleases and 2) CCR5 modified autologous T-cells (SB-728mR-T) that have undergone ex vivo T-cell activation, *ex vivo* genetic modification by the SB-728mR, expansion and formulation. The composition of the final T-Cell product is:

**Composition of SB-728mR-T**

| Component | Unit Formula |
|---|---|
| SB-728 Treated T-cells | 0.5-1.25 x $10^8$/mL |

| | |
|---|---|
| PlasmaLyte A | 31.25% |
| Dextran 40 and 5% Dextrose | 10% |
| 25% Human Serum Albumin | 20% |
| Dimethyl Sulfoxide (DMSO) | 7.5% |
| Dextrose 5%/.45% NaCl | 31.25% |

The final drug product is tested for identity, cell count, purity, viability, potency, mycoplasma, endotoxin, and sterility. Cells that have not met specifications or will not be infused will be destroyed by the manufacturer according to their procedures. A copy of the Certificate of Analysis (C of A) will accompany each infusion bag.

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

SB-728mR-T is cryopreserved in a 250 mL cryocyte infusion bag at ≤ -130°C. The infusion bags will contain approximately 50 mL of T-cells (actual volume dependent on number of cells) and have a label affixed containing the following information: protocol number, subject study number, lot number and "FOR AUTOLOGOUS USE ONLY". Each bag of cryopreserved genetically modified T-cells will contain approximately 0.5 x $10^{10}$ cells at a concentration of approximately 1 x $10^{8}$ cells/mL of infusible cryomedia.

The CCR5 ZFN-modified T-cells are not released from the manufacturer until the release criteria are met. Release tests are performed in process, on the pre-harvest cells, and on the final cryopreserved product. QC testing will be performed by contract manufacturer, Sangamo BioSciences, Inc. and commercial testing laboratories, prior to administration of cells to the subject. Quality control test results and documentation will be reviewed by external Quality Assurance personnel. The final release test for cell viability by Trypan Blue will be performed approximately 72 hours before the scheduled thaw and infusion. The final product will be split into 2 or 3 doses and will be stored frozen at the manufacturing facility until ready to be shipped to the clinical study center. The T-cell product and the C of A will be shipped frozen either via courier or overnight to the clinical study center prior to the scheduled infusion(s). The T-cell product should remain frozen at the clinical study center until successful placement of the IV infusion line into the subject.

The T-cell product is considered biohazard material therefore if any CCR5 ZFN-modified T-cells are not infused, the infusion bag and tubing will be disposed of according to the study center's procedures for safe handling of biological material.

Accessibility to labeled T-cell product should only be to those individuals authorized by the investigator to dispense this study drug.

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, return or destruction of all drug supplies must be coordinated with Sangamo BioSciences. 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.

### 8.1.2 SB-728mR-T Administration

Side effects following SB-728mR-T cell infusions may include transient fever, chills, and/or nausea. It is recommended that the subject be pre-medicated with acetaminophen 650 mg by mouth and diphenhydramine hydrochloride (Benadryl) 25-50 mg by mouth or IV, prior to the infusion of SB-728mR-T. These medications may be repeated every 3-4 hours as needed. A course of non-steroidal anti-inflammatory medication may be prescribed if the subject continues to have fever not relieved by acetaminophen. It is recommended that subjects not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol) or dexamethasone (Decadron) at any time, except in the case of a life-threatening emergency, since this may have an adverse effect on T-cells. If corticosteroids are required for an acute infusion reaction, an initial dose of hydrocortisone 100 mg is recommended.

SB-728mR-T will be shipped to the study site prior to the scheduled infusions. The first SB-728mR-T dose should be infused 2 days after completion of the CTX administration. The study product should be thawed just prior to the scheduled infusion. Prior to the infusions, two individuals will independently verify all information in the presence of the subject to confirm that the information is correctly matched to the subject. The cell product should be infused within 15 minutes after it is thawed and before the solution becomes warm in the IV bag to ensure viability of infused cells. Detailed instructions for the thaw and infusion of cells are in the Study Reference Manual.

### 8.1.3 Precautions

SB-728mR-T 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 as needed, then according to the study center procedures for a minimum of two hours. The subject will be asked to remain in the study unit until the study staff considers it safe for him/her to leave.

In the unlikely event that the subject develops sepsis or systemic bacteremia following SB-728mR-T infusion, appropriate cultures and medical management should be initiated. If possible contamination of the SB-728mR-T product is suspected, the product can be retested for sterility using archived samples that are stored at the manufacturing facility.

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood and blood products, appropriate blood and secretion precautions should be employed by all personnel in the drawing of blood and shipping and handling of specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

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.

### 8.1.4 Dose Modifications

The total dose of SB-728-mR-T will depend on the number of cells manufactured for each subject. No dose modifications are possible.

## 8.2 Cyclophosphamide

CTX is a sterile white powder containing CTX monohydrate. It is available in vials of 500 mg, 1.0 g and 2.0 g vials for single use only. The vials should be stored at 25°C. CTX 1.0 g/m$^2$ should be administered 2 days prior to SB-728mR-T infusion. CTX will not be administered to a subject until the subject's SB-728mR-T product lot is released and the number of cells manufactured meets the minimum dose requirement.

Subjects may be pre-medicated with acetaminophen 650 mg by mouth and diphenhydramine hydrochloride (Benadryl) 25-50 mg by mouth or IV, prior to the infusion of CTX. These medications may be repeated every 3-4 hours as needed.

**Antiemetics**

Recommended antiemetics such as Aloxi 0.25 mg IV and Emend 125 mg PO should be given 60 minutes before CTX followed by Emend 80 mg PO once a day for the following 6 days. Other antiemetic regimens may be given at the discretion of the investigator and with sponsor consultation, if possible. Subjects may be prescribed with an antiemetic (IV, oral or suppository) if nausea and vomiting develops during CTX administration.

**Filgrastim**

After CTX administration, if neutrophil count drops to ≤ 750/mm$^3$, administration of Filgrastim is recommended. Filgrastim can be discontinued when neutrophil count is ≥ 1000/mm$^3$.

The adverse effects of CTX that occur at a frequency of >10% are discussed in **Section 9.2**.

Please refer to the FDA approved manufacturer's package insert and the Study Reference Manual for additional information.

## 8.3 HAART

### 8.3.1 Discontinuation of HAART

Subjects with aviremia and CD4 cell counts ≥500 cells/μL 4 weeks after the last SB-728mR-T infusion will discontinue HAART under the supervision of the principal investigator during the TI. NNRTIs such as Rescriptor, Sustiva, Intelence, and Viramune have been reported to have a longer half life than NRTIs. Therefore, to avoid suboptimal drug exposure which may promote drug resistance, subjects on an NNRTI containing regimen should discontinue the NNRTI seven days before stopping their other antiretrovirals (Taylor et al., 2007). The time of medication interruption is noted in medication records and CRFs.

### 8.3.2 Reinstitution of HAART

During the 16-week TI, tests for HIV-RNA and CD4 count will be repeated in 14 days for values >100,000 copies/mL and <500 cells/μL, respectively. HAART therapy will be reinstituted if the subject experiences a sustained VL increase to >100,000 copies/mL (on 3 consecutive measurements tested every 2 weeks) and/or a sustained drop in the CD4 count <500 cells/μL (on 3 consecutive measurements tested every 2 weeks). The drug regimen that the subject will receive will be determined by the Principal Investigator in consultation with the subject's primary HIV physician. To guide the selection of therapy, the tropism and sensitivity of the virus to antivirals will be determined by HIV-1 coreceptor and resistance testing, respectively. If the VL or CD4 drop is not sustained, the subject will be advised not to reinstate HAART until after the TI to allow for evaluation of the subject's VL.

At the end of the 16-week TI at Week 22 (Cohort 1) and Week 24 (Cohort 2):

- HAART will be reinstituted in subjects with HIV RNA levels >10,000 copies/mL, and /or CD4 <500 cells/μL.
- Subjects with HIV RNA levels ≤10,000 copies/mL and CD4 count ≥ 500 cells/μL may elect to remain off HAART and undergo extended TI beyond 16 weeks (subjects with HIV RNA levels below the limit of detection will remain off HAART).

During extended TI, HIV-1 RNA and CD4 counts will be measured monthly. HAART will be reinstituted in subjects when one or both of the following criteria are met:

- HIV RNA levels > 10,000 copies/mL, confirmed by two additional consecutive monthly measurements
- CD4 count < 500 cells/μL, confirmed by an additional consecutive monthly measurement

Subjects will not be put back on HAART until all results are available.

Subjects may have HAART reinstituted at any time at the discretion of the subject and/or PI.

### 8.4 Concomitant Medication

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.

Aspirin, dipyridamole, Plavix, warfarin, or any other medications likely to affect platelet function or other aspects of blood coagulation are prohibited during the 2-week period prior to leukapheresis.

Oral corticosteroids, hydroxyurea, and immunomodulating agents are prohibited until completion of the Study Period. A brief course (< 1 week) of oral corticosteroids is allowed on study.

Routine vaccines are prohibited for six months following infusion of cells, unless medically indicated.

## 9. SAFETY AND POTENTIAL RISKS

### 9.1 SB-728mR-T

This is the first study in which SB-728mR-T will be administered to humans. Side effects for SB-728mR-T in man are unknown, they may or may not be the same or similar to SB-728-T.

SB-728-T at doses ranging from 5 to 40 billion cells has been safely administered to approximately 70 HIV-infected subjects in four clinical trials to date. One SB-728-T-related SAE (infusion reaction) occurred on the UPenn study. The longest duration of follow-up has been over 3 years in the first subject infused. No new clinical conditions or SAEs related to SB-728-T have been reported in the subjects participating in long-term follow-up.

#### 9.1.1 Emergence of CXCR4 HIV

There is a theoretical possibility that CXCR4 viral variants may emerge following inhibition of CCR5. CXCR4 variants are more common in late stage HIV infection. Even if the CCR5

depleted cells results in relative selection of low levels of CXCR4 variants, the antiretroviral treatment regimen will be able to maintain viral suppression therefore it is not expected that this will be a problem of clinical significance. Subjects in this study will be tested for presence of dual tropic or CXCR4 tropic virus prior to entering into the study and any subjects with evidence of dual or CXCR4 tropism will be excluded. During the TI, a sample will be sent for the HIV-1 coreceptor assay to asses for CXCR4 or dual tropism when the VL increases to > 1,000 copies/mL. Subjects with a CXCR4 or dual tropic virus will be restarted on HAART.

### 9.1.2 Carcinogenicity

There is a risk that people who receive gene transfer may develop new tumors derived from their genetically modified cells. This risk is primarily associated with viral gene transfer vectors that integrate into the cellular DNA where it may dysregulate genes controlling proliferation. The risk with mRNA electroporation is extremely low. Extensive preclinical safety studies have been carried out and support the safety of CCR5 specific ZFNs, are briefly summarized here and are recently published in Nature Biotechnology (Perez et al, 2008). Deep sequencing studies at genome sites chosen by their ability to bind to the SB-728mR ZFNs with up to 2 base mismatches have shown that the CCR5 specific ZFNs effect cleavage only at the target CCR5 gene and at approximately one tenth the CCR5 rate at the highly homologous site of the CCR2 gene. Extremely low levels of modification are also seen in the intron of a third gene, ABLIM-2 at an extremely low frequency of <1 in 18,000 genes. This data confirms the specificity of CCR5 specific ZFNs to the CCR5 gene. No specific effects on cell growth have been observed, indicating that in vitro CCR5 specific ZFN modification does not appear to affect cell biology and replication. Overall increases in double stranded DNA breaks as visualized by fluorescence microscopy has shown a transient increase just after ZFN treatment, which is self limiting, occurs at the time and level of expected CCR5 specific ZFN activity and is below the level induced by etoposide, which blocks topoisomerase II leading to DNA breaks during cell division. No T cell transformation has been detected in a soft agar transformation assay, or in multiple animal biotoxicity studies in which each animal received greater than the equivalent of a human dose, and over all animals a log equivalent of a human dose was evaluated. Taking this data together, there is currently no indication that CCR5 specific ZFN modified T-cells is unsafe and may cause T-cell tumors.

### 9.1.3 Immunogenicity

The immunogenicity of SB-728mR-T infusion is unknown. SB-728mR is short lived in the transduced cells. Immunogenicity tests for CCR5 specific ZFNs in subjects who received SB-728-T have been performed. Preliminary data show that no immunogenicity against CCR5 specific ZFNs was observed at 3 months post SB-728-T infusion.

## 9.2 Cyclophosphamide

CTX is associated with a variety of side effects. The adverse effects that occur at a frequency of >10% includes alopecia, infertility, nausea and vomiting, hemorrhagic cystitis and bone marrow suppression. Antiemetics will be given prophylactically and as needed for nausea and vomiting. Leukopenia is more common than thrombocytopenia and anemia with the onset 7 days after administration and a nadir at 10 to 14 days followed by recovery at 21 days. After CTX administration, if neutrophil count drops to $\leq 750/mm^3$, administration of Filgrastim is recommended. Filgrastim can be discontinued when neutrophil count is $\geq 1000/mm^3$. Subjects will be monitored, as needed, post CTX administration.

Hemorrhagic cystitis is a potential untoward effect of CTX therapy with the metabolite acrolein implicated as the major urothelial toxin. The incidence of hemorrhagic cystitis was reported to be 6% among subjects who received CTX (1.0-1.2 g/m$^2$) for ovarian cancer. At these low doses, the American Society of Clinical Oncology recommends administering fluids to induce a diuresis. Hemorrhagic cystitis has not been reported in the Sangamo study in which similar preventative measures were taken. In this study, subjects will be hydrated with 1 liter of IV fluids prior to CTX administration and with another liter prior to discharge from the study center. Subjects are instructed to drink 4L of fluids over the next 24 hrs to insure adequate diuresis.

CTX is a carcinogen and has been associated with malignancies. The risk depends upon the dose administered, other co-administered chemotherapy, use of radiotherapy, treatment intensity and duration of therapy. Cumulative doses totaling 10 g or less has been shown to be associated with an incidence of malignancy that is similar to that of the normal untreated population (Baker et al., 1987). Therefore, the low dose (1.0 g/m$^2$) that will be administered in this study is unlikely to be carcinogenic.

### 9.3 HAART Treatment Interruption (TI)

The efficacy and safety of HAART interruption for HIV patients has been reviewed by Patton (Patton, 2008). Data indicates that there is no clinical benefit to patients with acute HIV infection or those with virologic failure due to multidrug resistance. Indeed, TI may be harmful in patients with chronic successfully treated infections. Therefore, TI is currently only recommended in the context of clinical trials.

The safety of TI has been demonstrated in the SB-728-T studies conducted by UPenn and Sangamo. Subjects underwent varying lengths of TI (12 and 16 weeks) during these studies. HAART was interrupted beginning 4, 6, and 8 weeks after SB-728-T infusion. Subjects were closely monitored throughout the TI and HIV-1 coreceptor tropism and resistance testing were performed during TI. After reinstitution of HAART, subjects became aviremic in a short period of time. No subject has had a change in HIV tropism during the studies.

Several precautions have been instituted in this protocol to insure subject safety. Subjects will be monitored closely during the TI period with study visits every 2 weeks for the first 8 weeks and monthly for the remaining 8 weeks. If the HIV RNA increases to >100,000 copies/mL and/or the CD4 count drops to <500 cells/μL, the tests will be repeated every 2 weeks for a total of 3 consecutive measurements. HAART will be reinstituted in subjects whose CD4 cell counts drop to <500 cells/μL and/or whose HIV-RNA increases to >100,000 on three consecutive measurements. During extended TI, HIV-1 RNA and CD4 counts will be measured monthly and additional monitoring will be performed as needed for safety. CD4 T-cell count will be repeated monthly for a total of 2 consecutive measurements if CD4 count <500 cells/μL and HIV-1 RNA will be repeated monthly for a total of 3 consecutive measurements if HIV-1 RNA levels > 10,000 copies/mL. In addition, all subjects infected with a CXCR4 virus will resume HAART. The effectiveness of these stopping rules is demonstrated by the reinstitution of HAART in subjects in the studies cited above.

It is possible that some subjects could experience symptoms compatible with retroviral rebound syndrome, or rarely, other clinical events that occur before use of HAART (e.g. immune thrombocytopenia). The kinetics of viral rebound are well characterized, typically occurring within 2 to 4 weeks following discontinuation of drug, and viral replication is routinely re-suppressed with resumption of therapy.

The psychological risks associated with TI appear to be minimal. In a survey reported at the 2002 International AIDS Conference in Barcelona, study investigators quizzed enrollees about their experience in the Spanish Swiss Intermittent Treatment Trial, and found that the majority "viewed their experience positively." Only two stated they would not participate in a similar TI trial, compared to 72 that said they definitely would and 25 who answered that they would consider it. In terms of any problems taking HAART after interruptions, 73 reported that that it was no different, 10 said it felt easier while 17 found it more difficult. Furthermore, fewer side effects were reported upon restarting HAART than when therapy was first initiated (Le Braz et al., 2002).

# 10. ADVERSE EVENTS

## 10.1 Definitions of an Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. The term “adverse event” could include any of the following events which develop or increase in severity during the course of the study. Examples include:

- 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 study drug, including those occurring as a result of an overdose, abuse, withdrawal phenomena, sensitivity, or toxicity to study drug
- 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).

Suspected Adverse Reaction is any AE for which there is a reasonable possibility that the drug caused the AE. “Reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Unexpected AE or Unexpected Suspected Adverse Reaction: An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as

occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

### 10.2 Adverse Event Reporting Period

During the Study Period, subjects will be queried and events will be assessed at each clinic visit. Subjects will be reminded to immediately report any SAE to the investigator. Any study procedure related AEs that occur from enrollment to initiation of treatment will also be recorded. Refer to **Section 12** for reporting clinical conditions during LTFU.

### 10.3 Recording of an Adverse Event

The principal investigator is responsible for evaluating all AEs, obtaining supporting documents, and determining that documentation of the event is adequate. He/she is responsible for determining the severity 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 study drug. 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 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.

Noninfective cystitis will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 with the following criteria:

- Grade 1: Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence
- Grade 2: Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental activities of daily living (ADL)
- Grade 3: Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

- Grade 4: Life-threatening consequences; urgent radiologic or operative intervention indicated
- Grade 5: Death

The relationship of the AE to the investigational drug will be determined by the principal investigator and will be categorized as:

*Not Related*: Any AE that does not meet the definition of a suspected AE reaction.

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. If an autopsy is performed, a copy of the autopsy report should be obtained if possible.

## 11. SERIOUS ADVERSE EVENT

### 11.1 Definitions of a Serious Adverse Event

Any AE or suspected adverse reaction is considered "serious" " if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect in the offspring of an exposed patient

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator, or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the 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 the sponsor, a SAE includes any event suggesting significant risk to human subjects.

### 11.2 Serious Adverse Event Reporting Period

SAEs, whether or not unexpected or considered to be associated with the use of the labeled product, must be communicated to Sangamo BioSciences upon discovery of the event, either by telephone or fax within 24 hours.

| | |
|---|---|
| **Medical Monitor:** | Winson Tang, M.D. |
| **Phone Number:** | Office : (510) 970-7800<br>Mobile: (310) 497-7038 |
| **Fax Number:** | (510) 970-6009 |

The investigator is responsible for promptly notifying the Institutional Review Board (IRB) in accordance with local regulations, of all SAEs. The National Institutes of Health (NIH) requires that all investigators participating in gene transfer research report all serious AEs immediately to the FDA, NIH, and Institutional Biosafety Committee. Sangamo BioSciences will assume the responsibility for reporting SAEs to the FDA.

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

Refer to **Section 12** for reporting of SAEs during LTFU.

### 11.3 Recording of a Serious Adverse Event

SAEs reported by telephone must be recorded on a written SAE Report Form, provided by Sangamo BioSciences. The SAE report form must be faxed to Sangamo BioSciences within 24 hours.

The medical monitor will then advise the investigator regarding the nature of any further information or documentation that is required. Follow-up reports must be submitted in a timely fashion as additional information becomes available.

## 12 CLINICAL CONDITION AND SERIOUS ADVERSE EVENT DURING LONG-TERM FOLLOW-UP

### 12.1 Clinical Condition

During the LTFU period, the following clinical conditions should be reported to the Sponsor and recorded on the subject Case Report Form:

- Any new condition that may be considered to be related to treatment with SB-728mR-T
- The emergence of a new malignancy, neurologic, rheumatologic/autoimmune or hematologic disorder regardless of severity or relationship to treatment with SB-728mR-T.
- Exacerbation of a pre-existing neurologic, rheumatologic or other autoimmune disorder regardless of relationship to treatment with SB-728mR-T

Malignancies will be submitted to Sangamo within 7 days of learning of the diagnosis and will include the date of diagnosis and type of malignancy, stage at diagnosis, presence of metastasis, surgical procedures and therapy.

Severity of reportable clinical conditions will be categorized 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.

### 12.2 Reporting Serious Adverse Events in LTFU

SAEs will be reported to the Sponsor **(Section 11.2)** upon discovery of the event, either by telephone or fax within 24 hours and recorded **(Section 11.3)** in the Case Report Form **only if the event is serious, unexpected, and considered to be related to treatment of SB-728mR-T**. Refer to **Section 11.1** for SAE definitions.

## 13. SUBJECT WITHDRAWAL AND STOPPING RULES

### 13.1 Subject Withdrawal and Discontinuation from Study

Subjects 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.
- Pregnancy prior to SB-728mR-T infusion.
- 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, Office for Human Research (OHR), Food and Drug Administration (FDA), investigator, or Sangamo.

Subjects will be strongly encouraged to continue with follow-up safety evaluations if they withdraw consent. If a subject discontinues from the study a conference between the investigator and medical monitor may take place to ensure that all subjects will comply with the follow-up safety evaluations of the protocol. Subjects will be assessed for treatment-related AEs and disease status.

### 13.2 Stopping Rules

#### 13.2.1 Stopping Rules for Treatment Interruption

The TI will be stopped if the subject experiences a sustained VL increase to >100,000 copies/mL (at least 3 consecutive measurements tested every 2 weeks) and/or a sustained drop (at least 3 consecutive measurements tested every 2 weeks) in the CD4 count <500 cells/µL during the initial 16 weeks of TI. HAART will be reinstituted in these subjects. The drug regimen that the subject will receive will be determined by the Principal Investigator in consultation with the subject's primary HIV physician. To guide the selection of therapy, the tropism and sensitivity of the virus to antivirals will be determined.

At the end of the 16-week TI:

- HAART will be reinstituted in subjects with HIV RNA levels >10,000 copies/mL, and /or CD4 <500 cells/μL.
- Subjects with HIV RNA levels ≤10,000 copies/mL and CD4 count ≥ 500 cells/μL may elect to remain off HAART and undergo extended TI beyond 16 weeks (subjects with HIV RNA levels below the limit of detection will remain off HAART).

HAART will be reinstituted in subjects, whose TI is extended beyond 16 weeks, when one or both of the following criteria are met:

- HIV RNA levels >10,000 copies/mL, confirmed by two additional consecutive monthly measurements.
- CD4 count <500 cells/μL, confirmed by an additional consecutive monthly measurement.

Subjects may have HAART reinstituted at any time at the discretion of the subject and/or PI.

### 13.2.2 Stopping Rules for Study

Safety data including AEs, clinical laboratory results (chemistry, hematology, CD4 T-cell counts and VL) will be evaluated throughout the study

The study will be paused if there are excessive or unexpected toxicities associated with the protocol. Specifically, the study will be paused and reevaluated if it is determined:

- That one subject has a ≥ Grade 3 toxicity (with the exception of alopecia) as determined by the DAIDS Clinical Trial Toxicity Criteria of December 2004, Clarification 1.0, August 2009 and judged to be related to the study treatment.
- A subject experiences an absolute lymphocyte count greater than 10,000/uL, until the evaluation of the nature of the lymphocyte increase is determined. If it is found not to be related to the study treatment, then the study will resume.
- Confirmed CXCR4 or CXCR4 and CCR5 dual tropic virus: if at least two subjects develop a VL that can be assessed for tropism (>1,000 copies/mL) and they are both either CXCR4 or dual tropic.

The study will be stopped if:

- The Investigator, Sponsor, independent safety monitor or regulatory body 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.
- An analysis of clonal outgrowth of T-cells determines that it is a result of SB-728mR-T mediated oncogenesis.
- Sustained (confirmed) virologic failure without an alternative explanation: If any subject develops an increase in HIV-1 RNA of > 5000 copies/mL when not undergoing TI, the test will be repeated once a week for an additional 2 weeks. If the VL remains > 5000 copies/mL for at least 3 weeks, and has no alternative explanation (such as non-compliance) other than the study treatment, the study will be stopped.

## 14. STATISTICAL ANALYSIS AND DATA ANALYSIS

This is an 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.

### 14.1 Sample Size

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.

### 14.2 Statistical Methods/Data Analysis

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

### 14.3 Intent-to-Treat Population

All subjects enrolled in this study who receive any portion of the SB-728mR-T infusion will be included in the intent-to-treat population.

### 14.4 Demographics

Demographic and baseline characteristics will be summarized by treatment cohorts.

### 14.5 Endpoints and Analysis

Safety and efficacy analyses will be descriptive and exploratory in nature because of the small sample size. Continuous variables will be summarized by means, standard deviations, medians and ranges by cohort. Categorical variables will be summarized with counts and percentages per category by cohort.

#### 14.5.1 Primary Endpoint

Safety assessment will occur on all subjects who received SB-728mR-T. All reported AEs will be coded to a standard set of terms using the Medical Dictionary for Regulatory Activities (MedDRA) AE dictionary. The frequency of each event will be summarized by severity and by relatedness to the study treatment.

Terminations, premature withdrawals, AEs, concomitant medications, and laboratory data will be tabulated. Laboratory data will be summarized for each time-point that specimens are collected. Change-from-baseline values may be calculated for selected laboratory parameters. Shift-tables (change-from-baseline relative to the normal range) may be constructed for selected laboratory parameters.

#### 14.5.2 Secondary Endpoints

These exploratory endpoints may help to define the primary endpoints for future studies:

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

## 15. 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.

## 15.1 Informed Consent

According to 21 CFR Part 50.20, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.

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

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

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

## 15.2 Institutional Review Board and BioSafety Committee

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

### 15.2.1. Protocol Amendments

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

### 15.2.2. Other Reporting Obligations

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

## 15.3 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 FDA, other national or local health authorities, Sangamo, and the associated IRB/IEC.

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

### 15.4 Reporting Obligations

Sangamo BioSciences, Inc., the sponsor of this IND, is required to report to the FDA annually on the status of the trial. Status reports must be filed by the Principal Investigator with their IRB on an annual basis.

## 16. ADMINISTRATIVE CONSIDERATIONS

### 16.1 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 FDA 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 approved Informed Consent signed by subjects.

b) Study files containing all version of the IRB approved protocol with all amendments, IRB approved informed consent forms, copies of all pre-study documentation, Form FDA 1572 and all correspondence to and from the IRB 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.

### 16.2 Record Retention

According to 21 CFR 312.62(c), the investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the investigator shall retain these records until 2 years after the investigation is discontinued and the FDA is notified. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Sangamo BioSciences. It is the responsibility of Sangamo BioSciences to inform the investigator as to when these documents no longer need to be retained.

### 16.3 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. 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 study monitor for full inspection. In addition, all data queries should be resolved promptly.

### 16.4 Termination of the Study

Sangamo retains the right to terminate the study and remove all the study materials from the study site at any time. 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

### 16.5 Study Monitoring

Sangamo BioSciences, as sponsor of this study, is responsible to regulatory authorities 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 BioSciences 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 BioSciences in the maintenance of complete, legible, well-organized, and easily retrievable data. In addition, a Sangamo BioSciences study monitor will ensure an understanding of the protocol, reporting responsibilities, and the validity of the data.

Individual study sites will be monitored by a Sangamo representative at appropriate intervals to assure satisfactory consenting process, data recording, and protocol adherence. In order to perform their roles well, the Sangamo BioSciences 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, 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 Sections 10.0 and 11.0 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.

### 16.6 Publication Statement

The results of this clinical trial may be used by Sangamo 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 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 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 and Sangamo 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.

### 16.7 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 BioSciences.

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# APPENDIX I: SCHEDULE OF EVENTS – COHORT 1

| | Study Period | | | | | | | | | | | | | | | | | | | | | LTFU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | Screen | Pre-Leukapheresis (1 wk prior to leukapheresis) | Leukapheresis[a] | Baseline for Research Blood (between Leuk & CTX) | Baseline (~1 wk prior to CTX) | Day -2 CTX | Day 0 SB-728mR-T Infusion# 1 | Day 1 1 day post infu sion | Wk 1 (+/- 2d) | Wk 2 (+/- 1d) SB-728mR-T Infusion #2 | Day 15 1 day post infu sion | Wk 3 (+/- 2d) | Wk 4 (+/- 2d) | Wk 5 (+/- 2d) | Wk 6 ------ **Start TI** (+/- 3d) | Wk 8 (+/- 3d) | Wk 10 (+/- 3d) | Wk 12 (+/- 3d) | Wk 14 (+/- 3d) | Wk 18 (+/- 7d) | Wk 22 ------ **Evaluate TI** (+/- 7d) | M7, M9, M12 (+/- 7d) | M18 and M24 (+/- 1m) and M36 (=/- 3m) |
| Inclusion Exclusion / Informed Consent | X | | | | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | | | | |
| Physical Exam | X | | | | | | | | | | | | | | | | | | | | X M12 only | X M24 and M36 only |
| Vital Signs[b] | X | | | | X | X | X | | | X | | | | | X | | | | | | X | X M12 only | X M24 and M36 only |
| 12-lead ECG | X | | | | | | | | | | | | | | | | | | | | | |
| Leukapheresis | | | X | | | | | | | | | | | | | | | | | | | |
| CTX Administration | | | | | | X[c] | | | | | | | | | | | | | | | | |
| SB-728mR-T infusion | | | | | | | X[d] | | | X[d] | | | | | | | | | | | | |
| Adverse events[e] | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[e] |
| Concomitant medications | X | | | | X | X | X | | X | X | | X | X | X | X | X | X | X | X | X | X | X M24 and M36 only |
| Hepatitis B and C | X | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy Test[f] | X | | | | X | | X | | | X | | | | | | | | | | | | |
| Chemistry | X | X[g] | | | X | X | X | | X | | | X | | | | X | | X | | | X | X | X |
| CBC | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | | | | X | X | X | X | X | | | | X | | | | | | | | | X M7 and M12 only | |
| CD4+ T-cell counts | X | | | X | X | X | X | X | X | X | X | X | X | X | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] | X | X |
| HIV-1 RNA (Viral Load) | X | | | | X | | | | X | X | | X | X | X | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X | X |
| CCR5 SNP CEL-1 assay | X[j] | | | | | | | | | | | | | | | | | | | | | | |
| Pentamer | | | | | X[k] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| SB-728mR-T Immunogenicity | | | | | X[k] | | | | | | | | | | | | | X | | | | X M 7 & 12 only | |
| HIV-1 Tropism and/or Resistance test | X[j] | | | | | | | | | | | | | | X[m] | | | | | | | | |
| Research Blood | X | | | X | X[l] | | X | X | | X | | | | | X | | | X | | | X | X | |
| Upon request of sponsor: Additional 80 mL research blood collection, CBC with differential, and CD4+ T-cell Count: One to 2 times during the study. If subject agrees to participate in the optional leukapheresis procedure, this additional blood collection will not be performed. | | | | | | | | | | | | | | | | | | | | | | | |

[a] If second leukapheresis is required, it must be > 3 weeks after the first leukapheresis.
[b] Screen, Wk 6, Wk 22, and M12 (temp, pulse, BP and weight); Baseline (ht and wt); CTX, Day 0 and Wk 2 (temp, pulse, BP)
[c] Administer CTX 2 days prior to the first SB-728mR-T infusion.Refer to Protocol Sections 6.5.1 and 8.2 and the Study Reference Manual for further details
[d] Refer to Protocol Sections 6.5.2 and 8.1 and the Study Reference Manual for further details
[e] Refer to Protocol Section 12 for reporting of Clinical Conditions and SAEs in LTFU
[f] Serum pregnancy test at Screen and urine pregnancy tests at Baseline and prior to SB-728mR-T infusions on Day 0 and Wk 2
[g] Electrolytes (Na, K, $CO_2$, Cl), calcium, liver function tests (albumin, total protein, alkaline phosphatase, AST, ALT, total bilirubin)
[h] CD4 test will be repeated every 2 weeks for 3 consecutive measurements for values <500 cells/µL
[i] HIV-1 RNA test will be repeated every 2 weeks for 3 consecutive measurements for values >100,000 copies/mL
[j] Perform if not previously tested
[k] May be performed up to 4 weeks prior to the first SB-728mR-T infusion (Day 0).
[l] Research blood may be drawn on day of and prior to CTX infusion.
[m] HIV-1 Coreceptor Tropism and Resistance testing will be performed once if HIV RNA exceeds 1,000

# APPENDIX I: SCHEDULE OF EVENTS – COHORT 2

| | Study Period | | | | | | | | | | | | | | | | | | | | | | | | LTFU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | Screen | Pre-Leukapheresis (1 wk prior to leukapheresis) | Leukapheresis[a] | Baseline for Research Blood (between Leuk & CTX) | Baseline (~1 wk prior to CTX) | Day -2 CTX | Day 0 SB-728mR-T Infusion #1 | Day 1 1 day post infusion | Wk 1 (+/- 2d) | Wk 2 (+/- 1d) SB-728mR-T Infusion #2 | Day 15 1 day post infusion | Wk 3 (+/- 2d) | Wk 4 (+/- 1d) SB-728mR-T Infusion #3 | Day 29 1 day post infusion | Wk 5 (+/- 2d) | Wk 6 (+/- 3d) | Wk 7 (+/- 2d) | Wk 8 ------ **Start TI** (+/- 3d) | Wk 10 (+/- 3d) | Wk 12 (+/- 3d) | Wk 14 (+/- 3d) | Wk 16 (+/- 3) | Wk 20 (+/- 7d) | Wk 24 ------ **Evaluate TI** (+/- 7d) | M7, M9, M12 (+/- 7d) | M18 and M24 (+/- 1m) and M36 (=/- 3m) |
| Inclusion Exclusion / Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Physical Exam | X | | | | | | | | | | | | | | | | | | | | | | | X M12 only | X M24 and M36 only |
| Vital Signs[b] | X | | | | X | X | X | | | X | | | X | | | | | X | | | | | | X | X M12 only | X M24 and M36 only |
| 12-lead ECG | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Leukapheresis | | | X | | | | | | | | | | | | | | | | | | | | | | |
| CTX Administration | | | | | | X[c] | | | | | | | | | | | | | | | | | | | |
| SB-728mR-T infusion | | | | | | | X[d] | | | X[d] | | | X[d] | | | | | | | | | | | | |
| Adverse events[e] | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[e] |
| Concomitant medications | X | | | | X | X | X | | X | X | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X M24 and M36 only |
| Hepatitis B and C | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Pregnancy Test[f] | X | | | | X | | X | | | X | | | X | | | | | | | | | | | | |
| Chemistry | X | X[g] | | | X | X | X | | X | | | X | | | X | | | X | | X | | | | X | X | X |
| CBC | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | | | | X | X | X | X | X | | | | X | | | | | | | | | | | | X M7 and M12 only | |
| CD4+ T-cell counts | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] | X[h] | X | X |
| HIV-1 RNA (Viral Load) | X | | | | X | | | | X | X | | X | X | | X | X | X | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X | X |
| CCR5 SNP CEL-1 assay | X[j] | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pentamer | | | | | X[k] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| SB-728mR-T Immunogenicity | | | | | X[k] | | | | | | | | | | | | | | | X | | | | | X M 7 & 12 only | |
| HIV-1 Tropism and/or Resistance test | X[j] | | | | | | | | | | | | | | | | | X[m] | | | | | | | | |
| Research Blood | X | | | X | X[l] | | X | X | | X | | | | | | | | X | | | X | | | X | X | |
| Upon request of sponsor: Additional 80 mL research blood collection, CBC with differential, and CD4+ T-cell Count: One to 2 times during the study. If subject agrees to participate in the optional leukapheresis procedure, this additional blood collection will not be performed. | | | | | | | | | | | | | | | | | | | | | | | | | |

[a] If second leukapheresis is required, it must be > 3 weeks after the first leukapheresis.
[b] Screen, Wk 8, Wk 24, and M12 (temp, pulse, BP and weight); Baseline (ht and wt); CTX, Day 0 , Wk 2 and Wk 4 (temp, pulse, BP)
[c] Administered CTX 2 days prior to the first SB-728mR-T infusion. Refer to Protocol Sections 6.5.1 and 8.2 and the Study Reference Manual for further details
[d] Refer to Protocol Sections 6.5.2 and 8.1 and the Study Reference Manual for further details
[e] Refer to Protocol Section 12 for reporting of Clinical Conditions and SAEs in LTFU
[f] Serum pregnancy test at Screen and urine pregnancy tests at Baseline and prior to SB-728mR-T infusions on Day 0, Wk 2, and Wk 4
[g] Electrolytes (Na, K, $CO_2$, Cl), calcium, liver function tests (albumin, total protein, alkaline phosphatase, AST, ALT, total bilirubin)
[h] CD4 test will be repeated every 2 weeks for 3 consecutive measurements for values <500 cells/µL
[i] HIV-1 RNA test will be repeated every 2 weeks for 3 consecutive measurements for values >100,000 copies/mL
[j] Perform if not previously tested
[k] May be performed up to 4 weeks prior to the first SB-728mR-T infusion (Day 0).
[l] Research blood may be drawn on day of and prior to CTX infusion.
[m] HIV-1 Coreceptor Tropism and Resistance testing will be performed once if HIV RNA exceeds 1,000

# APPENDIX II: DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS

Version 1.0, December, 2004; clarification August 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

This clarification of the DAIDS Table for Grading the Severity of Adult and Pediatric AE's provides additional explanation of the DAIDS AE Grading Table and clarifies some of the parameters.

## I. INSTRUCTIONS AND CLARIFICATIONS

Grading Adult and Pediatric AEs

The DAIDS AE Grading Table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the Table. If there is no distinction in the Table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

> Note: In the classification of adverse events, the term "severe" is not the same as "serious." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "serious" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

Addenda 1-3 Grading Tables for Microbicide Studies

For protocols involving topical application of products to the female genital tract, male genital area or rectum, strong consideration should be given to using Appendices I-III as the primary grading scales for these areas. The protocol would need to specifically state that one or more of the Appendices would be primary (and thus take precedence over the main Grading Table) for items that are listed in both the Appendix and the main Grading Table.

Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - PDF
Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - PDF
Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - PDF

Grade 5

For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

Estimating Severity Grade for Parameters Not Identified in the Table

In order to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on Page 3.

Determining Severity Grade for Parameters "Between Grades"
If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1
Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges
In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local lab LLN.

For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1 – 3.8 mg/dL. A participant's actual lab value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.

## II. DEFINITIONS OF TERMS USED IN THE TABLE:

| | |
|---|---|
| Basic Self-care Functions | Adult<br>Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.<br>Young Children<br>Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement). |
| LLN | Lower limit of normal |
| Medical Intervention | Use of pharmacologic or biologic agent(s) for treatment of an AE. |
| NA | Not Applicable |
| Operative Intervention | Surgical OR other invasive mechanical procedures. |
| ULN | Upper limit of normal |
| Usual Social & Functional Activities | Adult<br>Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.<br>Young Children<br>Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.). |

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| **ESTIMATING SEVERITY GRADE** | | | | |
| Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table | Symptoms causing no or minimal interference with usual social & functional activities | Symptoms causing greater than minimal interference with usual social & functional activities | Symptoms causing inability to perform usual social & functional activities | Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death |
| **SYSTEMIC** | | | | |
| Acute systemic allergic reaction | Localized urticaria (wheals) with no medical intervention indicated | Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated | Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm | Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema |
| Chills | Symptoms causing no or minimal interference with usual social & functional activities | Symptoms causing greater than minimal interference with usual social & functional activities | Symptoms causing inability to perform usual social & functional activities | NA |
| Fatigue<br>Malaise | Symptoms causing no or minimal interference with usual social & functional activities | Symptoms causing greater than minimal interference with usual social & functional activities | Symptoms causing inability to perform usual social & functional activities | Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions |
| Fever (nonaxillary) | 37.7 – 38.6°C | 38.7 – 39.3°C | 39.4 – 40.5°C | > 40.5°C |
| Pain (indicate body site)<br>DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain)<br>See also Headache, Arthralgia, and Myalgia | Pain causing no or minimal interference with usual social & functional activities | Pain causing greater than minimal interference with usual social & functional activities | Pain causing inability to perform usual social & functional activities | Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated |

**Basic Self-care Functions – Adult**: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

**Basic Self-care Functions – Young Children**: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

**Usual Social & Functional Activities – Adult**: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

**Usual Social & Functional Activities – Young Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| Unintentional weight loss | NA | 5 – 9% loss in body weight from baseline | 10 – 19% loss in body weight from baseline | ≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)] |
| **INFECTION** | | | | |
| Infection (any other than HIV infection) | Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities | Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities | Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated | Life-threatening consequences (e.g., septic shock) |
| **INJECTION SITE REACTIONS** | | | | |
| Injection site pain (pain without touching) Or Tenderness (pain when area is touched) | Pain/tenderness causing no or minimal limitation of use of limb | Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities | Pain/tenderness causing inability to perform usual social & functional activities | Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness |
| Injection site reaction (localized) | | | | |
| **Adult > 15 years** | Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 $cm^2$ – 81$cm^2$) | Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 $cm^2$) | Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage | Necrosis (involving dermis and deeper tissue) |
| **Pediatric ≤ 15 years** | Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter | Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh) | Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage | Necrosis (involving dermis and deeper tissue) |

**Basic Self-care Functions – Adult**: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

**Basic Self-care Functions – Young Children**: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

**Usual Social & Functional Activities – Adult**: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

**Usual Social & Functional Activities – Young Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| Pruritis associated with injection<br>See also Skin: Pruritis (itching - no skin lesions) | Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment | Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment | Generalized itching causing inability to perform usual social & functional activities | NA |
| **SKIN – DERMATOLOGICAL** | | | | |
| Alopecia | Thinning detectable by study participant (or by caregiver for young children and disabled adults) | Thinning or patchy hair loss detectable by health care provider | Complete hair loss | NA |
| Cutaneous reaction – rash | Localized macular rash | Diffuse macular, maculopapular, or morbilliform rash OR Target lesions | Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site | Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN) |
| Hyperpigmentation | Slight or localized | Marked or generalized | NA | NA |
| Hypopigmentation | Slight or localized | Marked or generalized | NA | NA |
| Pruritis (itching – no skin lesions)<br>(See also Injection Site Reactions: Pruritis associated with injection) | Itching causing no or minimal interference with usual social & functional activities | Itching causing greater than minimal interference with usual social & functional activities | Itching causing inability to perform usual social & functional activities | NA |
| **CARDIOVASCULAR** | | | | |
| Cardiac arrhythmia (general)<br>(By ECG or physical exam) | Asymptomatic AND No intervention indicated | Asymptomatic AND Non-urgent medical intervention indicated | Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated | Life-threatening arrhythmia OR Urgent intervention indicated |
| Cardiac-ischemia/infarction | NA | NA | Symptomatic ischemia (stable angina) OR Testing consistent with ischemia | Unstable angina OR Acute myocardial infarction |

**Basic Self-care Functions – Adult**: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

**Basic Self-care Functions – Young Children**: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

**Usual Social & Functional Activities – Adult**: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

**Usual Social & Functional Activities – Young Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| Hemorrhage (significant acute blood loss) | NA | Symptomatic AND No transfusion indicated | Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated | Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated |
| Hypertension | | | | |
| **Adult > 17 years** (with repeat testing at same visit) | 140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic | 160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic | **≥** 180 mmHg systolic OR **≥** 110 mmHg diastolic | Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit) |
| **Correction**: in Grade 2 to 160 - 179 from > 160-179 (systolic) and to ≥ 100 -109 from > 100-109 (diastolic) and in Grade 3 to ≥ 180 from > 180 (systolic) and to ≥ 110 from > 110 (diastolic). | | | | |
| **Pediatric ≤ 17 years** (with repeat testing at same visit) | NA | 91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic) | ≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic) | Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit) |
| Hypotension | NA | Symptomatic, corrected with oral fluid replacement | Symptomatic, IV fluids indicated | Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure |
| Pericardial effusion | Asymptomatic, small effusion requiring no intervention | Asymptomatic, moderate or larger effusion requiring no intervention | Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated | Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated |
| Prolonged PR interval | | | | |
| **Adult > 16 years** | PR interval 0.21 – 0.25 sec | PR interval > 0.25 sec | Type II 2nd degree AV block OR Ventricular pause > 3.0 sec | Complete AV block |
| **Pediatric ≤ 16 years** | 1st degree AV block (PR > normal for age and rate) | Type I 2nd degree AV block | Type II 2nd degree AV block | Complete AV block |

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| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| Prolonged QTc | | | | |
| **Adult > 16 years** | Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline | Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline | Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline | Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia |
| **Pediatric ≤ 16 years** | Asymptomatic, QTc interval 0.450 – 0.464 sec | Asymptomatic, QTc interval 0.465 – 0.479 sec | Asymptomatic, QTc interval ≥ 0.480 sec | Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia |
| Thrombosis/embolism | NA | Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure) | Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure) | Embolic event (e.g., pulmonary embolism, life-threatening thrombus) |
| Vasovagal episode (associated with a procedure of any kind) | Present without loss of consciousness | Present with transient loss of consciousness | NA | NA |
| Ventricular dysfunction (congestive heart failure) | NA | Asymptomatic diagnostic finding AND intervention indicated | New onset with symptoms OR Worsening symptomatic congestive heart failure | Life-threatening congestive heart failure |
| **GASTROINTESTINAL** | | | | |
| Anorexia | Loss of appetite without decreased oral intake | Loss of appetite associated with decreased oral intake without significant weight loss | Loss of appetite associated with significant weight loss | Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)] |
| **Comment:** Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment. | | | | |
| Ascites | Asymptomatic | Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis) | Symptomatic despite intervention | Life-threatening consequences |

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**Usual Social & Functional Activities – Adult**: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

**Usual Social & Functional Activities – Young Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| Cholecystitis | NA | Symptomatic AND Medical intervention indicated | Radiologic, endoscopic, or operative intervention indicated | Life-threatening consequences (e.g., sepsis or perforation) |
| Constipation | NA | Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas | Obstipation with manual evacuation indicated | Life-threatening consequences (e.g., obstruction) |
| Diarrhea | | | | |
| **Adult and Pediatric ≥ 1 year** | Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period | Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period | Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated | Life-threatening consequences (e.g., hypotensive shock) |
| **Pediatric < 1 year** | Liquid stools (more unformed than usual) but usual number of stools | Liquid stools with increased number of stools OR Mild dehydration | Liquid stools with moderate dehydration | Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock |
| Dysphagia-Odynophagia | Symptomatic but able to eat usual diet | Symptoms causing altered dietary intake without medical intervention indicated | Symptoms causing severely altered dietary intake with medical intervention indicated | Life-threatening reduction in oral intake |
| Mucositis/stomatitis (clinical exam)<br>Indicate site (e.g., larynx, oral)<br>See Genitourinary for Vulvovaginitis<br>See also Dysphagia-Odynophagia and Proctitis | Erythema of the mucosa | Patchy pseudomembranes or ulcerations | Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma | Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking) |
| Nausea | Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake | Persistent nausea resulting in decreased oral intake for 24 – 48 hours | Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids) | Life-threatening consequences (e.g., hypotensive shock) |

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**Usual Social & Functional Activities – Adult**: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

**Usual Social & Functional Activities – Young Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| Pancreatitis | NA | Symptomatic AND Hospitalization not indicated (other than emergency room visit) | Symptomatic AND Hospitalization indicated (other than emergency room visit) | Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis) |
| Proctitis (functional-symptomatic)<br>Also see Mucositis/stomatitis for clinical exam | Rectal discomfort AND No intervention indicated | Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated | Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated | Life-threatening consequences (e.g., perforation) |
| Vomiting | Transient or intermittent vomiting with no or minimal interference with oral intake | Frequent episodes of vomiting with no or mild dehydration | Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids) | Life-threatening consequences (e.g., hypotensive shock) |
| **NEUROLOGIC** | | | | |
| Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis) | Alteration causing no or minimal interference with usual social & functional activities | Alteration causing greater than minimal interference with usual social & functional activities | Alteration causing inability to perform usual social & functional activities | Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions |
| Altered Mental Status<br>For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder) | Changes causing no or minimal interference with usual social & functional activities | Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities | Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities | Delirium OR obtundation, OR coma |
| Ataxia | Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities | Symptomatic ataxia causing greater than minimal interference with usual social & functional activities | Symptomatic ataxia causing inability to perform usual social & functional activities | Disabling ataxia causing inability to perform basic self-care functions |

**Basic Self-care Functions – Adult**: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

**Basic Self-care Functions – Young Children**: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

**Usual Social & Functional Activities – Adult**: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

**Usual Social & Functional Activities – Young Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder) | Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated | Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated | Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated | Disability causing inability to perform basic self-care functions OR Institutionalization indicated |
| CNS ischemia (acute) | NA | NA | Transient ischemic attack | Cerebral vascular accident (CVA, stroke) with neurological deficit |
| Developmental delay – **Pediatric ≤ 16 years** | Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting | Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting | Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting | Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting |
| Headache | Symptoms causing no or minimal interference with usual social & functional activities | Symptoms causing greater than minimal interference with usual social & functional activities | Symptoms causing inability to perform usual social & functional activities | Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function |
| Insomnia | NA | Difficulty sleeping causing greater than minimal interference with usual social & functional activities | Difficulty sleeping causing inability to perform usual social & functional activities | Disabling insomnia causing inability to perform basic self-care functions |
| Neuromuscular weakness (including myopathy & neuropathy) | Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities | Muscle weakness causing greater than minimal interference with usual social & functional activities | Muscle weakness causing inability to perform usual social & functional activities | Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation |

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**Usual Social & Functional Activities – Adult**: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

**Usual Social & Functional Activities – Young Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| Neurosensory alteration (including paresthesia and painful neuropathy) | Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities | Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities | Sensory alteration or paresthesia causing inability to perform usual social & functional activities | Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions |
| Seizure: (new onset) **– Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder) | NA | 1 seizure | 2 **–** 4 seizures | Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy) |
| Seizure: (known pre-existing seizure disorder) **– Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels. | NA | Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder | Change in seizure character from baseline either in duration or quality (e.g., severity or focality) | Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy) |
| Seizure **– Pediatric < 18 years** | Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state | Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state | Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes | Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation |
| Syncope (not associated with a procedure) | NA | Present | NA | NA |
| Vertigo | Vertigo causing no or minimal interference with usual social & functional activities | Vertigo causing greater than minimal interference with usual social & functional activities | Vertigo causing inability to perform usual social & functional activities | Disabling vertigo causing inability to perform basic self-care functions |

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**Usual Social & Functional Activities – Adult**: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).**

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| **RESPIRATORY** | | | | |
| Bronchospasm (acute) | FEV1 or peak flow reduced to 70 – 80% | FEV1 or peak flow 50 – 69% | FEV1 or peak flow 25 – 49% | Cyanosis OR FEV1 or peak flow < 25% OR Intubation |
| Dyspnea or respiratory distress | | | | |
| **Adult ≥ 14 years** | Dyspnea on exertion with no or minimal interference with usual social & functional activities | Dyspnea on exertion causing greater than minimal interference with usual social & functional activities | Dyspnea at rest causing inability to perform usual social & functional activities | Respiratory failure with ventilatory support indicated |
| **Pediatric < 14 years** | Wheezing OR minimal increase in respiratory rate for age | Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95% | Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90% | Respiratory failure with ventilatory support indicated |
| **MUSCULOSKELETAL** | | | | |
| Arthralgia<br>See also Arthritis | Joint pain causing no or minimal interference with usual social & functional activities | Joint pain causing greater than minimal interference with usual social & functional activities | Joint pain causing inability to perform usual social & functional activities | Disabling joint pain causing inability to perform basic self-care functions |
| Arthritis<br>See also Arthralgia | Stiffness or joint swelling causing no or minimal interference with usual social & functional activities | Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities | Stiffness or joint swelling causing inability to perform usual social & functional activities | Disabling joint stiffness or swelling causing inability to perform basic self-care functions |
| Bone Mineral Loss | | | | |
| **Adult ≥ 21 years** | BMD t-score -2.5 to -1.0 | BMD t-score < -2.5 | Pathological fracture (including loss of vertebral height) | Pathologic fracture causing life-threatening consequences |
| **Pediatric < 21 years** | BMD z-score -2.5 to -1.0 | BMD z-score < -2.5 | Pathological fracture (including loss of vertebral height) | Pathologic fracture causing life-threatening consequences |
| Myalgia (non-injection site) | Muscle pain causing no or minimal interference with usual social & functional activities | Muscle pain causing greater than minimal interference with usual social & functional activities | Muscle pain causing inability to perform usual social & functional activities | Disabling muscle pain causing inability to perform basic self-care functions |

**Basic Self-care Functions – Adult**: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

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| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| Osteonecrosis | NA | Asymptomatic with radiographic findings AND No operative intervention indicated | Symptomatic bone pain with radiographic findings OR Operative intervention indicated | Disabling bone pain with radiographic findings causing inability to perform basic self-care functions |
| **GENITOURINARY** | | | | |
| Cervicitis (symptoms)<br>(For use in studies evaluating topical study agents)<br>For other cervicitis see Infection: Infection (any other than HIV infection) | Symptoms causing no or minimal interference with usual social & functional activities | Symptoms causing greater than minimal interference with usual social & functional activities | Symptoms causing inability to perform usual social & functional activities | Symptoms causing inability to perform basic self-care functions |
| Cervicitis (clinical exam)<br>(For use in studies evaluating topical study agents)<br>For other cervicitis see Infection: Infection (any other than HIV infection) | Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface | Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface | Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface | Epithelial disruption > 75% total surface |
| Inter-menstrual bleeding (IMB) | Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination | Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle | Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle | Hemorrhage with life-threatening hypotension OR Operative intervention indicated |
| Urinary tract obstruction (e.g., stone) | NA | Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction | Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction | Obstruction causing life-threatening consequences |

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| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| Vulvovaginitis (symptoms)<br>(Use in studies evaluating topical study agents)<br>For other vulvovaginitis see Infection: Infection (any other than HIV infection) | Symptoms causing no or minimal interference with usual social & functional activities | Symptoms causing greater than minimal interference with usual social & functional activities | Symptoms causing inability to perform usual social & functional activities | Symptoms causing inability to perform basic self-care functions |
| Vulvovaginitis (clinical exam)<br>(Use in studies evaluating topical study agents)<br>For other vulvovaginitis see Infection: Infection (any other than HIV infection) | Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface | Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface | Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface | Vaginal perforation OR Epithelial disruption > 75% total surface |
| **OCULAR/VISUAL** | | | | |
| Uveitis | Asymptomatic but detectable on exam | Symptomatic anterior uveitis OR Medical intervention indicated | Posterior or pan-uveitis OR Operative intervention indicated | Disabling visual loss in affected eye(s) |
| Visual changes (from baseline) | Visual changes causing no or minimal interference with usual social & functional activities | Visual changes causing greater than minimal interference with usual social & functional activities | Visual changes causing inability to perform usual social & functional activities | Disabling visual loss in affected eye(s) |
| **ENDOCRINE/METABOLIC** | | | | |
| Abnormal fat accumulation (e.g., back of neck, breasts, abdomen) | Detectable by study participant (or by caregiver for young children and disabled adults) | Detectable on physical exam by health care provider | Disfiguring OR Obvious changes on casual visual inspection | NA |
| Diabetes mellitus | NA | New onset without need to initiate medication OR Modification of current medications to regain glucose control | New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification | Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma) |

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**Usual Social & Functional Activities – Adult**: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

**Usual Social & Functional Activities – Young Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| Gynecomastia | Detectable by study participant or caregiver (for young children and disabled adults) | Detectable on physical exam by health care provider | Disfiguring OR Obvious on casual visual inspection | NA |
| Hyperthyroidism | Asymptomatic | Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated | Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification | Life-threatening consequences (e.g., thyroid storm) |

**Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

| | | | | |
|---|---|---|---|---|
| Hypothyroidism | Asymptomatic | Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated | Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification | Life-threatening consequences (e.g., myxedema coma) |
| Lipoatrophy (e.g., fat loss from the face, extremities, buttocks) | Detectable by study participant (or by caregiver for young children and disabled adults) | Detectable on physical exam by health care provider | Disfiguring OR Obvious on casual visual inspection | NA |

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**Usual Social & Functional Activities – Young Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

| LABORATORY | | | | |
|---|---|---|---|---|
| **PARAMETER** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| **HEMATOLOGY** | ***Standard International Units are listed in italics*** | | | |
| Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY) | 300 – 400/$mm^3$<br>*300 – 400/µL* | 200 – 299/$mm^3$<br>*200 – 299/µL* | 100 – 199/$mm^3$<br>*100 – 199/µL* | < 100/$mm^3$<br>*< 100/µL* |
| Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY) | 600 – 650/$mm^3$<br>*0.600 x $10^9$ – 0.650 x $10^9$/L* | 500 – 599/$mm^3$<br>*0.500 x $10^9$ – 0.599 x $10^9$/L* | 350 – 499/$mm^3$<br>*0.350 x $10^9$ – 0.499 x $10^9$/L* | < 350/$mm^3$<br>*< 0.350 x $10^9$/L* |
| **Comment:** Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable. | | | | |
| Absolute neutrophil count (ANC) | | | | |
| **Adult and Pediatric, > 7 days** | 1,000 – 1,300/$mm^3$<br>*1.000 x $10^9$ – 1.300 x $10^9$/L* | 750 – 999/$mm^3$<br>*0.750 x $10^9$ – 0.999 x $10^9$/L* | 500 – 749/$mm^3$<br>*0.500 x $10^9$ – 0.749 x $10^9$/L* | < 500/$mm^3$<br>*< 0.500 x $10^9$/L* |
| **Infant*†, 2 – ≤ 7 days** | 1,250 – 1,500/$mm^3$<br>*1.250 x $10^9$ – 1.500 x $10^9$/L* | 1,000 – 1,249/$mm^3$<br>*1.000 x $10^9$ – 1.249 x $10^9$/L* | 750 – 999/$mm^3$<br>*0.750 x $10^9$ – 0.999 x $10^9$/L* | < 750/$mm^3$<br>*< 0.750 x $10^9$/L* |
| **Infant*†, ≤1 day** | 4,000 – 5,000/$mm^3$<br>*4.000 x $10^9$ – 5.000 x $10^9$/L* | 3,000 – 3,999/$mm^3$<br>*3.000 x $10^9$ – 3.999 x$10^9$/L* | 1,500 – 2,999/$mm^3$<br>*1.500 x $10^9$ – 2.999 x $10^9$/L* | < 1,500/$mm^3$<br>*< 1.500 x $10^9$/L* |
| **Comment:** Parameter changed from "Infant, < 1 day" to "Infant, ≤1 day" | | | | |
| Fibrinogen, decreased | 100 – 200 mg/dL<br>*1.00 – 2.00 g/L*<br>OR<br>0.75 – 0.99 x LLN | 75 – 99 mg/dL<br>*0.75 – 0.99 g/L*<br>OR<br>0.50 – 0.74 x LLN | 50 – 74 mg/dL<br>*0.50 – 0.74 g/L*<br>OR<br>0.25 – 0.49 x LLN | < 50 mg/dL<br>*< 0.50 g/L*<br>OR<br>< 0.25 x LLN<br>OR<br>Associated with gross bleeding |

* Values are for term infants. Preterm infants should be assessed using local normal ranges.
† Use age and sex appropriate values (e.g., bilirubin).

| LABORATORY | | | | |
|---|---|---|---|---|
| **PARAMETER** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| Hemoglobin (Hgb) | | | | |
| Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab. | | | | |
| **Adult and Pediatric ≥ 57 days** (HIV POSITIVE ONLY) | 8.5 – 10.0 g/dL<br>*5.24 – 6.23 mmol/L* | 7.5 – 8.4 g/dL<br>*4.62–5.23 mmol/L* | 6.50 – 7.4 g/dL<br>*4.03–4.61 mmol/L* | < 6.5 g/dL<br>*< 4.03 mmol/L* |
| **Adult and Pediatric ≥ 57 days** (HIV NEGATIVE ONLY) | 10.0 – 10.9 g/dL<br>*6.18* – 6.79 *mmol/L*<br>OR<br>Any decrease<br>2.5 – 3.4 g/dL<br>*1.58 – 2.13 mmol/L* | 9.0 – 9.9 g/dL<br>*5.55 - 6.17 mmol/L*<br>OR<br>Any decrease<br>3.5 – 4.4 g/dL<br>*2.14 – 2.78 mmol/L* | 7.0 – 8.9 g/dL<br>*4.34 - 5.54 mmol/L*<br>OR<br>Any decrease<br>≥ 4.5 g/dL<br>*> 2.79 mmol/L* | < 7.0 g/dL<br>*< 4.34 mmol/L* |
| **Comment:** The decrease is a decrease from baseline | | | | |
| **Infant*†, 36 – 56 days** (HIV POSITIVE OR NEGATIVE) | 8.5 – 9.4 g/dL<br>*5.24 – 5.86 mmol/L* | 7.0 – 8.4 g/dL<br>*4.31 – 5.23 mmol/L* | 6.0 – 6.9 g/dL<br>*3.72 – 4.30 mmol/L* | < 6.00 g/dL<br>*< 3.72 mmol/L* |
| **Infant*†, 22 – 35 days** (HIV POSITIVE OR NEGATIVE) | 9.5 – 10.5 g/dL<br>*5.87 - 6.54 mmol/L* | 8.0 – 9.4 g/dL<br>*4.93 – 5.86 mmol/L* | 7.0 – 7.9 g/dL<br>*4.34 – 4.92 mmol/L* | < 7.00 g/dL<br>*< 4.34 mmol/L* |
| **Infant*†, ≤ 21 days** (HIV POSITIVE OR NEGATIVE) | 12.0 – 13.0 g/dL<br>*7.42 – 8.09 mmol/L* | 10.0 – 11.9 g/dL<br>*6.18 – 7.41 mmol/L* | 9.0 – 9.9 g/dL<br>*5.59- 6.17 mmol/L* | < 9.0 g/dL<br>*< 5.59 mmol/L* |
| **Correction**: Parameter changed from "Infant < 21 days" to "Infant ≤ 21 days" | | | | |
| International Normalized Ratio of prothrombin time (INR) | 1.1 – 1.5 x ULN | 1.6 – 2.0 x ULN | 2.1 – 3.0 x ULN | > 3.0 x ULN |
| Methemoglobin | 5.0 – 10.0% | 10.1 – 15.0% | 15.1 – 20.0% | > 20.0% |
| Prothrombin Time (PT) | 1.1 – 1.25 x ULN | 1.26 – 1.50 x ULN | 1.51 – 3.00 x ULN | > 3.00 x ULN |
| Partial Thromboplastin Time (PTT) | 1.1 – 1.66 x ULN | 1.67 – 2.33 x ULN | 2.34 – 3.00 x ULN | > 3.00 x ULN |
| Platelets, decreased | 100,000 – 124,999/$mm^3$<br>*100.000 x $10^9$ – 124.999 x $10^9$/L* | 50,000 – 99,999/$mm^3$<br>*50.000 x $10^9$ – 99.999 x $10^9$/L* | 25,000 – 49,999/$mm^3$<br>*25.000 x $10^9$ – 49.999 x $10^9$/L* | < 25,000/$mm^3$<br>*< 25.000 x $10^9$/L* |
| WBC, decreased | 2,000 – 2,500/$mm^3$<br>*2.000 x $10^9$ – 2.500 x $10^9$/L* | 1,500 – 1,999/$mm^3$<br>*1.500 x $10^9$ – 1.999 x $10^9$/L* | 1,000 – 1,499/$mm^3$<br>*1.000 x $10^9$ – 1.499 x $10^9$/L* | < 1,000/$mm^3$<br>*< 1.000 x $10^9$/L* |

* Values are for term infants. Preterm infants should be assessed using local normal ranges.
† Use age and sex appropriate values (e.g., bilirubin).

| LABORATORY | | | | |
|---|---|---|---|---|
| **PARAMETER** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| **CHEMISTRIES** | ***Standard International Units are listed in italics*** | | | |
| Acidosis | NA | pH < normal, but ≥ 7.3 | pH < 7.3 without life-threatening consequences | pH < 7.3 with life-threatening consequences |
| Albumin, serum, low | 3.0 g/dL – < LLN<br>*30 g/L – < LLN* | 2.0 – 2.9 g/dL<br>*20 – 29 g/L* | < 2.0 g/dL<br>*< 20 g/L* | NA |
| Alkaline Phosphatase | 1.25 – 2.5 x ULN† | 2.6 – 5.0 x ULN† | 5.1 – 10.0 x ULN† | > 10.0 x ULN† |
| Alkalosis | NA | pH > normal, but ≤ 7.5 | pH > 7.5 without life-threatening consequences | pH > 7.5 with life-threatening consequences |
| ALT (SGPT) | 1.25 – 2.5 x ULN | 2.6 – 5.0 x ULN | 5.1 – 10.0 x ULN | > 10.0 x ULN |
| AST (SGOT) | 1.25 – 2.5 x ULN | 2.6 – 5.0 x ULN | 5.1 – 10.0 x ULN | > 10.0 x ULN |
| Bicarbonate, serum, low | 16.0 mEq/L – < LLN<br>*16.0 mmol/L – < LLN* | 11.0 – 15.9 mEq/L<br>*11.0 – 15.9 mmol/L* | 8.0 – 10.9 mEq/L<br>*8.0 – 10.9 mmol/L* | < 8.0 mEq/L<br>*< 8.0 mmol/L* |
| **Comment:** Some laboratories will report this value as Bicarbonate ($HCO_3$) and others as Total Carbon Dioxide ($CO_2$). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above. | | | | |
| Bilirubin (Total) | | | | |
| **Adult and Pediatric > 14 days** | 1.1 – 1.5 x ULN | 1.6 – 2.5 x ULN | 2.6 – 5.0 x ULN | > 5.0 x ULN |
| **Infant*†, ≤ 14 days** (non-hemolytic) | NA | 20.0 – 25.0 mg/dL<br>*342 – 428 µmol/L* | 25.1 – 30.0 mg/dL<br>*429 – 513 µmol/L* | > 30.0 mg/dL<br>*> 513.0 µmol/L* |
| **Infant*†, ≤ 14 days** (hemolytic) | NA | NA | 20.0 – 25.0 mg/dL<br>*342 – 428 µmol/L* | > 25.0 mg/dL<br>*> 428 µmol/L* |
| Calcium, serum, high | | | | |
| **Adult and Pediatric ≥ 7 days** | 10.6 – 11.5 mg/dL<br>*2.65 – 2.88 mmol/L* | 11.6 – 12.5 mg/dL<br>*2.89 – 3.13 mmol/L* | 12.6 – 13.5 mg/dL<br>*3.14 – 3.38 mmol/L* | > 13.5 mg/dL<br>*> 3.38 mmol/L* |
| **Infant*†, < 7 days** | 11.5 – 12.4 mg/dL<br>*2.88 – 3.10 mmol/L* | 12.5 – 12.9 mg/dL<br>*3.11 – 3.23 mmol/L* | 13.0 – 13.5 mg/dL<br>*3.245 – 3.38 mmol/L* | > 13.5 mg/dL<br>*> 3.38 mmol/L* |
| Calcium, serum, low | | | | |
| **Adult and Pediatric ≥ 7 days** | 7.8 – 8.4 mg/dL<br>*1.95 – 2.10 mmol/L* | 7.0 – 7.7 mg/dL<br>*1.75 – 1.94 mmol/L* | 6.1 – 6.9 mg/dL<br>*1.53 – 1.74 mmol/L* | < 6.1 mg/dL<br>*< 1.53 mmol/L* |
| **Infant*†, < 7 days** | 6.5 – 7.5 mg/dL<br>*1.63 – 1.88 mmol/L* | 6.0 – 6.4 mg/dL<br>*1.50 – 1.62 mmol/L* | 5.50 – 5.90 mg/dL<br>*1.38 – 1.51 mmol/L* | < 5.50 mg/dL<br>*< 1.38 mmol/L* |
| **Comment:** Do not adjust Calcium, serum, low or Calcium, serum, high for albumin | | | | |

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

| LABORATORY | | | | |
|---|---|---|---|---|
| **PARAMETER** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| Cardiac troponin I (cTnI) | NA | NA | NA | Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer |
| **Adult ≥ 18 years** | 200 – 239 mg/dL<br>*5.18 – 6.19 mmol/L* | 240 – 300 mg/dL<br>*6.20 – 7.77 mmol/L* | > 300 mg/dL<br>*> 7.77 mmol/L* | NA |
| **Pediatric < 18 years** | 170 – 199 mg/dL<br>*4.40 – 5.15 mmol/L* | 200 – 300 mg/dL<br>*5.16 – 7.77 mmol/L* | > 300 mg/dL<br>*> 7.77 mmol/L* | NA |
| Creatine Kinase | 3.0 – 5.9 x ULN† | 6.0 – 9.9 x ULN† | 10.0 – 19.9 x ULN† | ≥ 20.0 x ULN† |
| Creatinine | 1.1 – 1.3 x ULN† | 1.4 – 1.8 x ULN† | 1.9 – 3.4 x ULN† | ≥ 3.5 x ULN† |

| LABORATORY | | | | |
|---|---|---|---|---|
| **PARAMETER** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| Glucose, serum, high | | | | |
| Nonfasting | 116 – 160 mg/dL<br>*6.44 – 8.88 mmol/L* | 161 – 250 mg/dL<br>*8.89 – 13.88 mmol/L* | 251 – 500 mg/dL<br>*13.89 – 27.75 mmol/L* | > 500 mg/dL<br>*> 27.75 mmol/L* |
| Fasting | 110 – 125 mg/dL<br>*6.11 – 6.94 mmol/L* | 126 – 250 mg/dL<br>*6.95 – 13.88 mmol/L* | 251 – 500 mg/dL<br>*13.89 – 27.75 mmol/L* | > 500 mg/dL<br>*> 27.75 mmol/L* |
| **Adult and Pediatric ≥ 1 month** | 55 – 64 mg/dL<br>*3.05 – 3.55 mmol/L* | 40 – 54 mg/dL<br>*2.22 – 3.06 mmol/L* | 30 – 39 mg/dL<br>*1.67 – 2.23 mmol/L* | < 30 mg/dL<br>*< 1.67 mmol/L* |
| **Infant*†, < 1 month** | 50 – 54 mg/dL<br>*2.78 – 3.00 mmol/L* | 40 – 49 mg/dL<br>*2.22 – 2.77 mmol/L* | 30 – 39 mg/dL<br>*1.67 – 2.21 mmol/L* | < 30 mg/dL<br>*< 1.67 mmol/L* |
| Lactate | ULN - < 2.0 x ULN without acidosis | ≥ 2.0 x ULN without acidosis | Increased lactate with pH < 7.3 without life-threatening consequences | Increased lactate with pH < 7.3 with life-threatening consequences |
| **Comment:** Added ULN to Grade 1 parameter | | | | |
| LDL cholesterol (fasting) | | | | |
| **Adult ≥ 18 years** | 130 – 159 mg/dL<br>*3.37 – 4.12 mmol/L* | 160 – 190 mg/dL<br>*4.13 – 4.90 mmol/L* | ≥ 190 mg/dL<br>*≥ 4.91 mmol/L* | NA |
| **Pediatric > 2 - < 18 years** | 110 – 129 mg/dL<br>*2.85 – 3.34 mmol/L* | 130 – 189 mg/dL<br>*3.35 – 4.90 mmol/L* | ≥ 190 mg/dL<br>*≥ 4.91 mmol/L* | NA |
| Lipase | 1.1 – 1.5 x ULN | 1.6 – 3.0 x ULN | 3.1 – 5.0 x ULN | > 5.0 x ULN |
| Magnesium, serum, low | 1.2 – 1.4 mEq/L<br>*0.60 – 0.70 mmol/L* | 0.9 – 1.1 mEq/L<br>*0.45 – 0.59 mmol/L* | 0.6 – 0.8 mEq/L<br>*0.30 – 0.44 mmol/L* | < 0.60 mEq/L<br>*< 0.30 mmol/L* |

* Values are for term infants. Preterm infants should be assessed using local normal ranges.

† Use age and sex appropriate values (e.g., bilirubin).

| LABORATORY | | | | |
|---|---|---|---|---|
| **PARAMETER** | **GRADE 1 MILD** | **GRADE 2 MODERATE** | **GRADE 3 SEVERE** | **GRADE 4 POTENTIALLY LIFE-THREATENING** |
| Pancreatic amylase | 1.1 – 1.5 x ULN | 1.6 – 2.0 x ULN | 2.1 – 5.0 x ULN | > 5.0 x ULN |
| Phosphate, serum, low | | | | |
| **Adult and Pediatric > 14 years** | 2.5 mg/dL – < LLN<br>*0.81 mmol/L – < LLN* | 2.0 – 2.4 mg/dL<br>*0.65 – 0.80 mmol/L* | 1.0 – 1.9 mg/dL<br>*0.32 – 0.64 mmol/L* | < 1.00 mg/dL<br>*< 0.32 mmol/L* |
| **Pediatric 1 year – 14 years** | 3.0 – 3.5 mg/dL<br>*0.97 – 1.13 mmol/L* | 2.5 – 2.9 mg/dL<br>*0.81 – 0.96 mmol/L* | 1.5 – 2.4 mg/dL<br>*0.48 – 0.80 mmol/L* | < 1.50 mg/dL<br>*< 0.48 mmol/L* |
| **Pediatric < 1 year** | 3.5 – 4.5 mg/dL<br>*1.13 – 1.45 mmol/L* | 2.5 – 3.4 mg/dL<br>*0.81 – 1.12 mmol/L* | 1.5 – 2.4 mg/dL<br>*0.48 – 0.80 mmol/L* | < 1.50 mg/dL<br>*< 0.48 mmol/L* |
| Potassium, serum, high | 5.6 – 6.0 mEq/L<br>*5.6 – 6.0 mmol/L* | 6.1 – 6.5 mEq/L<br>*6.1 – 6.5 mmol/L* | 6.6 – 7.0 mEq/L<br>*6.6 – 7.0 mmol/L* | > 7.0 mEq/L<br>*> 7.0 mmol/L* |
| Potassium, serum, low | 3.0 – 3.4 mEq/L<br>*3.0 – 3.4 mmol/L* | 2.5 – 2.9 mEq/L<br>*2.5 – 2.9 mmol/L* | 2.0 – 2.4 mEq/L<br>*2.0 – 2.4 mmol/L* | < 2.0 mEq/L<br>*< 2.0 mmol/L* |
| Sodium, serum, high | 146 – 150 mEq/L<br>*146 – 150 mmol/L* | 151 – 154 mEq/L<br>*151 – 154 mmol/L* | 155 – 159 mEq/L<br>*155 – 159 mmol/L* | ≥ 160 mEq/L<br>*≥ 160 mmol/L* |
| Sodium, serum, low | 130 – 135 mEq/L<br>*130 – 135 mmol/L* | 125 – 129 mEq/L<br>*125 – 129 mmol/L* | 121 – 124 mEq/L<br>*121 – 124 mmol/L* | ≤ 120 mEq/L<br>*≤ 120 mmol/L* |
| Triglycerides (fasting) | NA | 500 – 750 mg/dL<br>*5.65 – 8.48 mmol/L* | 751 – 1,200 mg/dL<br>*8.49 – 13.56 mmol/L* | > 1,200 mg/dL<br>*> 13.56 mmol/L* |
| Uric acid | 7.5 – 10.0 mg/dL<br>*0.45 – 0.59 mmol/L* | 10.1 – 12.0 mg/dL<br>*0.60 – 0.71 mmol/L* | 12.1 – 15.0 mg/dL<br>*0.72 – 0.89 mmol/L* | > 15.0 mg/dL<br>*> 0.89 mmol/L* |
| **URINALYSIS** | ***Standard International Units are listed in italics*** | | | |
| Hematuria (microscopic) | 6 – 10 RBC/HPF | > 10 RBC/HPF | Gross, with or without clots OR with RBC casts | Transfusion indicated |
| Proteinuria, random collection | 1 + | 2 – 3 + | 4 + | NA |
| Proteinuria, 24 hour collection | | | | |
| **Adult and Pediatric ≥ 10 years** | 200 – 999 mg/24 h<br>*0.200 – 0.999 g/d* | 1,000 – 1,999 mg/24 h<br>*1.000 – 1.999 g/d* | 2,000 – 3,500 mg/24 h<br>*2.000 – 3.500 g/d* | > 3,500 mg/24 h<br>*> 3.500 g/d* |
| **Pediatric > 3 mo - < 10 years** | 201 – 499 mg/$m^2$/24 h<br>*0.201 – 0.499 g/d* | 500 – 799 mg/$m^2$/24 h<br>*0.500 – 0.799 g/d* | 800 – 1,000 mg/$m^2$/24 h<br>*0.800 – 1.000 g/d* | > 1,000 mg/ $m^2$/24 h<br>*> 1.000 g/d* |

[*] Values are for term infants. Preterm infants should be assessed using local normal ranges.
[†] Use age and sex appropriate values (e.g., bilirubin).