Clinical Study Protocol

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

Protocol Number: SB-728-1101

BB-IND: 14129

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Confidentiality Statement

Sangamo BioSciences, Inc.

Clinical Approval Signature Page

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Amendment 9: **January 30, 2014**

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1/30/14
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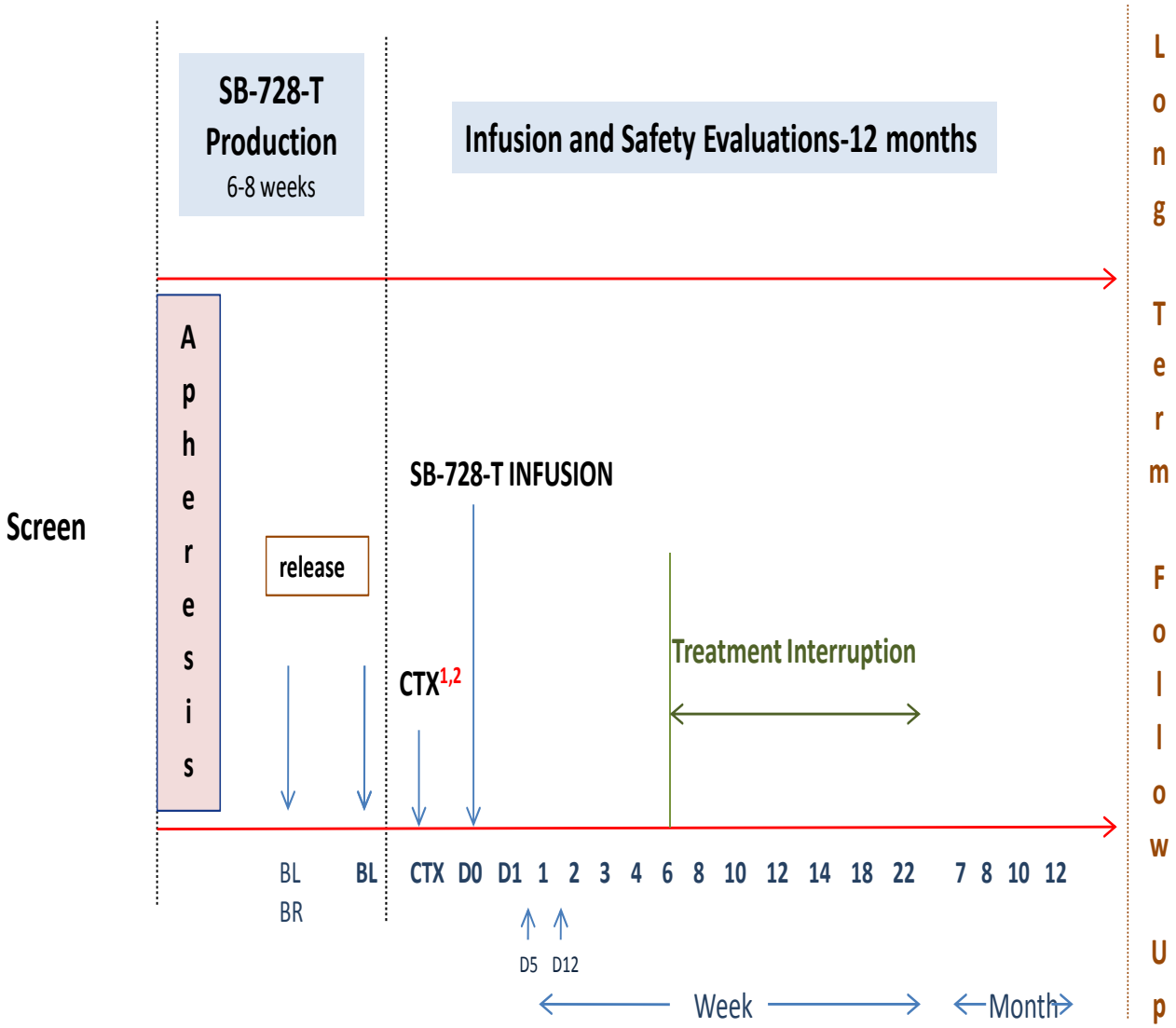
Protocol SB-728-1101 Synopsis

Title	A Phase I, Open-Label Study to Assess the Effect of Escalating Doses of Cyclophosphamide on the Engraftment of SB-728-T in Aviremic HIV-Infected Subjects on HAART
Sponsor	Sangamo BioSciences, Inc.
Investigational Products	SB-728-T (Autologous CD4+ T-cells genetically modified at the CCR5 gene by Zinc Finger Nucleases SB-728).
Objectives	**Primary:** To evaluate the safety and tolerability of escalating doses of cyclophosphamide administered up to 3 days prior to SB-728-T infusion. **Secondary:** 1. Evaluate the effect of escalating doses of cyclophosphamide on SB-728-T engraftment 2. Evaluate the effect of SB-728-T on plasma HIV-1 RNA levels following HAART interruption 3. Evaluate long-term persistence of SB-728-T in peripheral blood as measured by pentamer PCR 4. Evaluate change in CD4+ T-cell counts in peripheral blood after treatment with SB-728-T 5. Evaluate the change in HIV reservoirs as part of exploratory research
Study Population	Up to 40 aviremic HIV-infected subjects on stable HAART may be enrolled and treated in 5 dose cohorts.
Main Inclusion Criteria	HIV diagnosed men and women $\geq$ 18 years of age on HAART with undetectable viral loads for the preceding 3 months and peripheral blood CD4+ T-cell counts $\geq$500 cells/µL at screening.
Study Design	Phase 1, open-label, dose escalation, multi-center study.
Treatment Plan	Up to 40 subjects will be enrolled and treated in one of five treatment cohorts: Cohort 1: Intravenous cyclophosphamide 200 mg Cohort 2: Intravenous cyclophosphamide 0.5 g/m^2 Cohort 3: Intravenous cyclophosphamide 1.0 g/m^2 Cohort 4: Intravenous cyclophosphamide 2.0 g/m^2 Cohort 5: Intravenous cyclophosphamide 1.5 g/m^2 Within each cohort, treatment will be staggered so that each subsequent subject cannot be infused with cyclophosphamide until at least 2 weeks after the preceding subject. Up to 3 days after receiving cyclophosphamide, subjects will be infused with 0.5 to 4.0 x 10^{10} SB-728-T cells. A Safety Monitoring Committee will determine if it is safe to dose escalate prior to treatment of subsequent cohorts. If one subject within a cohort develops a dose limiting toxicity (DLT) defined

	as a Grade 3 non-hematological adverse event (AE) excluding alopecia or Grade 4 hematological AE related to cyclophosphamide, 3 additional subjects will be enrolled and treated in that cohort. If no DLT develops in 3 subjects in Cohort 5 (1.5 g/m^2), additional subjects may be enrolled into that cohort. Upon evaluation of data from Cohort 5 (1.5 g/m^2), the sponsor may elect to enroll additional subjects into Cohort 3 (1.0 g/m^2). Subjects with aviremia and CD4 cell counts ≥500 cells/μL will have their anti-retroviral treatment stopped 6 weeks after SB-728-T infusion. HAART will be discontinued for a period of at least 16 weeks. During the 16-week treatment interruption, 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. At the end of the 16-week treatment interruption: • 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 (subjects with HIV RNA levels below limit of detection will remain off HAART). During extended TI, 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
Study Duration	The duration of study participation will be approximately 15 months for each subject divided into approximately 3 months for screening, leukapheresis, and SB-728-T production, and 12 months for treatment and study follow-up.
Sample Size and Analyses	This is a phase 1 study in which three to six evaluable subjects in each cohort will be treated to evaluate safety of each cyclophosphamide dose level. A cohort can be expanded if there is no DLT in the first 3 subjects treated or no more than 1 DLT in 6 subjects treated in that cohort. The primary focus of this study is to evaluate the safety of escalating doses of cyclophosphamide administered prior to the SB-728-T infusion. As such, if no adverse events are observed in a group of three evaluable subjects, we can be 95% confident that the true adverse event rate is less than 70%. Expansion of each cohort to 6 subjects will decrease the rate to 46%.There will be limited statistical power to

	evaluate efficacy and related biological endpoints. Therefore, analyses will be primarily descriptive and exploratory in nature.

Schema of the Study Visits



[1]Cohort 1: IV cyclophosphamide 200 mg
Cohort 2: IV cyclophosphamide 0.5 g/m^2
Cohort 3: IV cyclophosphamide 1.0 g/m^2
Cohort 4: IV cyclophosphamide 2.0 g/m^2
Cohort 5: IV cyclophosphamide 1.5 g/m^2

[2] Administer CTX up to 3 days prior to Day 0.
Enrollment of cohorts will be sequential.

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
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
ELISA	enzyme linked immunoassay
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
INR	immunologic nonresponders
IR	immunologic responders
IV	intravenous
IRB	institutional review board
NCI	National Cancer Institute
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
RCA	replication-competent adenovirus
RNA	ribonucleic acid
RNAi	RNA interference
SAE	serious adverse event
SB-728-T	SB-728 modified CD4+ T-cells
SMC	Safety Monitoring Committee
TI	Treatment Interruption
TIL	tumor infiltrating lymphocytes
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 this therapy 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 CD4+ T-cells *ex vivo* at the CCR5 gene by zinc finger nucleases (ZFN) encoded by SB-728 in a replication deficient adenoviral vector. Since CCR5 is an important co-receptor for HIV entry, it is hypothesized that disruption of CCR5 in CD4+ T-cells with zinc finger nucleases will offer a survival advantage to these cells.

SB-728-T is the name of the experimental agent that has been administered to subjects infected with HIV. SB-728-T consists of autologous enriched CD4+ T-cells that have been transduced *ex vivo* with SB-728 resulting in modification of the CCR5 gene. SB-728 is a replication deficient recombinant Ad5/35 viral vector encoding the CCR5 specific ZFNs (SBS8196z and SBS8267) which through transient episomal expression delivers these nucleases to transduced cells. The two ZFNs bind to a composite 24-bp sequence found specifically in the region encoding the first transmembrane domain of the CCR5 gene, just upstream from the naturally occurring CCR5 delta 32 mutation. Expression of the CCR5-specific ZFNs induces a double stranded break which is repaired by the cell leading to random sequence insertions or deletions in ~30% of cells transduced with SB-728. These insertions and deletions disrupt the CCR5 coding sequence leading to frameshift mutation and termination of CCR5 protein expression. Additional human pre-clinical information can be found in the Clinical Investigator's Brochure for SB-728-T.

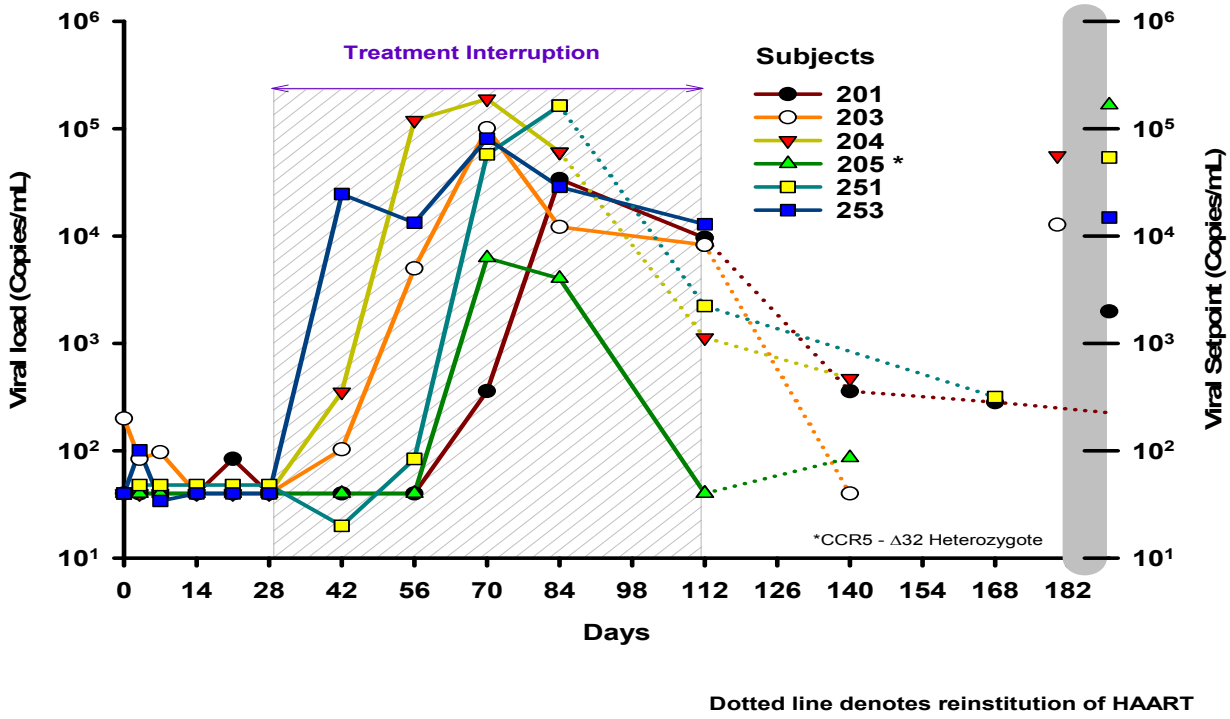
1.1 Clinical Experience with SB-728-T

SB-728-T has been administered to over 60 subjects in three ongoing Phase 1 studies to date, one sponsored by the University of Pennsylvania (protocol number 806383) and the other two by Sangamo (SB-728-0902 and SB-728-1002). SB-728-0902 and the PENN study have enrolled a total of 21 aviremic subjects on HAART to date; 6 immunologic responders (IR) with CD4 $\geq$450 cells/μL and 15 immunologic nonresponders (INR) with CD4 $\leq$500 cells/uL. Subjects were infused with 5 to 30 billion cells. The mean CD4 and SB-728-T count increased by 1533/μL (range 216-3025) and 83/μL, respectively, on day 7 in IR and by 820/uL (range 133-4467) and 19/μL, respectively, in INR from the 2 studies. Increases in CD4 over time correlated with SB-728-T engraftment ($r=0.78$, $p<0.0001$). SB-728-T was detected in the gut mucosa of all 18 subjects biopsied (median 6%).

A HAART treatment interruption (TI) was performed 4 weeks after SB-728-T infusion (5-10 billion cells) in the 6 IRs. HIV-RNA dropped ~0.8-2.1 log from their peak levels in 3 of the 6 subjects (**Figure 1.1-1**). In one CCR5 delta 32 heterozygous subject with a viral setpoint of 165,000 copies/mL, viral load (VL) peaked at 6247 copies/mL during Week 6 of TI and was undetectable by Week 12. Similarly, a subject in Sangamo Study SB-728-0902 had a >1-log decrease in his HIV-RNA when he underwent a TI one year after the infusion of 10 billion SB-728-T cells. Furthermore, in SB-728-0902, PBMC HIV proviral DNA was evaluated using a new Digital Droplet qPCR method. Samples with previously undetectable levels using traditional

qPCR now showed measurable proviral DNA. Three of the six subjects with >11 month follow-up had an ~1-log decrease over time.

Figure 1.1-1: Viral Load Following Treatment Interruption in Immunologic Responders



The results to date suggest SB-728-T infusion increases CD4 counts that persist over time. SB-728-T expands rapidly and home to the gut. Preliminary data suggest that SB-728-T may decrease proviral DNA. In one subject with the highest level of CCR5 modification, VL was controlled (< limit of detection) without HAART. There have been no serious adverse events (SAEs), associated with SB-728-T, reported to date. SB-728-T infusions were well tolerated with only mild reversible infusion related adverse events (AEs). The most common AEs were a garlic odor caused by the DMSO required for cell freezing, and fever and chills.

1.2 Cyclophosphamide to Enhance SB-728-T Engraftment

Cyclophosphamide is a nitrogen mustard alkylating agent that attaches an alkyl group to the guanine base of DNA. It is a prodrug that is converted by mixed function oxidase enzymes in the liver to the main active metabolite, phosphoramide mustard which forms DNA crosslink between and within DNA strands. The unchanged drug has a half-life of 3 to 12 hrs and is eliminated primarily in the form of metabolites although 5 to 25% of the drug is excreted unchanged in the urine.

Preclinical studies have shown that cyclophosphamide can deplete T-cells and macrophages with rapid repopulation of lymphoid tissues upon discontinuation of the drug. Normal numbers of different T-cell populations were fully restored in mice 16 to 30 days after a single dose of cyclophosphamide (Kolb, Poupon et al. 1977). In another study, the total lymphocyte count in mice nadired at <10% of normal in the thymus, bone marrow, spleen and lymph nodes three days

after a single injection of cyclophosphamide (300mg/kg). The repopulation kinetics differed markedly within these tissues with the thymus reaching normal numbers by day 14 and twice normal by day 21. The bone marrow and spleen were normal by day 7 and 11, respectively but the lymph nodes were only at 30% of normal by day 21 (Willers and Sluis, 1975). These data demonstrate that the lymphodepleting effects of cyclophosphamide are readily reversible with rapid repopulation of lymphoid organs when the drug is discontinued.

1.2.1 Cyclophosphamide and Adaptive Immunotherapy

Cyclophosphamide has been shown to have 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 use of autologous T-cells 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 there has been significant clinical success with this approach, with lymphodepletion an important contributing factor. Dudley and Rosenberg at the NCI treated melanoma subjects with cyclophosphamide and fludarabine prior to adoptive cell transfer of expanded tumor infiltrating lymphocytes and showed a 51% objective clinical response rate of tumor shrinkage (Dudley et al., 2005; Dudley and Rosenberg, 2003). More recently, the beneficial effect of a non-myeloablative lymphodepleting regimen on adoptive T-cell therapy was demonstrated in chronic lymphocytic leukemia patients treated with low doses of chimeric antigen receptor CD19 (CART19) transduced autologous T-cells (Porter et al., 2011). These results demonstrate 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.

1.2.2 Safety of Cyclophosphamide in Autoimmune Disease

Cyclophosphamide has been successfully deployed as therapy for numerous autoimmune diseases including Goodpasture's syndrome, systemic lupus erythematous, rheumatoid arthritis, Wegener's granulomatosis, and membranous glomerulonephritis. Adverse effects and toxicities, including hemorrhagic cystitis and gonadal dysfunction are dose dependent and are uncommon with total cumulative doses below 10 g. The risk of malignancy with oral therapy is proportional to the cumulative dose and increases substantially at cumulative doses greater than 30 g. Treatment with cumulative doses of 10 g or less has been shown to be associated with incidence of malignancy similar to that of a control population (Baker et al., 1987). Importantly, unlike other cytoreductive agents, cyclophosphamide has no cumulative bone marrow toxicity.

Table 1.2.2-1 is reproduced from a paper detailing the side-effects of cyclophosphamide in subjects with autoimmune disease (Martin et al, 1997). A total of 329 subjects with a variety of autoimmune diseases received intravenous (IV) cyclophosphamide in nine studies. The mean cumulative dose ranged from 1.4 g to 16 g. Infection was the most common side effect but most of the subjects were also receiving glucocorticoid. Hemorrhagic cystitis was seen in only 2 of the studies and may be prevented by adequate fluid intake to induce a diruesis. Only two of the studies reported cancer and the total was seven subjects. The cumulative dose of cyclophosphamide that was administered in these two studies was 4.7 and 10 grams.

Table 1.2.2-1: Literature Review of the Side Effects of Intravenous Cyclophosphamide Pulse Therapy in Subjects with Autoimmune Disease

Author	*Patients*		*Treatment*		*Side-effects*					
	n	*Disease*	*CPM*[b]	*Pred.*[c]	*Major inf. (%)*	*Herpes zoster (%)*	*Cancer (%)*	*Haemor. cystitis (%)*	*Premature menopause (%)*	*Death*[d] *(%)*
Haga[14]	55	CTD	1.8	NA	7	2	0	2	2	2
Belmont[7]	45	SLE	9.9	1	4	0	0	0	6	0
Boumpas[3]	40	SLE	10	0.5	5	7	2	0	20	0
De Bandt[9]	37	SLE	7.2	NA	8	8	0	5	5	8
Austin[4]	20	SLE	16	0.5	10	25	0	0	45	10
Valeri[6]	20	SLE	6	1.5	15	10	0	0	10	0
Reiner[13]	20	AITP	4.9	NA	10	0	0	0	0	0
Houssiau[5]	17	SLE	1.4	0.5	12	6	0	0	0	6
This series	75	AID	4.7	0.6	9	1	5	0	0	0

[a] Series with at least 15 patients given IV CPM as single immunosupressive agent are summarized
[b] Mean cumulated IV CPM dose (g) extrapolated from the standard regimen
[c] Mean initial daily prednisolone dose (mg/kg)
[d] Death attributed to IV CPM therapy; %: percentage of patients; NA; not available; CTD: various connective tissue diseases; SLE: systemic lupus erythematosus; AITP: autoimmune thrombocytopenic purpura; AID: autoimmune diseases.

1.2.3 Use of Cyclophosphamide in HIV

The effect of cyclophosphamide on HIV cellular reservoir in subjects receiving HAART was evaluated in Clinical Study ACTG 380 (Bartlett et al., 2002). Ten treatment naïve HIV subjects were treated with stavudine, lamivudine and nelfinavir. When the subjects became aviremic on two serial tests, they were randomized equally to HAART alone or HAART plus cyclophosphamide. Cyclophosphamide was administered every 6 weeks at three escalating dose levels (750 mg/m^2, 1.2 g/m^2 and 1.8 g/m^2, or a cumulative dose of 3.75 g/m^2 over 12 weeks). Total lymphocyte counts decreased by a mean of 709 cells/mm^3 ($p<0.02$ compared with control patients), and CD4 counts were not significantly affected. HIV proviral DNA decreased similarly in both groups but HIV RNA increased in the cyclophosphamide group, an observation that was attributed to non-compliance with HAART. The study demonstrated that the use of cyclophosphamide was lymphodepleting, did not significantly reduce total CD4 counts, and was adequately tolerated. Toxicity included transient nausea following the infusion; one subject with Grade 3 neutropenia and one subject with Grade 2 thrombocytopenia. Additional information on the safety of cyclophosphamide is discussed in **Section 9.2.**

1.3 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 the currently ongoing U Penn study suggest 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-728-T.

In the current study, only subjects with aviremia and CD4 cell counts ≥500 cells/μL at the initiation of the TI will have HAART interrupted. In addition, subjects will be monitored closely during the TI period and HAART will be reinstituted in subjects in whom CD4 cell counts drop to <500 cells/μL and/or whose HIV-RNA increases to >100,000 copies/mL over a sustained period (defined as three consecutive measurements tested every 2 weeks).

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 (subjects with HIV RNA levels below the limit of detection will remain off HAART).

During extended TI, 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 may have HAART reinstituted at any time at the discretion of the subject and/or PI.

1.4 Risk Benefit Analysis

Following myeloablative conditioning regimens for hematopoietic stem cell transplants, T cell proliferation and immunoglobulin production are usually impaired for 6 to 12 months post transplant but may persist for as long as 4 to 10 years after autologous stem cell transplantation (Nordoy T et al., 2001). Adoptive T-cell therapy has been successfully applied to the rescue of chemotherapy induced lymphopenia in the setting of non-Hodgkin's lymphoma (Laport et al, 2003), chronic myelogenous leukemia (Rapoport et al, 2004), relapsed acute leukemia (Porter et al, 2006) and refractory multiple myeloma by Dr. Carl June and his colleagues at UPENN.

The kinetics of immune reconstitution with autologous polyclonal CD3/CD28 stimulated T-cells (~$1x10^{10}$ cells) following high dose chemotherapy with busulfan and autologous stem cell transplantation in multiple myeloma was evaluated in three successive trials. In the first study, 52 subjects were randomized to receive a single infusion of CD3/CD28 stimulated T- cells, either 12 or 100 days after stem cell transplantation (Rapoport et al., 2005). T-cells were infused two days after stem cell infusion in the subsequent study (Rapoport et al., 2011 and Stadtmauer et al., 2011). There was a rapid reconstitution of lymphocytes with normal circulating levels achieved by day 5. A lymphocytosis was observed in ~30% of the patients that persisted for up to 8 weeks.

Reconstitution of T cell to normal levels occurs by 5 days post T-cell infusion but the lymphocyte count was higher in subjects that received T-cells on day 2 relative to those who were infused on day 12 or day 100. These data suggest that T-cell expansion following adoptive transfer may be time-dependent with more proliferation occurring when the cells are infused early after lymphocyte depletion.

T-cell infusions in these studies were well tolerated with chills/rigors, nausea and low grade fevers the most common AEs. Similarly, cyclophosphamide has been safely administered to patients with a variety of conditions including autoimmune diseases and infection with HIV (**Section 1.2)**. At the non-myeloablative doses of cyclophosphamide (200 mg to 2.0 g/m^2) that will be administered in this study, the adverse effects are readily managed by routine medical interventions such as antiemetics and adequate hydration (**Section 9.2**). The top dose of cyclophosphamide selected for this study, 2.0 g/m^2, is below the total cumulative dose of 3.75 g/m^2 that had been safely administered to HIV infected patients in a previous study (**Section 1.2.3**). 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 cyclophosphamide.

1.5 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 CD4+ T-cells that leads to clinical AIDS. SB-728-T has been safely administered to over 60 HIV-infected subjects in three clinical trials conducted to date. The level of engraftment has varied from negligible to ~10% of the CD4+ T-cells in the vascular compartment. Preliminary analyses of HAART TI in the UPENN study suggest that an anti-HIV effect may correlate with the level of SB-728-T engraftment. Concurrently, non-myeloablative lymphodepletion with cyclophosphamide has been demonstrated to enhance engraftment of adoptively transferred T-cells through a variety of mechanisms (**Section 1.2**). The current study is being undertaken to increase SB-728-T engraftment through the administration of low non-myeloablative doses of cyclophosphamide.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of escalating doses of cyclophosphamide administered up to 3 days prior to SB-728-T infusion.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate:

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

3. STUDY DESIGN

3.1 Overview

This is a Phase 1, open-label, dose-escalation, multi-center study. Subjects who satisfy all inclusion/exclusion criteria (**Section 4**) are eligible to participate in this study. Within each cohort, treatment will be staggered so that each subsequent subject cannot be infused with cyclophosphamide until at least 2 weeks after the preceding subject. Up to 3 days after receiving cyclophosphamide, subjects will be infused with 0.5 to 4.0 x 10^{10} SB-728-T cells. Subjects who are aviremic and have CD4 cell counts ≥500 cells/μL will undergo a minimum 16 week TI beginning 6 weeks after infusion of SB-728-T. TI may be extended beyond 16 weeks for subjects whose HIV RNA levels ≤ 10,000 copies/mL and CD4 count ≥ 500 cells/μL at the end of the 16-week TI. Subjects will be followed for 12 months after the infusion.

Additional research blood collection and/or an optional leukapheraesis may be performed during the study upon sponsor request.

3.2 Number of Subjects

Up to 40 aviremic HIV-infected subjects on stable HAART will be enrolled and treated in 5 dose cohorts (3-6 subjects/cohort).

3.3 Dose Escalation

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

3.4 Cohort Expansion

If no DLT develops in 3 subjects in Cohort 5 (1.5 g/m^2), additional subjects may be enrolled into that cohort.

Upon evaluation of data from Cohort 5 (1.5 g/m^2), the sponsor may elect to enroll additional subjects into Cohort 3 (1.0 g/m^2).

3.5 Study Duration

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

3.6 Visit Schedule

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

10, 12, 14, 18 and 22 during the TI. After completion of the 16-week TI or during TI extension (Section 9.3), subjects will be seen at Month 7, Month 8, Month 10, and Month 12.

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

3.7 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) $\geq$ 2500/mm^3.
6. Hemoglobin level $\geq$ 13 g/dL (males); $\geq$ 12 g/dL (females).
7. Platelet count $\geq$ 200,000/mm^3.
8. Serum creatinine $\leq$ 1.5 mg/dL.
9. AST and ALT $\leq$ 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 at screening.
13. All subjects must have received at least 6 months of continuous HAART therapy and have had undetectable VLs for the preceding 3 months. Subjects who had intermittent isolated episodes of detectable low-level viremia <500 copies RNA/mL; blips) will remain eligible.
14. On stable antiretroviral medication (no changes to treatment within 4 weeks of screening.
15. CD4+ T-cell count $\geq$500 cells/μL.
16. HIV-1 RNA below the limit of assay detection obtained at screening.
17. Willing to discontinue current antiretroviral therapy during the treatment interruption.
18. Adenoviral Neutralizing Antibody $\leq$40
19. Low innate immune system activation as determined by the sponsor

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 infusion of SB-728-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-728-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-728-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 1**).

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
6. 12-lead ECG
7. Hepatitis B surface antigen (HBsAG) and hepatitis C antibody (HCV) (not required if HBsAG or HCV antibody are negative within 60 days of screen visit)
8. Serum pregnancy test (female of childbearing potential)
9. Urinalysis for presence of glucose, protein, bilirubin, blood, pH, and specific gravity
10. CBC with differential, platelet count, and ANC
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 and CD4/CD8 ratio
13. HIV-1 RNA
14. CCR5 SNP Cel-I assay
15. Ad and SB-728 Immunogenicity
16. HIV-1 Co-receptor Tropism
17. Innate immune system activation

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 with differential and platelet count
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-728-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 cyclophosphamide administration:

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

6.4.2 Baseline:

Baseline assessments will be performed approximately one week prior to cyclophosphamide 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 with differential, platelet count, and ANC
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 cyclophosphamide infusion and prior to cyclophosphamide infusion)

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

11. Pentamer assay
12. Ad and SB-728 immunogenicity

6.5 Study Treatment and Follow-up

After baseline tests are reviewed, the study center will contact Sangamo BioSciences to schedule SB-728-T dosing. Refer to the Study Reference Manual for details. All subjects will be followed for a total of 12 months after SB-728-T infusion according to the schedule in Appendix 1.

6.5.1 Cyclophosphamide Administration

Cyclophosphamide should be administered up to 3 days prior to SB-728-T infusion. Subjects should consume at least 4L of fluids over the 24 hrs prior to receiving cyclophosphamide (Cohorts 4 and 5 only). All subjects will remain at the study site after cyclophosphamide administration until vital signs are satisfactory and stable. Subject may be released from the study site at investigator's discretion. Subjects in Cohorts 4 and 5 will have additional testing of CBC (with differential), platelet count, and ANC on Day 5 and Day 12. Subjects will be monitored, as needed, post cyclophosphamide administration.

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

Pre-Cyclophosphamide administration:

4. Chemistry
5. CBC with differential, platelet count, and ANC
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 cyclophosphamide 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 cyclophosphamide. Other antiemetics may be given at the discretion of the investigator and with sponsor consultation if possible.

Cyclophosphamide Administration:

11. Cyclophosphamide administration

Post-Cyclophosphamide Administration:

12. 1L of IV fluids infused over approximately 1-2 hrs after cyclophosphamide administration
13. Subjects in Cohorts 1-3 should consume at least 4L of fluids over the 24 hrs after receiving cyclophosphamide. Subjects in Cohorts 4 and 5 should consume 4L of fluids per day over the next 7 days.
14. Subjects will be sent home with urine dipsticks and are to test their urine twice daily (once in the morning and again in the evening) for 7 days following administration of cyclophosphamide. Subjects are to call the study center if any hematuria is detected. (Cohorts 4 and 5 only)
15. Recommended antiemetic regimen: Aprepitant (Emend) 80mg 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.

Subjects in Cohorts 4 and 5 will have additional testing of CBC (with differential), platelet count, and ANC on Day 5 and Day 12.

Post cyclophosphamide 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 Day 0 – SB-728-T infusion

All subjects will remain at the study site for approximately 2 hours after SB-728-T infusion and vital signs are satisfactory and stable. SB-728-T should be infused up to 3 days after completion of the cyclophosphamide administration. (**Section 8.1**)

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

Pre-SB-728-T Infusion:

4. Chemistry
5. CBC with differential, platelet count, and ANC
6. Urinalysis
7. CD4+ T-cell count
8. Research blood

SB-728-T Infusion:

9. SB-728-T infusion (0.5 to 4.0 x 10^{10} cells)

6.5.3 Day 1

1. AE assessment
2. Chemistry
3. CBC with differential, platelet count, and ANC
4. Urinalysis
5. CD4+ T-cell count
6. Pentamer assay
7. Research blood

6.5.4 Day 5 (- 1 day) (Cohorts 4 and 5 only)

1. CBC with differential, platelet count, and ANC

6.5.5 Week 1, Day 12 (-1 day) (Cohorts 4 and 5 only), Week 2, Week 3, and Week 4 (+/- 2 day)

1. AE assessment
2. Review of concomitant medications (weekly visits only)
3. Chemistry (Weeks 1 and 3 only)
4. CBC with differential, platelet count, and ANC
5. Urinalysis (Weeks 1 and 4 only)

6. CD4+ T-cell count (weekly visits only)
7. HIV-1 RNA (weekly visits only)
8. Ad and SB-728 immunogenicity (Weeks 1 and 4 only)
9. Pentamer assay (weekly visits only)
10. Research blood (Week 2 only)

6.5.6 Weeks 6, 8, 10, 12, 14, 18 and 22: 16-Week HAART Treatment Interruption

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 (weeks 6, 8, 10, 12, 14) and then every month (+/- 1 week) for the remaining 8 weeks of the TI (weeks 18 and 22). (**Section 8.3**)

Subjects will discontinue HAART under the supervision of the principal investigator. Non-nucleoside reverse transcriptase inhibitors (NNRTI) such as Rescriptor, Sustiva, Intelence, and Viramune have been reported to have a longer half life than nucleoside reverse transcriptase inhibitors (NRTI). 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)
2. AE assessment
3. Assessment of concomitant medications
4. Vital signs (temperature, pulse, blood pressure, and weight) (Weeks 6 and 22 only)
5. Chemistry (Weeks 6, 8, 12, 18, and 22 only)
6. CBC with differential and platelet count
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. Ad and SB-728 immunogenicity (Week 12 only)
12. Research blood (Weeks 6, 14, and 22 only)

At the end of the 16-week TI at Week 22:

- 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, 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.

6.5.7 Month 7, Month 8, Month 10, Month 12 (+/- 1 week)

1. AE assessment
2. Assessment of concomitant medications
3. Complete Physical Exam (Month 12 only)
4. Vital signs (temperature, pulse, blood pressure, and weight) (Month 8 only)
5. Chemistry (Months 7, 10 and 12 only)
6. CBC with differential and platelet count
7. Urinalysis (Months 7 and 12 only)
8. CD4+ T-cell count

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

   (For subjects in extended TI, test will be repeated monthly for a total of 3 consecutive measurements if HIV-1 RNA levels > 10,000 copies/mL)
10. Pentamer (Months 8 and 12 only)
11. Ad and SB-728 immunogenicity (Months 7 and 12 only)
12. Research blood

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 with differential, platelet count
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 with differential 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.

6.5.8 Long-Term Follow-up

Long term follow-up for this study will be conducted under a separate protocol. At the time of informed consent for this protocol, subjects will be made aware of the long term follow-up requirement.

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 including absolute neutrophil count at screening and baseline.
- 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 within 60 days prior to study entry. Subjects who have not previously had the test or subjects who were negative more than 60 days prior will have a test at screen prior to leukapheresis.
- Hepatitis C: subjects must have documentation of a negative HCV antibody test within 60 days prior to screening. Subjects who have not previously had the test or subjects who were negative more than 60 days prior to screening will have a HCV antibody test at screening and results must be reviewed prior to leukapheresis. 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. HCV RNA must be by any RT-PCR or bDNA assay performed by a laboratory with a CLIA certification or its equivalent and results evaluated prior to leukapheresis. The test is not required if documentation of a negative result of a HCV RNA test performed within 60 days prior to screening is provided.

- 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, and protease inhibitors.

8. MEDICATIONS

8.1 SB-728-T

SB-728-T is autologous CD4+ T-cells modified at the CCR5 gene by ZFN expressed by SB-728, a replication deficient adenoviral vector. Autologous CD4+ T lymphocytes are transduced ex vivo with SB-728 adenoviral vector. The final T-cell product, SB-728-T, is generated using 2 major elements: 1) a replication deficient chimeric Ad5/F35 adenoviral vector SB-728, used as an accessory product for gene delivery of CCR5 specific zinc finger nucleases and 2) CCR5 modified autologous CD4+ T-cells (SB-728-T) that have undergone ex vivo T-cell activation, ex vivo genetic modification by the SB-728 vector, expansion and formulation. The composition of the final T-Cell product is:

Composition of SB-728-T

Component	Unit Formula
SB-728 Treated CD4+ T-cells	0.5-1.25 x 10^{10}/100 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. A copy of the C of A and an addendum to the C of A that report the cell viability will be sent with each subsequent lot.

8.1.1 Inventory, Storage, and Handling of the Drug Product

SB-728-T is cryopreserved in a 500 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 CD4+ T-cells will contain approximately 0.5-1.0 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 for the infused cells 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 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 C of A will include the actual number of cells and volume contained within the infusion bag. The T-cell product 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. 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-728-T Administration

Side effects following SB-728-T cell infusions 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-728-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-728-T will be shipped to the study site prior to the scheduled infusion. SB-728-T should be infused up to 3 days after completion of the cyclophosphamide administration. The study product should be thawed just prior to the scheduled infusion. Prior to the infusion, 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-728-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, 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-728-T infusion, appropriate cultures and medical management should be initiated. If possible contamination of the SB-728-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

No dose modifications are possible since this is a single infusion study.

8.2 Cyclophosphamide

Cyclophosphamide is a sterile white powder containing cyclophosphamide 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. Cyclophosphamide should be administered up to 3 days prior to SB-728-T infusion. The following doses of cyclophosphamide will be infused IV: Cohort 1 (200 mg), Cohort 2 (0.5 g/m^2), Cohort 3 (1.0 g/m^2), Cohort 4 (2.0 g/m^2), and Cohort 5 (1.5 g/m^2).

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 cyclophosphamide. 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 cyclophosphamide followed by Emend 80mg 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 cyclophosphamide administration.

Filgrastim

After cyclophosphamide 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 cyclophosphamide 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 at Week 6 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:

- 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, 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 this study. 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-728-T

SB-728-T at doses ranging from 5 to 40 billion cells has been safely administered to approximately 60 HIV-infected subjects in four clinical trials to date. The longest duration of follow-up has been over 3 years in the first subject infused. There was one SAE to date, cellulitis and MRSA-abscess of left arm, grade 3, unrelated to study drug. It occurred approximately 9 months after the SB-728-T infusion. Most of the AEs have been mild to moderate in severity and the majority were related to SB-728-T infusion. These include chills, fever, headache, myalgia, sweats, dizziness, fatigue, and a "garlic" body odor. All AEs resolved without sequelae.

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 they may dysregulate genes controlling proliferation. The risk with non-integrating adenoviral DNA gene transfer is extremely low. Extensive preclinical safety studies have been carried out and support the safety of SB-728 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-728 ZFNs with up to 2 base mismatches have shown that the SB-728 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 SB-728 to the CCR5 gene. No SB-728 specific effects on cell growth have been observed, indicating that in vitro SB-728 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 SB-728 modified T-cells is unsafe and may cause T-cell tumors.

9.1.3 Replication Competent Adenovirus (RCA)

The A5/F35 SB-728 vector used in this study is derived from the common cold adenovirus. SB-728 is tested for presence of RCA and meets FDA specification of less than 1 RCA in 3 x 10^{10} vector particles. The tropism of this adenoviral vector is that of Type B adenoviruses, and it is more efficient at transducing hematopoietic cells than the more commonly used Type C adenovirus (Ad5).

Previous experience has shown that systemically distributed replication competent adenovirus vectors (Ad5) induce elevated liver enzymes at the dose of $6x10^{12}$ vector particles and that the lethal dose is $1x10^{14}$ vector particles when administered systemically (Small et al., 2006a). The current protocol will use approximately $6x10^{12}$ viral particles to transduce T-cells *ex vivo.* However, at the completion of the ex vivo T-cell culture expansions, there is a significant reduction of the level of adenovirus in the T-cells. Preclinical data indicates that during the 8 to 10 days of culture of the T-cells after transduction with SB-728, there is at least a 4,000-fold reduction of detectable adenoviral genomes by PCR at cell harvest.

Previous studies with the intentional systemic administration of replication competent but selective adenovirus has shown circulating virus for up to 29 days at IV doses of 3 x10^{12} and 6 x10^{12} vector particles and, with the concomitant development of high levels of neutralizing anti-adenoviral antibodies in all subjects by day 28. This was associated with self limited and asymptomatic increases in liver function tests (Small et al., 2006b). There has been no evidence of hepatitis in the 35 subjects treated to date. Nonetheless, subjects participating in the study will be monitored carefully for liver function abnormalities and signs or symptoms of hepatitis.

Subjects in this study will be evaluated for replication competent adenovirus (by an E1 gene PCR assay), as well as adenovirus neutralizing antibody titers. The clearance of any adenovirus (whether replication deficient or competent) should be quite rapid since most subjects will have preexisting antibodies to the Ad 5 penton base and hexon proteins.

9.1.4 Immunogenicity

The Ad5 fiber 35 vector utilizes AD5 hexon and penton capsid proteins and the AD 35 fiber capsid protein (Nilsson et al. 2004). Pre-existing neutralizing anti bodies to Ad5, which is the most prevalent adenoviral serotype antibody in man, could be reactive to SB-728-T (Aste-Amezaga et al. 2004). After infusion of SB-728-T, all of the patients tested to date have developed elevated neutralizing adenovirus antibodies. There were no associated AEs. In general, subjects with higher pre-existing antibody titer had a lower level of engraftment of SB-728-T in peripheral blood as measured by Quantitative PCR for a common CCR5 modification (pentamer assay, units = number of copies of pentamer/1e6 genomes) compared to the subjects with low pre-existing antibody levels.

9.2 Cyclophosphamide

Cyclophosphamide 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. Subjects in Cohorts 4 and 5 will have additional testing of CBC (with differential), platelet count, and ANC on Day 5 and Day 12. After cyclophosphamide 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 cyclophosphamide administration. The majority of the adverse effects require the administration of high cumulative doses of cyclophosphamide **(Section 1.2.2)**.

Hemorrhagic cystitis is a potential untoward effect of cyclophosphamide 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 cyclophosphamide (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. In this study, subjects in Cohorts 1-3 will be hydrated with 1 liter of IV fluids prior to cyclophosphamide 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. Subjects in Cohorts 4 and 5 will be instructed to drink 4L of fluids over the 24 hrs prior to receiving cyclophosphamide and will receive 1L of fluids administered IV over 1-2 hrs immediately prior to cyclophosphamide infusion. At discharge from the study center, subjects will be instructed to drink 4L of fluids per day for 7 days following cyclophosphamide administration to insure adequate diuresis. Subjects will be instructed to test their urine twice daily for microscopic hematuria with urine dipsticks and to contact the study center immediately if hematuria (either micro or macro) is detected.

Cyclophosphamide 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 doses (200 mg to 2.0 g/m^2) that will be administered in this study are unlikely to be carcinogenic.

9.3 HAART Treatment Interruption (TI)

The efficacy and safety of HAART interruption for HIV patients has been reviewed by Paton (Paton, 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 by unpublished data from the Penn study. In that study, six subjects had HAART interrupted beginning 4 weeks after receiving SB-728-T (**Table 9.3-1**). Five of the subjects have completed the TI. HIV-RNA which was below the limit of detection at the time of the TI became detectable at 2 to 6 weeks, peaking at 6 to 8 weeks and then declined at 12 weeks. In subjects 1, 2 and 6, the VL dropped 0.5- to 2-log within 4 to 6 weeks and declined after reinstituting HAART. The TI was halted in Subjects 3 and 4 as per the stopping

rules. In Subject 3, HAART was reinitiated because the HIV-RNA increased to >100,000 copies/mL on three consecutive measurements while Subject 4 was found to be infected with dual-tropic HIV. Subject 5 became aviremic 12 weeks following initiation of the TI; this subject was subsequently found to be a CCR5 delta-32 heterozygote by genotyping.

Table 9.3-1: Plasma HIV-1 RNA (copies/mL) during TI

	TI					HAART	
Subject	**0**	**2 wks**	**4 wks**	**6 wks**	**8 wks**	**12 wks**	**16 wks**
1	<48	<48	<48	359	33,885	9,596	358
2	<40	103	4991	100,635	12,149	8,248	<40
3	<40	353	119,855	189,054	Halted	1131	473
4	<48	<20	84	57643	163,837	Halted	86
5	<40	<40	<40	6247	4020	<40	---
6	<48	24,604	13,288	80,658	28,628	12,871	---

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, 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 3 and 4 in the PENN study cited above.

It is possible that some patients 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 Adverse Event Reporting Period

During both the treatment and follow-up periods, 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.

10.2 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.

10.3 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 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 Mobile: (310) 497-7038
Assistant to Dr. Tang:	Vivian Tran
Phone Number:	(510)-970-6000, extension 200
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.

11.2 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.

11.3 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. SUBJECT WITHDRAWAL, DOSE ESCALATION, AND STOPPING RULES

12.1 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-728-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 will 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.

12.2 Dose Escalation Rules

A SMC will determine if it is safe to dose escalate to the next cohort. If one subject within Cohorts 1-5 experiences a DLT defined as a Grade 3 non-hematological AE excluding alopecia or Grade 4 hematological AE (all deemed related to cyclophosphamide), 3 additional subjects will be enrolled and treated in that cohort. Dose escalation to the next cohort may proceed if there is not more than one DLT (all deemed related to cyclophosphamide) in a cohort of 6 subjects. Safety data including AEs, clinical laboratory results (chemistry, hematology, CD4 T-

cell counts and VL) through Week 4 from all subjects within a cohort will be reviewed by this group to determine if it is safe to proceed with SB-728-T infusion.

Treatment of subjects will be staggered at least 2 weeks apart.

12.3 Cohort Expansion

If no DLT develops in 3 subjects in Cohort 5 (1.5 g/m^2), additional subjects may be enrolled into that cohort.

Upon evaluation of data from Cohort 5 (1.5 g/m^2), the sponsor may elect to enroll additional subjects into Cohort 3 (1.0 g/m^2).

12.4 Stopping Rules

12.4.1 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.

12.4.2 Stopping Rules for Study

Safety data for subjects in each cohort will be evaluated for consideration of dose escalation by a SMC one month after the last SB-728-T infusion in the cohort. Safety data including AEs, clinical laboratory results (chemistry, hematology, CD4 T-cell counts and VL) will be evaluated. Subjects in the subsequent cohort may be screened and enrolled prior to the safety review. However they will not be infused until the SMC has reviewed the data and approved for dose escalation of that cohort. The SMC will convene at any time, as needed.

<u>The study will be paused if</u>:

- There are excessive or unexpected toxicities associated with the protocol. Specifically, the study will be paused if it is determined that two subjects in a cohort (Cohorts 1-5) have a non-hematological Grade 3 toxicity excluding alopecia and/or hematological

Grade 4 toxicity, or if one subject has Grade 5 toxicity 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. The study will be paused and available data will be evaluated by the SMC.

- 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 paused and available data will be evaluated by the SMC.

The study will be stopped if:

- The Investigator, Sponsor, SMC, 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-728-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.

13. 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.

13.1 Sample Size

This is a phase 1 study in which three to six evaluable subjects in each cohort will be treated to evaluate safety of each cyclophosphamide dose level. A cohort can be expanded if there is no DLT in 3 subjects treated or no more than 1 DTL in 6 subjects treated in that cohort. In order to have an evaluable sample size, subjects who prematurely discontinue the study prior to the conclusion of the TI will be replaced with another subject. Safety will be evaluated after each cohort before treating the next dose cohort. **Table 13.1-1** provides the probability of failing to observe an AE in a sample size of three or six evaluable subjects, for various underlying true AE rates. Thus, only AEs that occur at least 60% of the time are likely to be detected in a cohort of three subjects.

Table 13.1-1

	Probability of Failing to Observe an Adverse Event	
True Adverse Event Rate	N=3	N=6

5%	86%	74%
10%	73%	53%
20%	51%	26%
30%	34%	12%
40%	22%	5%
50%	13%	2%
60%	6%	<1%
70%	3%	<1%

Table 13.1-2 shows the exact 95% confidence intervals for possible number of observed safety outcomes in three or six subjects. For example, if no AEs are observed in a group of six evaluable subjects, we can be 95% confident that the true AE rate is less than 46%.

Table 13.1-2

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

13.2 Statistical Methods/Data Analysis

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

13.3 Intent-to-Treat Population

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

13.4 Demographics

Demographic and baseline characteristics will be summarized by treatment cohorts.

13.5 Endpoints and Analysis

Since this is a dose ranging study to evaluate safety, efficacy analyses will be descriptive and exploratory in nature. 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.

13.5.1 Primary Endpoint

Safety assessment will occur on all subjects who received cyclophosphamide. 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.

13.5.2 Secondary Endpoints

The secondary endpoints of this study are exploratory in nature and will assess if cyclophosphamide increases SB-728-T engraftment as well as provide evidence of anti-viral activity. These exploratory endpoints may help to define the primary endpoints for future studies.

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

14. 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.

14.1 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.

14.2 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.

14.2.1. 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.

14.2.2. 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.

14.3 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.

14.4 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.

15. ADMINISTRATIVE CONSIDERATIONS

15.1 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.

15.2 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.

15.3 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.

15.4 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

15.5 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.

15.6 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.

15.7 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 1: SCHEDULE OF EVENTS

Procedure	Screen	Pre-Leukapheresis (1 wk prior to leukapheresis)	Leukapheresis[a]	Baseline for Research Blood (between Leuk and CTX)	Baseline (~1 wk prior to CTX)	CTX	Day 0	Day 1	Day 5 (-1 day) Cohorts 4 & 5 only	Wk 1 (±2 days)	Day 12 (-1 day) Cohorts 4 & 5 only	Wk 2 (±2 days)	Wk 3 (±2 days)	Wk 4 (±2 days)	Wk 6 (+3 days) --- Start TI	Wk 8 (±3 days)	Wk 10 (±3 days)	Wk 12 (±3 days)	Wk 14 (±3 days)	Wk 18 (±1 wk)	Wk 22 (±1 wk) ___ Evaluate TI[m]	M 7, M 8, M 10, M 12 (±1 wk)
Inclusion Exclusion / Informed Consent[b]	X																					
Medical History	X																					
Physical Exam	X																					X M12 only
Vital Signs[c]					X	X	X								X						X	X M8 only
12-lead ECG	X																					
Leukapheresis			X																			
Cyclophosphamide Administration						X[d]																
SB-728-T infusion							X[e]															
Adverse events			X		X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X				X	X	X			X		X	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C[f]	X																					
Pregnancy Test[g]	X				X																	
Chemistry	X	X[h]			X	X	X	X		X			X		X	X		X		X	X	X M7, M10, M12 only
CBC w diff / platelets(ANC at Screen through Week 4)	X	X		X (CBC w/diff only)	X	X[i]	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, M12 only
CD4+ T-cell counts	X			X	X	X	X	X		X		X	X	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X
HIV-1 RNA (Viral Load)	X				X					X		X	X	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X
CCR5 SNP CEL-1 assay	X																					
Ad and SB-728 immunogenicity	X				X[k]					X				X								X M7, M12 only
Pentamer					X[k]			X		X		X	X	X	X	X	X	X	X	X	X	X Month 8 and 12 only
HIV-1 Coreceptor and resistance test	X														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] Inform subjects of Long-term, Follow-up study
[c] Ht and wt at BL, Vital signs on CTX and Day 0 (temp., pulse, BP) and on Wks 6, 22 and M8 and M12 (temp, pulse, BP and weight)
[d] Cyclophosphamide should be administered up to 3 days prior to the SB-728-T infusion. Refer to Protocol Sections 6.5.1 and 8.2 and the Study Reference Manual for further details
[e] Refer to Protocol Sections 6.5.2 and 8.1 and the Study Reference Manual for further details
[f] Not required if negative results within 60 days of screening visit
[g] Serum pregnancy test at Screen and urine pregnancy test at Baseline
[h] Electrolytes (Na, K, CO_2, Cl), calcium, liver function tests (albumin, total protein, alkaline phosphatase, AST, ALT, total bilirubin)
[i] CD4 test will be repeated every 2 weeks for 3 consecutive measurements for values <500 cells/µL
[j] HIV-1 RNA test will be repeated every 2 weeks for 3 consecutive measurements for values >100,000 copies/mL
[k] May be performed up to 4 weeks prior to the SB-728-T infusion, Day 0.
[l] Research blood may be drawn on day of and prior to cyclophosphamide infusion.
[m] HIV-1 coreceptor and resistance testing will be performed once if HIV RNA exceeds 1,000 copies/mL during TI. Refer to protocol sections 6.5, 8.3, and 9.3

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 Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children 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 Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. 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
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 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) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) 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 – 81cm^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 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) (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) (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

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
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

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
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) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis 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)

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
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) 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 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

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
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

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
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 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 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.

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
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) (For use in studies evaluating topical study agents) 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) (For use in studies evaluating topical study agents) 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

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
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) 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) (Use in studies evaluating topical study agents) 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)

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
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

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.).

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 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 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 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Comment: Parameter changed from "Infant, < 1 day" to "Infant, ≤1 day"				
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR 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 *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62–5.23 mmol/L*	6.50 – 7.4 g/dL *4.03–4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18* – 6.79 *mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 - 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL *> 2.79 mmol/L*	< 7.0 g/dL *< 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 *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 - 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant*†, ≤ 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59- 6.17 mmol/L*	< 9.0 g/dL *< 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 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 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 *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 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 *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 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 *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				

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† 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 *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 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 *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 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 *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 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 *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*

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† 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 *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 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 *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

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