A5315

A Phase I/II Study of Romidepsin in HIV-Infected Adults with Suppressed Viremia on Antiretroviral Therapy to Assess Safety, Tolerability, and Activation of HIV-1 Expression

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:

The National Institute of Allergy and Infectious Diseases

In collaboration with Gilead Sciences

IND #119,069

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ACTG
AIDS CLINICAL TRIALS GROUP

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SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

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Protocol E-mail Group
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- Send an e-mail message to actg.user.support@fstrf.org

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Laboratory
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Data Management
CRFs can be downloaded from the FSTRF website at www.fstrf.org.

For nonclinical questions about transfers, inclusion/exclusion criteria, case report forms (CRF), the CRF schedule of events, randomization/registration, delinquencies, and other data management issues, contact the data manager**s**, Jennifer Janik, at janik@fstrf.org **and Apsara Nair, at anair@fstrf.org**.

For transfers, reference the Study Participant Transfer SOP 119, and contact Jennifer Janik directly (janik@fstrf.org).

- For other questions, send an e-mail message to Jennifer Janik (janik@fstrf.org) **and Apsara Nair (anair@fstrf.org),** with a cc to: actg.corea5315@fstrf.org.
- Include the protocol number in the subject line. In the body of the message, include the PID and any relevant details.

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Copies of the Protocol
Electronic copies can be downloaded from the ACTG Web site (https://www.actgnetwork.org).

To request a hard copy of the protocol, send a message to ACTGNCC@s-3.com.

Product Package Inserts
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Protocol Registration
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Protocol-Specific Web Page
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GLOSSARY OF PROTOCOL-SPECIFIC TERMS

ANA	antinuclear antibody
ANC	absolute neutrophil count
ART	antiretroviral therapy
AUC	area under curve
BSA	body surface area
CTCL	cutaneous T-cell lymphoma
DTG	dolutegravir
EFV	efavirenz
FACS	fluorescence activated cell sorting
HBV	hepatitis B virus
HCV	hepatitis C virus
HDACi	histone deacetylase inhibitors
HLA-DR	human leukocyte antigen disease resistance
LTR	long terminal repeat
MS	milliseconds
MTD	maximum tolerated dose
PBMC	**peripheral blood mononuclear cell**
PMA	phorbol 12-myristate 13-acetate
PTEF-b	positive transcription elongation factor b
qVOA	**quantitative viral outgrowth assay**
RAL	raltegravir
RMD	romidepsin
SAHA	suberoylanilide hydroxamic acid (Vorinostat or Zolinza®)
SCA	single copy assay of HIV-1 RNA in plasma
TVR	total virus recovery (assay)

SCHEMA

A5315
A Phase I/II Study of Romidepsin in HIV-Infected Adults with Suppressed Viremia on Antiretroviral Therapy to Assess Safety, Tolerability, and Activation of HIV-1 Expression

DESIGN

A5315 is a phase I/II, double-blinded, randomized, placebo-controlled, dose-escalation study to evaluate the safety and efficacy of single dose and multiple dose administration of romidepsin (RMD). Four cohorts (1-4) of 15 participants each will be sequentially enrolled into the study (depending on safety outcomes, which will determine whether to dose escalate or not). Toxicity related to the administration of RMD will be evaluated systematically in all cohorts. The effect of RMD on HIV expression will be evaluated in all cohorts. Samples will also be collected for pharmacokinetic (PK) evaluation of antiretroviral drugs (ARVs) and RMD.

DURATION

For participants in Cohorts 1 – 3, study duration is 4 weeks. For participants in Cohort 4, study duration is a minimum of 24 weeks; study duration will be increased if any of the infusions after the first one must be delayed. The maximum study duration for Cohort 4 participants will be 48 weeks.

SAMPLE SIZE

60 evaluable participants (approximately 15 evaluable participants in each cohort)

POPULATION

HIV- infected adults at least 18 years of age with CD4+ counts ≥300 cells/mm^3 who have suppressed viremia on a raltegravir (RAL), dolutegravir (DTG), or efavirenz (EFV)-based regimen **or, for Cohort 4, on a RAL- or DTG-based regimen** (plasma HIV-1 RNA levels <50 copies/mL and no blips >50 copies/mL on standard commercial assays) and, for Cohorts 1-3 only, who have ≥0.4 HIV-1 RNA copies/mL by single-copy assay (SCA) at screening. Plasma HIV-1 RNA ≥0.4 HIV-1 RNA copies/mL by SCA is not required as part of eligibility for Cohort 4.

REGIMEN

Participants will be sequentially enrolled to cohorts and randomized 4:1 to receive RMD or placebo as shown below.

Cohort 1: 12 participants will receive 0.5 mg/m^2 RMD in 0.9% saline 3 participants will receive placebo in 0.9% saline

Cohort 2: 12 participants will receive 2 mg/m^2 RMD in 0.9% saline 3 participants will receive placebo in 0.9% saline

Cohort 3: 12 participants will receive 5 mg/m^2 RMD in 0.9% saline 3 participants will receive placebo in 0.9% saline

Cohort 4: 12 participants will receive a total of 20 mg/m2 RMD in 0.9% saline (5 mg/m2 RMD at each of four dosing time points) 3 participants will receive placebo in 0.9% saline (at each of four dosing time points)

Accrual of the first five participants in any cohort will be limited to one participant in a 3-day period. Participants who do not receive or who do not complete any of the scheduled infusions of study treatment (RMD or placebo) will be replaced.

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

We hypothesize that adjunctive therapy with the potent histone deacetylase inhibitor (HDACi) romidepsin (RMD) administered at doses well below the maximum tolerated dose (MTD), will be well tolerated and lead to activation of proviral HIV-1 expression in latently-infected cells in HIV-infected participants receiving suppressive antiretroviral therapy (ART).

NOTE: Due to insufficient numbers of resting CD4+ T-cells available from some Cohort 4 participants to perform all the planned assays (e.g., cell-associated HIV-1 RNA, total HIV-1 DNA, histone acetylation, PTEF-b activation), those assays will be performed using peripheral blood mononuclear cells (PBMCs). The team carefully reassessed the priorities for the use of these cells based on advances in the field since the prior protocol version. Accordingly, the relevant objectives and outcomes measures sections have been updated.

1.2 Primary Objectives

1.2.1 To determine the safety and tolerability of the intravenous administration of a single dose of RMD to HIV-infected participants with HIV-1 RNA levels <50 copies/mL on a stable ART regimen in Cohorts 1-3, and of multiple doses of RMD in Cohort 4.

1.2.2 To assess the induction of HIV-1 expression in HIV-infected participants with suppressed viremia by measuring plasma viremia using a single copy HIV-1 RNA assay prior to and following a single dose of RMD in Cohorts 1-3 **and prior to and following each of multiple doses of RMD in Cohort 4**.

1.2.**3** To assess changes in cell-associated HIV-1 RNA levels in resting CD4+ T-cells obtained prior to and following a single dose of RMD in Cohorts 1-3 and **in PBMCs** prior to and following each of multiple RMD doses in Cohort 4.

NOTE: Due to insufficient numbers of resting CD4+ T-cells available from some Cohort 4 participants to perform all the planned assays (e.g., cell-associated HIV-1 RNA, total HIV-1 DNA, histone acetylation, PTEF-b activation), those assays will be performed using peripheral blood mononuclear cells (PBMCs). The team carefully reassessed the priorities for the use of these cells based on advances in the field since the prior protocol version. Accordingly, the relevant objectives and outcomes measures sections have been updated.

1.3 Secondary Objectives

1.3.**1** To assess changes in histone acetylation levels and P-TEFb **activation** in **CD4+ and CD8+ T-cells** prior to and following a single dose of RMD in Cohorts 1-3 and **in PBMCs** prior to and following each of multiple RMD doses in Cohort 4.

1.3.**2** To assess changes in total HIV-1 DNA in resting and total CD4+ T-cells prior to and following a single dose of RMD in Cohorts 1-3 and **in PBMCs** prior to and following each of multiple RMD doses in Cohort 4.

1.3.**3** To obtain pharmacokinetic (PK) data for RMD and coadministered antiretroviral drugs prior to and following a single dose of RMD in Cohorts 1-3 and following the third and fourth doses in Cohort 4 to assess potential drug-drug interactions.

1.3.4 To assess changes in the levels of cellular immune activation by evaluating the proportion of CD4+ and CD8+ T-cells co-expressing CD38/HLA-DR or CD69/CD25 on CD4+ and CD8+ T cells prior to and following a single dose or multiple doses of RMD.

1.3.5 To assess apoptosis by evaluating the proportion of total lymphocytes staining with annexin V alone (early apoptosis) or both annexin V (apoptotic) and 7-amino-actinomycin D (7-AAD) (dead cells) prior to and following a single dose or multiple doses of RMD.

1.4 Exploratory Objectives

1.4.1 **To examine the efficacy of multiple doses of RMD for reducing the latent, inducible HIV-1 reservoir, as measured by the quantitative viral outgrowth assay (qVOA) assay in Cohort 4.**

1.4.**2** To assess changes in the proportion of cycling CD4+ and CD8+ T-cells by evaluating Ki67 expression prior to and following a single dose or multiple doses of RMD.

1.4.**3** To assess changes in systemic inflammation by evaluating the levels of soluble biomarkers such as IL-6, C-reactive protein (CRP), and D-dimer prior to and following a single dose or multiple doses of RMD.

1.4.**4** In Cohort 4, to assess HIV-specific immune response**s** following **the first and fourth** doses of RMD.

1.4.5 In Cohort 4, to assess host RNA expression profiles by RNAseq of PBMC prior to the first dose of RMD and following the first and fourth doses of RMD.

1.4.6 In Cohort 4, to assess the impact of multiple doses of RMD on the proportion of CD4+ T-cells with intact proviral DNA.

2.0 INTRODUCTION

2.1 Background

A major obstacle to eradicating HIV-1 infection is the persistence of virus in long-lived cells, such as latently-infected memory CD4+ T-cells. It has been estimated that the decay half-life of these cells exceeds 40 months and that more than 70 years of suppressive ART would be required to eliminate this viral reservoir [1-3]. A current estimate of the size of the latent HIV-1 reservoir is that approximately one in a million memory CD4+ T-cells contains integrated replication-competent HIV-1 provirus [4]. In addition, recent studies have shown that the majority of patients on ART with viremia suppressed to <50 HIV-1 RNA copies/mL have residual viremia that can be detected by assays with single copy sensitivity [5]. Studies of ART intensification [6-8] that involve the addition of a potent antiretroviral drug to a suppressive regimen have failed to show any effect of this approach on the level of residual viremia. These results are consistent with viremia arising from stable reservoirs of long-lived, chronically infected cells and not from ongoing, complete cycles of viral replication, underscoring the need for new therapeutic approaches to eliminate these HIV-1 reservoirs.

Because viral replication in activated CD4+ T-cells usually results in the death of the host cell, one approach for eliminating the HIV-1 reservoir is to specifically activate viral replication in latently-infected CD4+ T-cells. If induction of HIV-1 expression kills the infected cell and ART prevents infection of new cells, there may be depletion of the HIV-1 reservoir. Alternatively, based on recent in vitro work, induction of HIV-1 from latency with vorinostat may not be sufficient to eliminate infected cells, and additional measures, such as stimulation of cytotoxic T lymphocytes, may be necessary to deplete cells that have been induced to express HIV-1 [9]. Nevertheless, activation of virus from latency is likely to be required in any strategy that seeks to eliminate HIV-1 infection.

Multiple agents have the potential to activate HIV-1 from latency, but to be optimally useful these drugs need to target the subset of CD4+ T-cells which harbor the virus. Immune activation with anti-CD3 and recombinant human interleukin (IL)-2 in HIV-1-infected patients on potent ART was studied a number of years ago with limited success and, in some cases, substantial toxicity [10, 11]. More recently, IL-7 has been shown to induce expression of latent HIV in vitro and in the SCID-hu mouse model of HIV-1 infection [12]. IL-7 induces expression of latent HIV-1 with minimal effects on T-cell phenotype but may also expand latent virus reservoirs by promoting T-cell proliferation [13 -14]. The effect of IL-7 on HIV-1 reservoirs is currently being tested in clinical trials such as ERAMUNE [15].

Another approach to inducing HIV-1 expression in latently-infected cells is to target cellular mechanisms that repress proviral transcription. Perhaps the most promising of these approaches is modulation of the activity of histone deacetylases, a family of chromatin remodeling enzymes that control gene expression, through the use of specific inhibitors of these enzymes.

2.2 Rationale

Studies of Histone Deacetylase Inhibitors to Reverse HIV-1 Latency

Histone deacetylase inhibitors (HDACi) induce HIV-1 expression by increasing histone acetylation and facilitating transcriptional activation of HIV-1. Several HDACi have been studied in vitro as inducers of HIV-1 expression, of which two, valproic acid and vorinostat, have been studied in HIV-infected participants [16-23].

Valproic Acid

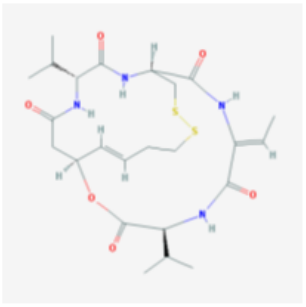
Valproic acid is used clinically as an anticonvulsant. In addition to blocking voltage gated sodium channels and Type-T calcium channels, valproic acid is a weak HDACi. Ylisastiqui et al. [16] demonstrated that valproic acid induced outgrowth of HIV from resting memory CD4+ cells of aviremic HIV-1 infected participants. Lehrman et al. [17] dosed patients with valproic acid and also intensified the suppressive ART regimen with enfuvirtide. In three of four participants studied, they observed a reduction in the frequency of resting memory T-cells from which infectious virus could be recovered. Other studies of valproic acid were not able to confirm that finding [18]. Of note, valproic acid is a nonspecific and weak HDACi. Therefore, the Food and Drug Administration (FDA)-approved doses of valproic acid are not likely to result in HIV-1 activation in vivo [19], and doses that may be required to exert a significant effect on virus activation may have unacceptable long-term toxicities.

Vorinostat

Vorinostat (suberoylanilide hydroxamic acid [SAHA] or Zolinza®) is the other HDACi that is currently being evaluated as an inducer of latent HIV-1 [20-22]. Vorinostat is a class I and class II HDACi that is FDA-approved for the treatment of cutaneous T-cell lymphoma (CTCL). Archin [23] and Contreras [22] found that vorinostat induced HIV-1 production from resting CD4+ T-cells of HIV-1 infected patients with suppressed viremia on ART. These findings provided in vitro data supportive of two ongoing phase I/II clinical trials of vorinostat in HIV-infected people. In a recent report from an ongoing trial, eight participants who received a single 400 mg dose of oral vorinostat had a mean 4.8-fold (range 1.5-10) induction of cell-associated RNA levels in resting CD4+ cells [23]. The single dose of vorinostat was well-tolerated. It should be noted, however, that vorinostat scores positive in the AMES test indicating that it is mutagenic. This presents a potential barrier to multiple dose administration of vorinostat to otherwise healthy HIV-infected patients on suppressive ART. Nevertheless, a clinical trial of vorinostat administered daily for 14 days in HIV-infected participants with suppressed viremia in Australia has concluded and demonstrated an increase in HIV transcription from latency in the majority of the trial participants [40].

Romidepsin

Figure·1::Romidepsin¶



(1S,4S,7Z,10S,16E,21R)-7-ethylidene-4,21-di(propan-2-yl)-2-oxa-12,13-dithia-5,8,20,23-tetrazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone¶

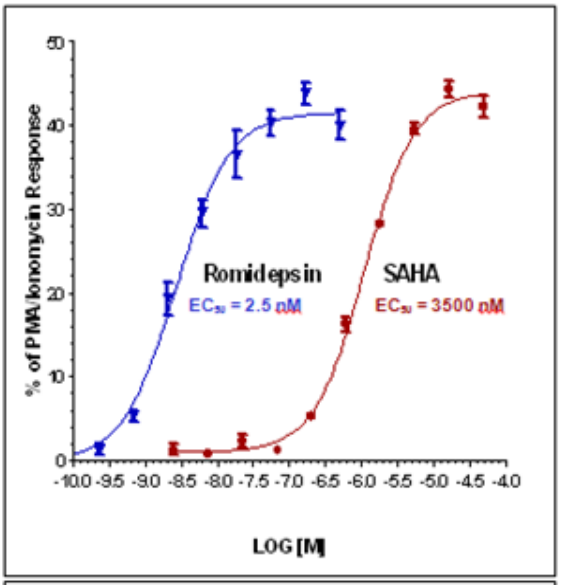


Figure 2: Induction of HIV-1 by romidepsin and vorinostat (SAHA) in a primary cell latency model*

\Romidepsin (Istodax® package insert October 2014) is a cyclic peptide HDACi (Figure 1) that was FDA-approved in 2009 for the treatment of CTCL. Romidepsin (RMD) is a substantially more potent HDACi (1000 to 20,000-fold) than vorinostat. RMD inhibits HDACs 1, 2, and 3 (IC_{50} ~30 pM vs. 100 - 500 nM for SAHA), HDAC 5 (IC_{50} = 12 pM vs. ~200 nM for SAHA) and HDACs 9, 10, 11 (IC_{50} ~100 – 400 pM vs. 300 – 500 nM). In patients with CTCL, RMD is administered as a 4-hour intravenous infusion at a dose of 14mg/m^2, which is the maximum tolerated dose (MTD), as three sequential doses given

on days 1, 8, and 15 of a 28-day cycle, usually for multiple cycles. Following a 4-hour intravenous administration of RMD at 14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle in patients with T-cell lymphomas, the terminal half-life (t1/2) was approximately 3 hours. No accumulation of RMD was observed after repeated dosing. Early clinical trials of RMD in CTCL patients revealed a potentially increased risk of QTc prolongation. As a result, the package insert for this drug indicates that it should not be given to a patient with a prolonged QTc. Side effects of RMD at the MTD include nausea, fatigue, vomiting, and anorexia. Common first cycle toxicities reported include bone marrow suppression and transient elevations of liver function tests [24-25, 32]. In clinical trials of RMD for T-cell lymphoma, bone marrow suppression has been associated with fatal and serious infections as well as reactivation of EBV and hepatitis B virus. RMD is predominantly metabolized by the cytochrome P450 enzyme CYP3A4. RMD is highly protein bound in plasma (92% to 94%) over the concentration range of 50 ng/mL to 1000 ng/mL with α1-acid-glycoprotein (AAG) being the principal binding protein. Although there are no formal drug interaction studies for RMD, strong CYP3A4 inhibitors may increase plasma concentrations of RMD. RMD is also a substrate of the efflux transporter P-gp (ABSB1); hence drugs that inhibit P-gp may increase plasma concentrations of RMD. Finally, RMD competes with beta estradiol for binding to estrogen receptors, which inhibits their function (RMD Investigators Brochure v 10.0 May 2012).

Table **2.2-1**: Induction of HIV-1 RNA *ex vivo*

HIV-infected donor	Fold increase over no drug control	*p* value vs. control
1	4.8	0.03
2	5.6	0.006
3	14.0	0.0008
4	3.0	0.0005
5	5.9	0.02
6	14.0	0.02
7	5.2	0.00002
8	2.8	0.01
9	16.0	0.00003
10	20.1	0.0003
11	1.8	0.4
12	5.8	0.005
13	12.3	0.001
	Avg = 8.6	
HIV-1 RNA levels were measured by Roche Taqman v2.0 at day 6 in culture supernatants of CD4+ memory T-cells from patients on suppressive ART. Intracellular HIV RNA was not measured.		

In laboratory studies, Gilead Sciences has found that RMD is approximately 1000-fold more potent than vorinostat for inducing latent HIV-1 expression, using both a modified version of the primary cell latency model described by Bosque and Planelles [26] (Figure 2) and memory T-cells from HIV-infected participants on suppressive ART (Table **2.2-1**). When tested at 5 nM [approximately 6% of the free fraction at the peak plasma concentration (C_{max}) after a 4 hour IV infusion of 14mg/m^2], RMD induced HIV-1 expression in cells from 12 of 13 HIV-infected participants (92% response rate; Table **2.2-1**) with an average induction over the no drug control of 8.6-fold. Of note, when vorinostat was tested at a concentration of 2.5 μM (approximately 5 times the free fraction at C_{max} after a 400 mg dose) in a similar assay, HIV-1 expression was induced in only 3 of 25 participants (17%) [27].

We have also found that a 4-hour in vitro pulse of 5 nM RMD, which mimics the 4-hour IV infusion administered to CTCL patients, is sufficient to induce HIV-1 expression ex vivo in cells from HIV-infected participants on suppressive ART. When tested at higher levels (20 nM, 40nM, and 80 nM) in cells from HIV-infected participants on suppressive ART, a 4-hour pulse of RMD increased HIV-1 RNA expression in culture supernatants by 6-, 8- and 10-fold, respectively (Unpublished observations, Gilead Sciences, Inc.).

Of note, the free fraction of RMD at C_{max} after a 14 mg/m^2 dose is well in excess (16-fold greater) of the EC_{50} required to induce latent HIV. This same ratio for vorinostat after a 400 mg oral dose is 0.15-fold (ie, only 15% of the EC_{50} for HIV-1 induction in vitro). Collectively, these data suggest that RMD may be a more robust inducer of HIV-1 expression in vivo than vorinostat. The in vitro potency of RMD for HIV-1 induction suggests that a much lower dose than that used to treat CTCL patients will be able to induce latent HIV-1 in vivo. A dose of RMD that corresponds to only 4% of the MTD should produce a plasma concentration that is approximately equivalent to the EC_{50} for induction of latent HIV-1 in vitro. A summary of the C_{max} values derived from five human PK studies (26a, 26b, 26c, 26d, 26e) following 4-hour intravenous infusions of RMD is presented in Table 2**.2-2**.

Table 2**.2-2**: RMD Human Pharmacokinetics (units for doses = mg/m^2; n = number of participants dosed)

	Dose	1	1	1.7	2	2.5	3.25	3.5	5	6.5	7.5
	n=	*3*	*3*	*3*	*4*	*3*	*4*	*1*	*2*	*3*	*1*
Mean Cmax (ng/mL)		35.6	90	40.8	17	49.5	230	129.9	420	211.8	690
SD		22.2	10	20.9	6	31.7	110	NA	NA	77.1	NA

	Dose	9.1	10	12.7	13.3	17.7	17.8	18	23.5	24.9
	n=	*4*	*2*	*3*	*6*	*2*	*11*	*12*	*1*	*8*
Mean Cmax (ng/mL)		162.6	740	224.7	540	370	553.8	800	210	478.2
SD		53.8	NA	241	680	NA	299.5	700	NA	316.6

	Dose	10	13	17	22
	n=	*3*	*4*	*3*	*2*
Median Cmax (ng/mL)		1364	1017	2414	3103
Range		318-6865	610-2192	1069-4850	1570-4636

Based on the preclinical work presented in this protocol, three dose levels of RMD will be studied in HIV-infected participants on suppressive ART: 0.5 mg/m^2 (0.6 times EC_{50}, 4% of the MTD of 14 mg/ m^2); 2 mg/m^2 (2.3 times EC_{50}, 14% of the MTD), and 5 mg/m^2 (6 times EC_{50}, 35% of the MTD). As described above, the MTD for RMD was determined following three sequential 14 mg/m^2 doses (on days 1, 8, 15), but only a single dose will be administered in the current study. Thus, the percent of the MTD that will be given in this study will be 3-fold lower than the 4%, 14%, and 35% noted. Finally, in contrast to vorinostat, RMD is AMES negative (and therefore not expected to be mutagenic); as a result, multiple doses could be investigated in HIV-infected populations if single doses are safe and well tolerated.

In addition to the preclinical results summarized above, RMD has been studied in a single-arm trial of 6 HIV-infected participants on long-term ART. Each participant received 3 weekly infusions of RMD at 5 mg/m^2. Following the RMD infusions, cell-associated HIV-1 RNA and, in five of 6 cases, plasma HIV-1 RNA increased modestly (range 46-103 copies/ml, p=0.04)) following the second infusion, suggesting the drug may be activating virus expression. However, HIV-1 DNA and virus outgrowth levels did not decrease. RMD was well tolerated with no Grade 3 or 4 study-related adverse events (AE) [35]. T cell function was not reduced by RMD, allaying a concern raised by an in vitro study [36]. In a second single-arm trial, 17 participants received a therapeutic vaccine (Vacc-4x) followed by RMD 5 mg/m^2 once a week for 3 weeks. There was a decline in HIV-1 DNA after RMD treatment. In terms of adverse events, 95% were Grade 1 and there were no grade 4 events [37].

The ACTG is committed to studying novel therapies to potentially reduce and eradicate the HIV-1 latent reservoir. As a potent HDACi, RMD administered in combination with ART may serve as an important component of an eradication strategy. It is acknowledged, however, that activation of viral expression may not kill HIV-infected cells [28], and that additional interventions, including the stimulation of cytotoxic T lymphocytes, may be required to deplete HIV-1 reservoirs [29].

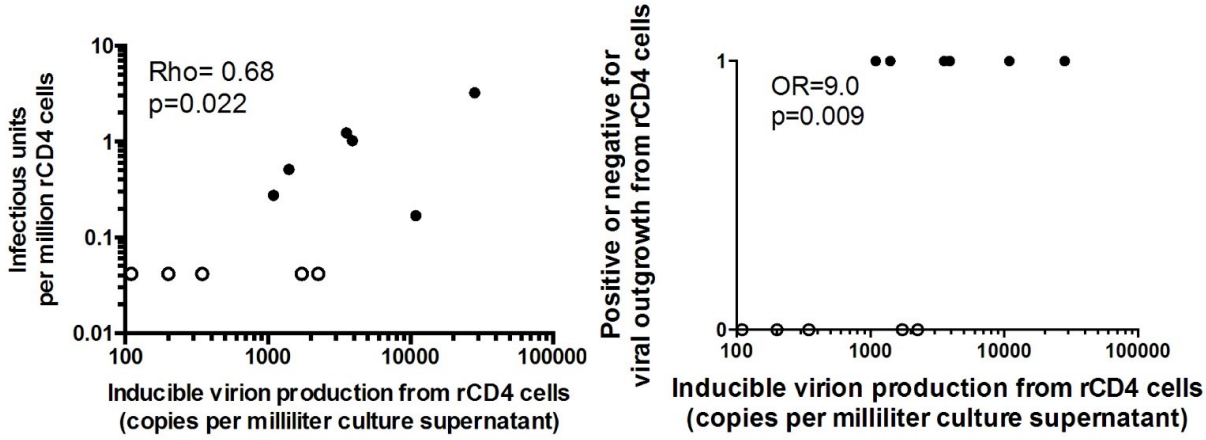
Total Virus Recovery Assay

In Cohorts 1 and 2, changes in the inducible HIV-1 reservoir were assessed using the total virus recovery (TVR) assay. Samples for this assay were obtained from leukapheresis products. However, because leukapheresis was a major logistical barrier to study enrollment, it was removed beginning in Cohort 3. Following optimization of a revised version of the assay, it will be feasible in Cohort 4 for the TVR assay to be performed without requiring leukapheresis. Modification of the TVR assay for blood samples has been accomplished at the Pitt Virology Laboratory and Monogram, with support from Gilead.

TVR was chosen as the measure of the inducible HIV-1 reservoir for this study **in Cohorts 1-2** because it is capable of detecting a quantitative and significant reduction in the total inducible HIV-1 reservoir. TVR is less variable than the quantitative viral outgrowth assay (qVOA): 2-3 fold variation with TVR compared to 6-fold with qVOA [38]. The TVR assay is also more efficient, more sensitive (rare censoring), and 5-fold less costly than qVOA. The goal of A5315 is to detect any effect of RMD on the total

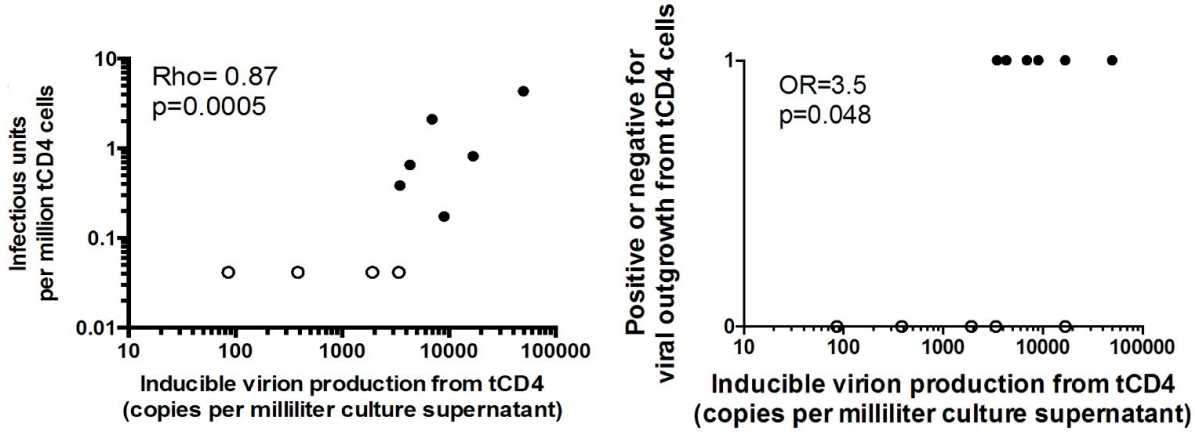
inducible HIV-1 reservoir and although TVR does not distinguish infectious from defective virus, developmental work at the Pitt Virology Laboratory shows that TVR from resting $CD4^+$ cells (Fig 1) and total $CD4^+$ cells (Fig 2) are highly correlated with qVOA (Cillo et al, preliminary unpublished data). These data show that TVR can be a reasonable surrogate in studies where full qVOA is not feasible. The expected lower limit of detection using the TVR assay is 40 copies of HIV-1 RNA produced by 1 million resting CD4+ T cells.

Figure 1



Exact logistic regression with PVR from rCD4 cells is significantly related to IUPM from resting CD4 cells

Figure 2



Exact logistic regression with PVR from total CD4 cells is significantly related to IUPM from rCD4 cells

Monogram TVR Development
For Cohorts 1 and 2, Monogram Biosciences used leukopaks collected pre- and post-treatment from participants. Standard Ficoll separation of the blood components in a partial leukopak/RPMI mixture yielded 2-5 billion PBMCs. Resting $CD4^+$ T cells were isolated using a Stem Cell Easy SepTM negative selection procedure.

Summary of Cohorts 1 – 3
Fifteen participants enrolled into Cohort 1 and received a single infusion of 0.5 mg/m^2 of RMD or placebo for RMD. This dose was well tolerated: no AEs or serious AEs (SAEs) definitely related to RMD were reported. Accordingly, following an SMC review, Cohort 2 was opened to accrual. Fourteen participants enrolled into this cohort and received a single dose of 2 mg/m^2 of RMD or placebo for RMD. Again, this dose was well-tolerated: no AEs or SAEs definitely related to RMD were reported. Note that self-reported low-grade AEs that were deemed possibly related to study treatment in both Cohorts 1 and 2 included, but were limited to, fatigue, headache, and diarrhea.

Following the second SMC review, Cohort 3, was opened to accrual. Starting with this cohort, leukapheresis was replaced by blood collections. As noted previously, this change was made based on the strong correlation of virologic measures in total and resting CD4+ T cells isolated from blood and from leukopaks. Twelve to fifteen participants will enroll into Cohort 3 and receive a single infusion of 5 mg/m^2 of RMD or placebo for RMD. As with the previous cohorts, safety and tolerability data will be reviewed by the SMC before enrollment to Cohort 4 is permitted. Safety data from at least 12 evaluable Cohort 3 participants should be sufficient to determine if it is safe to proceed with Cohort 4 enrollment. In addition, since the study was originally designed, published safety data regarding dosing of RMD in HIV-infected individuals is now available from other studies of RMD (REDUC A and B) that support administering multiple doses of RMD at 5 mg/m^2 [35, 37].

Data from Cohorts 1, 2, and 3 will be analyzed collectively once available.

Rationale for Cohort 4
In Version 3.0 of the study, a new cohort (Cohort 4) is being added to evaluate the safety and tolerability of multiple doses of RMD and study its effect on HIV reactivation and reduction in the latent HIV reservoir. Fifteen participants will be randomized to receive 4 infusions of 5 mg/m^2 RMD or placebo for RMD, every 2 weeks, over a 6-week period. As in the three earlier cohorts, the randomization will be 4:1 (12 participants randomized to receive RMD and 3 to receive placebo infusions). Three RMD infusions of 5 mg/m^2 have been found to be well tolerated thus far in REDUC-A and REDUC-B studies [35, 37]. The safety and tolerability of a single dose of RMD 5 mg/m^2 in HIV-infected individuals will also be evaluated in Cohort 3 of this study.

Data from RMD studies conducted to date are insufficient to address whether RMD can reduce HIV reservoirs. A modest reduction in the inducible HIV reservoir was noted in the REDUC-B study that combined 3 doses of RMD (5 mg/m^2) with immunization with a Vacc-4x peptide, but there was extensive censoring of the viral outgrowth data below the

limit of detection, making it difficult to draw firm conclusions. The question of reservoir reduction will be addressed in Cohort 4.

For Cohort 4, a quantitative viral outgrowth assay (qVOA) will be performed instead of the modified TVR assay [41]. **The team opted to perform the qVOA since it is the current gold-standard assay for quantifying the latent reservoir.**

Testing Plan for Study Samples
Study endpoint assessments to be performed include plasma HIV-1 RNA monitoring (by standard ultrasensitive and single copy assays) and cell-associated HIV-1 RNA analyses to determine whether RMD activates HIV-1 expression in vivo [33]. In addition, ex vivo HIV-1 induction from study participants' resting CD4+ T-cells by RMD and PMA/ionomycin will be performed to determine the size of the RMD and PMA/ionomycin inducible HIV-1 reservoirs, before and 14 days after in vivo RMD dosing. Histone acetylation will be measured in total CD4+ T-cells to determine if RMD modulates HDAC activity in vivo. P-TEFb upregulation and phosphorylation status will be assessed since activation of this kinase complex is essential for HIV transcriptional elongation. Measurements of CycT1 levels provide an estimate of the total amount of P-TEFb in the cells, while measurements of the CDK9 Ser-175 phosphorylation provides an estimate of the amount of P-TEFb that is actively engaged in transcription. Since P-TEFb is minimally expressed in resting memory T-cells but becomes activated within 30 minutes after T-cell receptor stimulation, this assay provides a biologically-relevant early marker that may be correlated with extent of HIV expression. **HIV-specific immune responses** will be **assessed** on samples collected in Cohort 4 prior to the first RMD or placebo infusion and following the fourth infusion (two separate collections at each of these time points).

Much of this testing plan was developed at the time that PBMCs were to be collected via leukapheresis. Starting in Cohort 3, leukapheresis has been replaced with a blood collection.

3.0 STUDY DESIGN

This is a multicenter, phase I/II safety, dose-escalation, and preliminary efficacy study. The study will be conducted in two stages. Stage 1 is a placebo-controlled, double-blinded, randomized, single administration with inter-group dose escalations in three distinct dosing cohorts, followed by Stage 2, a placebo-controlled, double-blinded, randomized, multi-dose administration in a single cohort. Because safety is a primary objective, and there are limited data on longitudinal changes in cell-associated HIV-1 RNA levels, a placebo-controlled cohort is considered necessary to accurately assess treatment-related toxicity and efficacy. Accrual of the first five participants in any cohort will be limited to one participant in a 3-day period.

The overall goal of the Stage 1 cohorts (Cohorts 1-3) in this exploratory study is to identify single doses of RMD that are safe and well-tolerated in HIV-infected patients on ART, and that induce HIV-1 expression. If safety is established in Cohort 3 (i.e., dose-escalation criteria are met), then Cohort 4, with multiple doses of RMD, will be opened

with the goal of assessing safety, tolerability, induction of HIV-1 expression, and depletion of latent reservoirs, as assessed by infectious virus recovery from resting CD4+T-cells [30,31]. Toxicity related to the infusion of a single dose and of multiple doses of RMD or placebo will be evaluated systematically. Dose escalation will be based on safety outcomes. Efficacy and response data from lower dose cohorts will not be available prior to the enrollment of the subsequent dose cohorts.

In all cohorts, RMD or placebo infusion will occur over 4 hours. An electrocardiogram (ECG) will be performed prior to and following RMD administration. In Cohorts 1 – 3, pharmacokinetic (PK) sampling will be performed prior to and following RMD infusion to measure ARV (RAL, DTG, and EFV) and RMD plasma concentrations and to evaluate any drug-drug interactions. In Cohort 4, similar PK testing will be performed before and after the third and fourth RMD infusions.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria – Cohorts 1, 2, and 3

4.1.1 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen or plasma HIV-1 RNA.

Note: The term “licensed” refers to a US FDA-approved kit, which is required for all IND studies.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (eg, indirect versus competitive), or a Western blot or a plasma HIV-1 RNA assay.

4.1.2 Receiving two (or more) nucleoside or nucleotide reverse transcriptase inhibitors with raltegravir, dolutegravir, or efavirenz for at least 90 days prior to study entry with no intention to change for the duration of the study.

NOTE: Candidates receiving PI-based regimens or regimens containing rilpivirine, maraviroc, etravirine, or cobicistat will be excluded to avoid drug-drug-interactions. RMD is metabolized by CYP3A4, and co-administration of PIs or other agents that inhibit CYP3A4 could significantly increase RMD concentrations.

4.1.3 Documentation of at least two historical HIV-1 RNA measurements <50 copies/mL while on ART obtained by standard ultrasensitive assay. Documentation of the first measurement must be from a result obtained between 365 days and 91 days, inclusive, prior to study entry. Documentation of the second measurement must be from a result obtained between 730 days and 366 days, inclusive, prior to study entry. In addition, there must be no HIV-1 RNA values ≥50 copies/mL for at least 365 days prior to study entry.

4.1.4 CD4+ cell count ≥300 cells/mm^3 obtained within 90 to 50 days prior to study entry at any US laboratory that has a CLIA certification or its equivalent.

4.1.5 HIV-1 RNA level of <50 copies/mL obtained by standard ultrasensitive assay within 90 to 50 days prior to study entry.

4.1.6 HIV-1 RNA level ≥0.4 copies/mL obtained by single copy assay (SCA) within 90 to 50 days prior to study entry.

NOTE: This result must be available prior to the pre-entry visit.

4.1.7 The following laboratory values obtained within 21 to 0 days prior to study entry by any laboratory that has a CLIA certification or its equivalent.

- Absolute neutrophil count (ANC) ≥1500 cells/mm^3
- Hemoglobin ≥12.0 g/dL for men and >11.0 g/dL for women
- Platelet count ≥120,000/mm^3

4.1.8 The following laboratory values obtained within 21 to 7 days prior to study entry by any laboratory that has a CLIA certification or its equivalent.

- Creatinine clearance (CrCl) ≥60 mL/min
- Potassium and magnesium within normal limits (see section 6.3.7 for details)
- Aspartate aminotransferase (AST) (SGOT) <2.0 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) (SGPT) <2.0 x ULN
- Alkaline phosphatase <2.0 x ULN
- Total bilirubin <2.5 x ULN

4.1.9 HCV antibody negative result within 90 to 50 days prior to study entry or, for study candidates who are HCV antibody positive (based on testing performed at any time prior to study entry), a negative HCV RNA result obtained within 90 to 50 days prior to study entry.

4.1.10 Negative HBsAg result obtained within 90 to 50 days prior to study entry or a positive HBsAb result at any time prior to study entry.

4.1.11 For females of reproductive potential, negative serum or urine pregnancy test (latter with a sensitivity of ≤25 mIU/mL) at the screening visit**,** pre-entry visit within 21 to 7 days prior to study entry, and at entry prior to romidepsin infusion, by any US laboratory that has a CLIA certification or its equivalent.

Note A: Reproductive potential is defined as:

- Girls who have reached menarche or
- Women who have had menses within the past 12 months and who do not have an FSH >40 IU/L or
- Women who have had menses within the past 24 consecutive months if an FSH measurement is not available
- Women who have not undergone surgical sterilization (eg, hysterectomy, or bilateral oophorectomy, or bilateral salpingectomy).

Note B: Confirmation of the lack of reproductive potential is required. Written documentation or oral communication from a clinician or clinician's staff documented in source documents of one of the following must be provided: Physician report/letter, operative report or other source documentation in the patient record, discharge summary, laboratory report of azoospermia (required to document successful vasectomy), FSH measurement elevated into the menopausal range (as established by the reporting laboratory).

Note C: If the female candidate cannot provide written proof of a male partner's vasectomy status, the oral report of her partner's status should be written into the source documents.

4.1.12 Female candidates of reproductive potential must refrain from participating in active attempts to become pregnant, and, if participating in sexual activity that could lead to pregnancy, must agree to use at least two reliable forms of contraception that are non-estrogen based. All female participants of reproductive potential (as defined in section 4.1.11) must be instructed to use contraceptives for 6 months/180 days after completing RMD/placebo infusion.

Acceptable forms of contraception include:

- Condoms (male or female) with or without spermicidal agent
- Diaphragm or cervical cap with spermicide
- Non-hormonal or progestin-only containing intrauterine device (IUD) (eg, Mirena, Implanon, Nuva Ring)
- Tubal ligation
- Non-estrogen containing formulations of hormonal birth control drugs, given by pills, shots, or placed on or under the skin, for at least 90 days prior to study entry

NOTE: Providers and candidates/participants should be advised that not all contraceptive choices listed above can prevent HIV transmission and that some may actually increase the risk of HIV acquisition. Participants who are sexually active with HIV negative or unknown HIV serostatus partners should be advised that they need to consider effective strategies for reducing the risk of HIV transmission, as well as meeting the requirement for effective contraception

during their participation in the study. Participants should discuss contraceptive choices and HIV risk reduction methods with their health care provider**.**

Females who are not of reproductive potential are not required to practice contraception.

4.1.13 Karnofsky performance score ≥ 80 within 21 to 7 days prior to study entry.

4.1.14 Men and women age ≥ 18 years

4.1.15 Ability and willingness to provide written informed consent.

4.1.16 Site investigator anticipates that a fully active alternative ART regimen could be constructed in the event of virologic failure on the current ART regimen.

4.2 Exclusion Criteria – Cohorts 1, 2, and 3

4.2.1 History of or current malignancy requiring cytotoxic therapy.

4.2.2 Bacterial, fungal or viral infection (other than HIV) requiring systemic therapy within 30 days prior to entry.

4.2.3 History of or current cytomegalovirus (CMV) end organ disease (e.g., retinitis).

4.2.4 History of or current AIDS-related syndromes or symptoms that pose a perceived excessive risk for study drug-related morbidity, as determined by the site investigator.

4.2.5 Chronic, acute, or recurrent infections that are current and serious, in the opinion of the site investigator, for which the participant has not completed at least 14 consecutive days of therapy within 30 days prior to study entry and/or is not clinically stable.

4.2.6 Active autoimmune disorders including but not limited to inflammatory bowel diseases, scleroderma, severe psoriasis as determined by the site investigator, systemic lupus erythematosus, rheumatoid arthritis, and optic neuritis.

4.2.7 History of seizure disorders.

4.2.8 History of anticonvulsant use within 60 days prior to study entry.

4.2.9 History of myocardial infarction (MI) within 6 months prior to study entry, history of QTc prolongation (defined as ECG with QTc intervals > 450 ms) at any time prior to study entry, New York Heart Association (NYHA) class III or IV heart failure at any time prior to study entry, or family history of prolonged QTc syndrome.

NOTE: See section 6.3.8 for information about calculating QTc.

4.2.10 Breastfeeding

4.2.11 Use of immunomodulators (eg, interleukins, interferons, cyclosporine), HIV vaccine, systemic cytotoxic chemotherapy, or investigational therapy within 60 days prior to study entry.

NOTE: Study candidates receiving stable physiologic glucocorticoid doses, defined as prednisone ≤10 mg/day, will not be excluded. Study candidates receiving inhaled or topical corticosteroids will not be excluded.

4.2.12 Any vaccination within 30 days prior to entry or intent to receive an elective vaccination (e.g., flu shot, hepatitis A or B vaccine) during the course of the study.

4.2.13 Intent to use cytokines (e.g., IL-2 or IL-12) during the course of the study.

NOTE: Prior administration of cytokines is not an exclusion criterion; however, at least 60 days between the most recent cycle of any cytokine and study entry is required.

4.2.14 Within 60 days prior to study entry, use of systemic azole antifungals (voriconazole, itraconazole, ketoconazole), dexamethasone, macrolide antibiotics (azithromycin, clarithromycin, erythromycin), antiretrovirals that are inhibitors of, or are metabolized by CYP3A4 (atazanavir, ritonavir, nelfinavir, indinavir, saquinavir, darunavir, lopinavir, rilpivirine, maraviroc), cobicistat, warfarin, nefazodone, rifamycins (rifabutin, rifampin, rifapentine), St. John's Wort, carbamazepine, phenytoin, phenobarbital, amiodarone, dofetilide, pimozide, procainamide, quinidine, sotalol, and birth control products containing estrogen, drugs that are p-glycoprotein inhibitors, and drugs that prolong the QTc interval with a risk of Torsades de Pointes [see the A5315 Manual of Procedures (MOPS) on the PSWP for a complete list of drugs related to this criterion].

NOTE: The use of fluconazole is permitted.

4.2.15 Known allergy/sensitivity or any hypersensitivity to components of RMD or its formulation.

4.2.16 Use of histone deacetylase inhibitors (e.g., vorinostat, valproic acid) at any time prior to study entry.

4.2.17 Active illicit drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.18 Acute or serious illness requiring systemic treatment and/or hospitalization that is not resolved within 30 days prior to entry.

4.2.19 Psychosocial conditions that would prevent study compliance and follow-up, as determined by the site investigator.

4.2.20 Documented opportunistic infections within 60 days prior to entry.

4.3 Inclusion Criteria – Cohort 4, Step 1

4.3.1 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen or plasma HIV-1 RNA.

NOTE: The term “licensed” refers to a US FDA-approved kit, which is required for all IND studies.

WHO and CDC guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA assay.

4.3.2 Receiving two or more nucleoside or nucleotide reverse transcriptase inhibitors with raltegravir or dolutegravir for at least 90 days prior to study entry with no intention to change for the duration of the study.

NOTE A: The use of other ART regimens for ≤7 days within 90 days prior to study entry will be permitted.

NOTE B: Candidates receiving PI-based regimens or regimens containing efavirenz, rilpivirine, maraviroc, etravirine, or cobicistat will be excluded to avoid drug-drug-interactions. RMD is metabolized by CYP3A4, and co-administration of PIs or other agents that inhibit CYP3A4 could significantly increase RMD concentrations.

NOTE C: Candidates who switch from a tenofovir disoproxil fumarate to a tenofovir alafenamide formulation will be considered as being on a stable regimen because this change in formulation is not regarded as a regimen change.

4.3.3 Documentation of at least two historical HIV-1 RNA measurements <50 copies/mL while on ART obtained by standard ultrasensitive assay. Documentation of the first measurement must be from a result obtained between 365 days and 61 days, inclusive, prior to study entry. Documentation of the

second measurement must be from a result obtained between 730 days and 366 days, inclusive, prior to study entry. In addition, there must be no HIV-1 RNA values ≥50 copies/mL for at least 365 days prior to study entry.

4.3.4 CD4+ cell count ≥300 cells/mm^3 obtained between 36 and 60 days prior to study entry (screening visit) at any US laboratory that has a CLIA certification or its equivalent.

4.3.5 HIV-1 RNA level of <50 copies/mL obtained by standard ultrasensitive assay at screening (between 36 and 60 days prior to study entry).

4.3.6 The following laboratory values obtained at pre-entry (between 3 and 14 days prior to study entry) by any laboratory that has a CLIA certification or its equivalent.

- Absolute neutrophil count (ANC) ≥1500 cells/mm^3
- Hemoglobin ≥12.0 g/dL for men and >11.0 g/dL for women
- Platelet count ≥120,000/mm^3
- Creatinine clearance (CrCl) ≥60 mL/min
  NOTE: A calculator for estimating the CrCl can be found at www.fstrf.org/ACTG/ccc.html
- Potassium and magnesium within normal limits (see section 6.3.7 for details.)
- Aspartate aminotransferase (AST) (SGOT) <2.0 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) (SGPT) <2.0 x ULN
- Alkaline phosphatase <2.0 x ULN
- Total bilirubin <2.5 x ULN

4.3.7 HCV antibody negative result at screening (between 36 and 60 days prior to study entry) or, for study candidates who are HCV antibody positive (based on testing performed at any time prior to study entry), a negative HCV RNA result obtained at screening.

4.3.8 Negative HBsAg result obtained at screening (between 36 and 60 days prior to study entry) or a positive HBsAb result at any time prior to study entry.

4.3.9 For females of reproductive potential, negative urine pregnancy test (with a sensitivity of ≤25 mIU/mL) at screening (between 36 and 60 days prior to study entry), at pre-entry (between 3 and 14 days prior to study entry), and at entry prior to infusion, by any US laboratory that has a CLIA certification or its equivalent.

NOTE A: Reproductive potential is defined as:

- Girls who have reached menarche or
- Women who have had menses within the past 12 months and who do not have an FSH >40 IU/L or
- Women who have had menses within the past 24 consecutive months if an FSH measurement is not available
- Women who have not undergone surgical sterilization (eg, hysterectomy, or bilateral oophorectomy, or bilateral salpingectomy).

NOTE B: Confirmation of the lack of reproductive potential is required. Written documentation or oral communication from a clinician or clinician's staff documented in source documents of one of the following must be provided: Physician report/letter, operative report or other source documentation in the patient record, discharge summary, laboratory report of azoospermia (required to document successful vasectomy), FSH measurement elevated into the menopausal range (as established by the reporting laboratory).

NOTE C: If the female candidate cannot provide written proof of a male partner's vasectomy status, the oral report of her partner's status should be written into the source documents.

4.3.10 Female candidates of reproductive potential must refrain from participating in active attempts to become pregnant, and, if participating in sexual activity that could lead to pregnancy, must agree to use at least two reliable forms of contraception that are non-estrogen based. All participants of reproductive potential will be instructed to use contraceptives for 6 months or 180 days after completing RMD/placebo infusion.

Acceptable forms of contraception include:

- Condoms (male or female) with or without spermicidal agent
- Diaphragm or cervical cap with spermicide
- Non-hormonal or progestin-only containing intrauterine device (IUD) (e.g., Mirena, Implanon, Nuva Ring)
- Tubal ligation
- Non-estrogen containing formulations of hormonal birth control drugs, given by pills, shots, or placed on or under the skin, for at least 90 days prior to study entry

NOTE: Providers and candidates/participants should be advised that not all contraceptive choices listed above can prevent HIV transmission and that some may actually increase the risk of HIV acquisition. Participants who are sexually active with HIV negative or unknown HIV serostatus partners should be advised

that they need to consider effective strategies for reducing the risk of HIV transmission, as well as meeting the requirement for effective contraception during their participation in the study. Participants should discuss contraceptive choices and HIV risk reduction methods with their health care provider.

Females who are not of reproductive potential are not required to practice contraception.

4.3.11 Karnofsky performance score ≥ 80 at pre-entry (between 3 and 14 days prior to study entry)

4.3.12 Men and women age ≥18 years

4.3.13 Ability and willingness to provide written informed consent.

4.3.14 Site investigator anticipates that a fully active alternative ART regimen could be constructed in the event of virologic failure on the current ART regimen.

4.4 Exclusion Criteria – Cohort 4, Step 1

4.4.1 History of or current malignancy requiring cytotoxic therapy.

4.4.2 Bacterial, fungal or viral infection (other than HIV) requiring systemic therapy within 30 days prior to entry.

4.4.3 History of or current cytomegalovirus (CMV) end organ disease (e.g., retinitis).

4.4.4 History of or current AIDS-related syndromes or symptoms that pose a perceived excessive risk for study drug-related morbidity, as determined by the site investigator.

4.4.5 Chronic, acute, or recurrent infections that are current and serious, in the opinion of the site investigator, for which the participant has not completed at least 14 consecutive days of therapy within 30 days prior to study entry and/or is not clinically stable.

4.4.6 Active autoimmune disorders including but not limited to inflammatory bowel diseases, scleroderma, severe psoriasis as determined by the site investigator, systemic lupus erythematosus, rheumatoid arthritis, and optic neuritis.

4.4.7 History of seizure disorders.

4.4.8 History of anticonvulsant use within 60 days prior to study entry.

4.4.9 History of myocardial infarction (MI) within 6 months prior to study entry, history of QTc prolongation (defined as ECG with QTc intervals > 450 ms) at any time prior to study entry, New York Heart Association (NYHA) class III or IV heart

failure at any time prior to study entry, or family history of prolonged QTc syndrome.

NOTE: The correction formula expected to be used is the Fridericia correction (available on the DMC website: https://www.fstrf.org).

4.4.10 Breastfeeding

4.4.11 Use of immunomodulators (e.g., interleukins, interferons, cyclosporine), HIV vaccine, systemic cytotoxic chemotherapy, or investigational therapy within 60 days prior to study entry.

NOTE: Study candidates receiving stable physiologic glucocorticoid doses, defined as prednisone ≤10 mg/day, will not be excluded. Study candidates receiving inhaled or topical corticosteroids will not be excluded.

4.4.12 Any vaccination within 30 days prior to entry or intent to receive an elective vaccination (e.g., flu shot, hepatitis A or B vaccine) during the course of the study.

4.4.13 Intent to use cytokines (e.g., IL-2 or IL-12) during the course of the study.

NOTE: Prior administration of cytokines is not an exclusion criterion; however, at least 60 days between the most recent cycle of any cytokine and study entry is required.

4.4.14 Within 60 days prior to study entry, use of systemic azole antifungals (voriconazole, itraconazole, ketoconazole), dexamethasone, macrolide antibiotics (azithromycin, clarithromycin, erythromycin), antiretrovirals that are inhibitors of, or are metabolized by CYP3A4 (atazanavir, ritonavir, nelfinavir, indinavir, saquinavir, darunavir, lopinavir, rilpivirine, maraviroc), cobicistat, warfarin, nefazodone, rifamycins (rifabutin, rifampin, rifapentine), St. John's Wort, carbamazepine, phenytoin, phenobarbital, amiodarone, dofetilide, pimozide, procainamide, quinidine, sotalol, and birth control products containing estrogen, drugs that are p-glycoprotein inhibitors, and drugs that prolong the QTc interval with a risk of Torsades de Pointes (see the A5315 Manual of Procedures [MOPS] on the PSWP for a complete list of drugs related to this criterion).

NOTE: The use of fluconazole is permitted.

4.4.15 Known allergy/sensitivity or any hypersensitivity to components of RMD or its formulation.

4.4.16 Use of histone deacetylase inhibitors (e.g., vorinostat, valproic acid) at any time prior to study entry.

4.4.17 Active illicit drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.4.18 Acute or serious illness requiring systemic treatment and/or hospitalization that is not resolved within 30 days prior to entry.

4.4.19 Psychosocial conditions that would prevent study compliance and follow-up, as determined by the site investigator.

4.4.20 Documented opportunistic infections within 60 days prior to entry.

4.4.21 Use of any of the medications listed in the Prohibited Medications table in the current A5315 MOPS, within the timeframes listed in that table.

4.5 Inclusion Criteria – Cohort 4, Step 2

4.5.1 HIV-1 RNA level of <50 copies/mL obtained by TaqMan v2.0 assay within 14 days prior to Step 2 registration.

4.5.2 For females of reproductive potential, negative urine pregnancy test (with sensitivity of ≤25 mIU/mL) obtained within 2 days prior to Step 2 registration by any US laboratory that has a CLIA certification or its equivalent.

4.5.3 Potassium and magnesium values within normal limits obtained within 7 days prior to Step 2 registration by any laboratory that has a CLIA certification or its equivalent (see section 6.3.7 for details).

4.5.4 The following laboratory values obtained within 7 days prior to Step 2 registration by any laboratory that has a CLIA certification or its equivalent.

- **Absolute neutrophil count (ANC) ≥1500 cells/mm^3**
- **Hemoglobin ≥12.0 g/dL for men and >11.0 g/dL for women**
- **Platelet count ≥120,000/mm^3**

4.6 Exclusion Criteria – Cohort 4, Step 2

4.6.1 Acute or serious illness requiring systemic treatment and/or hospitalization and that is not resolved by 7 days prior to Step 2 registration.

4.6.2 Receipt of any vaccination within 14 days prior to Step 2 registration.

NOTE: The infusion must not be performed within 14 days following any vaccination.

4.7 Inclusion Criteria – Cohort 4, Step 3

4.7.1 HIV-1 RNA level of <50 copies/mL obtained by TaqMan v2.0 assay within 14 days prior to Step 3 registration.

4.7.2 For females of reproductive potential, negative urine pregnancy test (with sensitivity of ≤25 mIU/mL) obtained within 2 days prior to Step 3 registration by any US laboratory that has a CLIA certification or its equivalent.

4.7.3 Potassium and magnesium values within normal limits obtained within 7 days prior to Step 3 registration by any laboratory that has a CLIA certification or its equivalent (see section 6.3.7 for details).

4.7.4 The following laboratory values obtained within 7 days prior to Step 3 registration by any laboratory that has a CLIA certification or its equivalent.
- **Absolute neutrophil count (ANC) ≥1500 cells/mm^3**
- **Hemoglobin ≥12.0 g/dL for men and >11.0 g/dL for women**
- **Platelet count ≥120,000/mm^3**

4.8 Exclusion Criteria – Cohort 4, Step 3

4.8.1 Acute or serious illness requiring systemic treatment and/or hospitalization and that is not resolved by 7 days prior to Step 3 registration.

4.8.2 Receipt of any vaccination within 14 days prior to Step 3 registration.

NOTE: The infusion must not be performed within 14 days following any vaccination.

4.9 Inclusion Criteria – Cohort 4, Step 4

4.9.1 HIV-1 RNA level of <50 copies/mL obtained by TaqMan v2.0 assay within 14 days prior to Step 4 registration.

4.9.2 For females of reproductive potential, negative urine pregnancy test (with sensitivity of ≤25 mIU/mL) obtained within 2 days prior to Step 4 registration by any US laboratory that has a CLIA certification or its equivalent.

4.9.3 Potassium and magnesium values within normal limits obtained within 7 days prior to Step 4 registration by any laboratory that has a CLIA certification or its equivalent (see section 6.3.7 for details).

4.9.4 The following laboratory values obtained within 7 days prior to Step 4 registration by any laboratory that has a CLIA certification or its equivalent.
- **Absolute neutrophil count (ANC) ≥1500 cells/mm^3**
- **Hemoglobin ≥12.0 g/dL for men and >11.0 g/dL for women**
- **Platelet count ≥120,000/mm^3**

4.10 Exclusion Criteria – Cohort 4, Step 4

4.10.1 Acute or serious illness requiring systemic treatment and/or hospitalization and that is not resolved by 7 days prior to Step 4 registration.

4.10.2 Receipt of any vaccination within 14 days prior to Step 4 registration.

NOTE: The infusion must not be performed within 14 days following any vaccination.

4.11 Study Enrollment Procedures

4.11.1 Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form approved, as appropriate, by its local institutional review board (IRB) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approvals for any subsequent full version amendments, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICFs will not be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the final amendment Registration Notification issued by the DAIDS PRO should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for study entry has been identified, details will be carefully discussed with the candidate. The candidate (or, when necessary, the legal representative if the candidate is under guardianship) will be asked to read and sign the approved protocol consent form.

For candidates from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the Data Management Center (DMC) Participant Enrollment System.

4.11.2 Protocol Activation

Following initial registration to the protocol, sites must complete the Protocol Activation Checklist found on the ACTG Member website. The completed checklist must be approved before screening of study candidates can begin.

4.11.3 Randomization/Participant Registration

At entry, candidates will be enrolled according to standard ACTG DMC procedures. For candidates from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database.

4.12 Coenrollment Guidelines

Sites are encouraged to coenroll participants in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.” Coenrollment in A5128 does not require permission from the protocol chairs of either study. Because of blood volume limitations in A5315, sites must NOT collect a separate blood sample during the A5315 study follow up period from participants who coenroll in A5128.

For specific questions and approval for coenrollment into other studies, sites should check the PSWP or contact the core team via e-mail (actg.corea5315@fstrf.org).

5.0 STUDY TREATMENT

Study treatment is defined as Romidepsin (RMD) or Placebo for RMD. ART is required but it will not be provided by the study.

5.1 Regimens, Administration, and Duration

At entry, participants will be randomized (4:1) to receive blinded RMD or Placebo for RMD. The first fifteen study participants enrolled in Cohort 1 and received one dose of blinded RMD or Placebo for RMD by intravenous (IV) infusion over 4 hours on Day 0. Additional participants are enrolled, approximately 15 per cohort, into different cohorts as these are opened to accrual.

Participants in Cohorts 2 and 3 received one dose of blinded RMD, at increased dosages, or placebo for RMD by IV infusion over 4 hours on Day 0. Participants in Cohort 4 will receive a dose of blinded RMD or placebo for RMD by IV infusion over 4

hours on Days 0, 14, 28, and 42, for a total of four doses. Each Cohort 4 participant will receive four doses of either RMD or placebo for RMD.

After Cohort 1, Cohorts 2 and 3 were opened sequentially, based on safety outcomes as defined in section 9.0. The decisions to open these two subsequent cohorts were made after two separate reviews of available safety data by the A5315 core team and SMC.

Body Surface Area (BSA) Calculation
The dose of RMD to be administered will be calculated based on body surface area (BSA) expressed in square meters (m^2), which will be determined by weight and height measurement. Measured height and weight obtained during the complete physical exam at pre-entry is to be used for calculating the BSA for the first infusion. For Cohort 4, the weight **and height recorded at the first pre-entry visit** will be used for calculating the BSA for **Step 1**. **Weight recorded at Days 7, 21, and 35 and height recorded at the first pre-entry visit will be used for calculating the BSA for Cohort 4 Steps 2, 3, and 4, respectively.**

The BSA should be calculated using the BSA calculator available on the FSTRF portal.

$BSA\ (m^2) = ([Height\ (cm) \times Weight\ (kg)] / 3600)^{1/2}$

5.1.1 Cohort 1

Upon randomization, the participant PID and SID will be provided to the site clinic for the clinic to send a prescription to the pharmacy.

- Arm 1A (RMD)
  RMD intravenously (IV) over 4-hours starting at Hour 0 on Day 0. The mg dose and corresponding volume of RMD to be added to 500 mL 0.9% Sodium Chloride for Injection, USP IV bag for infusion is based on participant's BSA per Table 5.1**.1-1**.

OR

- Arm 1B (Placebo for Romidepsin)
  0.9% Sodium Chloride (NaCl) for Injection USP, IV over 4 hours starting at Hour 0 on Day 0. The volume of 0.9% NaCl for injection, USP to be added to 500 mL 0.9% Sodium Chloride for Injection, USP IV bag for infusion is based on participant's BSA per Table **5.1.1-1**.

Table **5.1.1-1**: RMD and Placebo for RMD Dosing at 0.5 mg/m^2 Dose Level in Cohort 1

BSA Range	Arm 1A: RMD		Arm 1B: Placebo for RMD
	Dose of RMD (mg)	Volume of RMD to add to 500 mL 0.9% Sodium Chloride for Injection, USP IV Bag in Arm 1A	Volume of 0.9% NaCl for Injection, USP to add to 500 mL 0.9% Sodium Chloride for Injection USP IV Bag in Arm 1B
1.35 - 1.74	0.75 mg	0.15 mL	0.15 mL
1.75 - 2.24	1 mg	0.2 mL	0.2mL
2.25 - 2.54	1.25 mg	0.25 mL	0.25 mL
2.55 - 3	1.5 mg	0.3 mL	0.3 mL

5.1.2 Cohort 2

Upon randomization, the participant PID and SID will be provided to the site clinic for the clinic to send a prescription to the pharmacy.

- Arm 2A (RMD)
  RMD intravenously (IV) over 4-hours starting at Hour 0 on Day 0. The mg dose and corresponding volume of RMD to be added to 500 mL 0.9% Sodium Chloride for Injection, USP IV bag for infusion is based on participant's BSA per Table **5.1.2-1**.

OR

- Arm 2B (Placebo for RMD)
  0.9% Sodium Chloride for Injection, USP IV over 4 hours starting at Hour 0 on Day 0. The volume of 0.9% NaCl for injection, USP to be added to 500 mL 0.9% Sodium Chloride for Injection, USP IV bag for infusion is based on participant's BSA per Table **5.1.2-1.**

Table **5.1.2-1**: RMD and Placebo for RMD Dosing at 2 mg/m^2 Dose Level in Cohort 2

BSA Range	Arm 2A: RMD		Arm 2B: Placebo for RMD
	Dose of RMD (mg)	Volume of RMD to add to 500 mL 0.9% Sodium Chloride for Injection USP IV Bag in Arm 2A	Volume of 0.9% NaCl for Injection, USP to add to 500 mL 0.9% Sodium Chloride for Injection USP IV Bag in Arm 2B
1.35 - 1.74	3 mg	0.6 mL	0.6 mL
1.75 - 2.24	4 mg	0.8 mL	0.8 mL
2.25 - 2.54	5 mg	1 mL	1 mL
2.55 - 3	6 mg	1.2 mL	1.2 mL

5.1.3 Cohort 3

Upon randomization, the participant PID and SID will be provided to the site clinic for the clinic to send a prescription to the pharmacy.

- Arm 3A (RMD)
  RMD intravenously (IV) over 4-hours starting at Hour 0 on Day 0. The mg dose and corresponding volume of RMD to be added to 500 mL 0.9% Sodium Chloride for Injection, USP IV bag for infusion is based on participant's BSA per Table **5.1.3-1**..

OR

- Arm 3B (Placebo for RMD)
  0.9% Sodium Chloride for Injection, USP IV over 4 hours starting at Hour 0 on Day 0. The volume of 0.9% NaCl for injection, USP to be added to 500 mL 0.9% Sodium Chloride for Injection, USP IV bag for infusion is based on participant's BSA per Table **5.1.3-1**.

Table **5.1.3-1:** RMD and Placebo for RMD Dosing at 5 mg/m^2 Dose Level in Cohort 3

BSA Range	Arm 3A: RMD		Arm 3B: Placebo for RMD
	Dose of RMD (mg)	Volume of RMD to add to 500 mL 0.9% Sodium Chloride for Injection, USP IV Bag in Arm 3A	Volume of 0.9% NaCl for Injection, USP to add to 500 mL 0.9% Sodium Chloride for Injection, USP IV Bag in Arm 3B
1.35 - 1.74	8 mg	1.6 mL	1.6 mL
1.75 - 2.24	10 mg	2 mL	2L
2.25 - 2.54	12 mg	2.4 mL	2.4 mL
2.55 - 3	14 mg	2.8 mL	2.8 mL

5.1.4 Cohort 4

Upon randomization **to each step**, the participant's PID and SID will be provided to the site clinic for the clinic to send a prescription to the pharmacy. A new prescription that includes the participant's most recent BSA must be provided to the pharmacy at least 5 days prior to each subsequent infusion.

Arm 4A (RMD)
RMD intravenously (IV) over 4 hours starting at Hour 0 on Day 0 and at Hour 0 on Days 14, 28, and 42, for a total of four doses. The mg dose and corresponding volume of RMD to be added to 500 mL **0.9%** Sodium Chloride for Injection, USP IV bag for infusion is based on the participant's BSA per Table **5.1.4-1**.

OR

Arm 4B (Placebo for RMD)
0.9% Sodium Chloride for Injection, USP IV over 4 hours starting at Hour 0 on Day 0 and at Hour 0 on Days 14, 28, and 42, for a total of four doses. The volume of 0.9% NaCl for injection, USP, to be added to 500 mL **0.9%** Sodium Chloride for Injection, USP IV bag for infusion is based on the participant's BSA per Table **5.1.4-1**.

Table **5.1.4-1**: RMD and Placebo for RMD Dosing at 5 mg/m^2 Dose Level in Cohort 4

BSA Range	Arm 4A: RMD		Arm 4B: Placebo for RMD
	Dose of RMD (mg)	Volume of RMD to add to 500 mL 0.9% Sodium Chloride for Injection, USP IV Bag in Arm **4**A	Volume of 0.9% NaCl for Injection, USP to add to 500 mL 0.9% Sodium Chloride for Injection, USP IV Bag in Arm **4**B
1.35 - 1.74	8 mg	1.6 mL	1.6 mL
1.75 - 2.24	10 mg	2 mL	2 mL
2.25 - 2.54	12 mg	2.4 mL	2.4 mL
2.55 - 3	14 mg	2.8 mL	2.8 mL

5.2 Study Product Formulation and Preparation

5.2.1 Study Product Formulation

RMD
RMD (Istodax®) is supplied as a kit in a single carton that includes a sterile, lyophilized powder in a single-use vial containing 10 mg of RMD and 20 mg of the bulking agent, povidone, USP. In addition, each kit includes 1 sterile vial containing 2 mL (deliverable volume) of the Diluent composed of 80% propylene glycol, USP, and 20% dehydrated alcohol, USP. RMD for injection vial and diluent vial in a single carton must be stored at 20° to 25°C, excursions permitted between 15° to 30°C. (See USP Controlled Room Temperature.)

Placebo for RMD
0.9% Sodium Chloride for Injection, USP in single use vial will be used as the Placebo for RMD and must be stored as directed by the manufacturer.

5.2.2 Study Product Preparation and IV Administration

5.2.2.1 RMD Preparation

One vial of RMD 10 mg and one vial containing 2 mL of diluent included in the RMD kit in a single carton will be needed to prepare RMD dose.

RMD should be handled in a manner consistent with recommended safe procedures for handling cytotoxic drugs. Caution should be exercised in handling RMD. The use of gloves and gown is recommended. If RMD

comes in contact with the skin or mucosa, immediately wash thoroughly with soap and water.

The pharmacist will prepare RMD dose in a biological safety cabinet or an isolator using aseptic technique.

RMD must be reconstituted with the supplied Diluent and further diluted with 0.9% Sodium Chloride for Injection, USP before intravenous infusion.

Using aseptic technique, reconstitute RMD 10 mg vial with supplied Diluent. Using a 3 mL or 5 ml size syringe, withdraw 2 mL from the supplied Diluent vial and slowly inject it into the 10 mg RMD for injection vial.

Swirl the contents of the RMD vial until there are no visible particles in the resulting solution. The reconstituted solution will contain RMD 5 mg/mL.

The reconstituted RMD solution in the vial is chemically stable for 8 hours at room temperature.

Withdraw the specified amount of participant's dose of RMD in mL from the reconstituted RMD vial. Refer to the RMD and Placebo for RMD dosing Tables for the specified amount of participant's dose for each dosing cohort and BSA for each participant.

If the participant's specified dose volume of RMD is less than 1 mL, then use a 1 mL size syringe to withdraw the participant's dose from the reconstituted RMD vial.

If the participant's specified dose volume of RMD is equal to 1 mL, then use a 3 mL size syringe to withdraw the participant's dose volume (mL) from the reconstituted RMD vial.

If the participant's dose volume of RMD is greater than 1 mL and less than 2 mL, then use a 3 mL size syringe to withdraw 1 mL of reconstituted RMD solution and a 1 mL size syringe to withdraw less than 1 mL volume of reconstituted RMD solution from the vial.

If the participant's specified dose volume of RMD is equal to 2 mL, then use a 3 mL size syringe to withdraw the participant's dose volume (mL) from the reconstituted RMD vial.

If the participant's specified dose volume of RMD is greater than 2 mL and less than 3 mL, then use a 3 mL size syringe to withdraw 2 mL of

reconstituted RMD solution and a 1 mL size syringe to withdraw less than 1 mL volume of reconstituted RMD solution from the vial.

Inject the participant's specified RMD dose volume (mL) into a 500 mL 0.9% Sodium Chloride for injection, USP IV bag for infusion.

Label the participant's prepared blinded RMD study drug for infusion in 500 mL 0.9% NaCl IV bag as *"Romidepsin ___mg or Placebo for Romidepsin"* study product.

The RMD mg amount to state on the blinded label is the participant's specified RMD total dose in mg that was withdrawn into the syringe(s) and injected into a 500 mL 0.9% NaCl injection, USP IV bag for infusion.

The solution for infusion prepared as above is stable for up to 24 hours when stored at room temperature. The infusion must be completed within 24 hours from the time the RMD vial is reconstituted to the end of infusion of the prepared IV solution.

Discard any unused RMD solution according to proper handling and disposal procedures for cytotoxic drugs.

5.2.2.2 Placebo for RMD Preparation

0.9% Sodium Chloride for Injection, USP in a single use vial will be needed to prepare Placebo for RMD dose.

The pharmacist will prepare Placebo for RMD dose in a biological safety cabinet or an isolator using aseptic technique.

Withdraw the specified amount of participant's Placebo for RMD dose volume in mL from 0.9% Sodium Chloride for Injection, USP single use vial. Refer to the RMD and Placebo for RMD Dosing Tables for the specified amount of participant's dose for each dosing cohort and BSA for each participant and corresponding mL volume of 0.9%, NaCl for injection, USP to withdraw into the syringe(s) to prepare Placebo for RMD dose.

If the participant's specified dose volume of Placebo for RMD is less than 1 mL, then use a 1 mL size syringe to withdraw the participant's dose from 0.9% NaCl for injection, USP vial.

If the participant's specified dose volume of Placebo for RMD is equal to 1 mL, then use a 3 mL size syringe to withdraw the participant's dose volume (mL) from 0.9% NaCl for injection, USP vial.

If the participant's dose volume of Placebo for RMD is greater than 1 mL and less than 2 mL, then use a 3 mL size syringe to withdraw 1 mL from

0.9% NaCl for injection, USP vial and a 1 mL size syringe to withdraw less than 1 mL volume from 0.9% NaCl for injection, USP vial.

If the participant's specified dose volume of Placebo for RMD is equal to 2 mL, then use a 3 mL size syringe to withdraw the participant's dose volume (mL) from 0.9% NaCl for injection, USP vial.

If the participant's specified dose volume of Placebo for RMD is greater than 2 mL and less than 3 mL, then use a 3 mL size syringe to withdraw 2 mL from 0.9% NaCl for injection, USP vial and a 1 mL size syringe to withdraw less than 1 mL volume from 0.9% NaCl for injection, USP vial.

Inject the participant's specified Placebo for RMD dose (0.9% NaCl for injection, USP) volume (mL) into a 500 mL IV bag of 0.9% Sodium Chloride for injection, USP for infusion.

Label the participant's prepared blinded Placebo for RMD study product for infusion in 500 mL 0.9% NaCl, USP IV bag as *"Romidepsin___mg or Placebo for Romidepsin"* study product.

The RMD mg amount to state on the blinded label is the mg amount that is appropriate for that participant's BSA and dose cohort as listed in the RMD and Placebo for RMD Dosing Table that corresponds to the volume (mL) of 0.9% NaCl for injection, USP injected into a 500 mL NaCl 0.9% injection, USP IV bag for infusion.

The solution for infusion prepared as above is stable for up to 24 hours when stored at room temperature. The infusion must be completed within 24 hours from the time the Placebo for RMD IV solution is prepared to the end of infusion of the prepared IV solution.

5.2.2.3 RMD or Placebo for RMD IV Administration

RMD or Placebo for RMD blinded study product for infusion should be handled in a manner consistent with recommended safe procedures for handling cytotoxic drugs.

Inspect the prepared study product for infusion visually for particulate matter and discoloration before administration. Do not administer if the prepared solution for infusion has particulate matter or discoloration is present.

Infuse over 4 hours.

The prepared study product solution for infusion is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polyethylene (PE) infusion bags as well as glass bottles.

The prepared study product solution for infusion is stable for 24 hours when stored at room temperature. However, it should be administered as soon as possible.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Supply

Romidepsin (Istodax®) manufactured by Ben Venue Laboratories, Inc. for Celgene Corporation will be supplied through the study for Cohorts 1-3 by the ACTG with funding support from Gilead Sciences.

Romidepsin (Istodax®) manufactured by Ben Venue Laboratories, Inc. for Celgene Corporation will be supplied through the study for Cohort 4 by Celgene.

Clinical Research Sites are responsible for locally obtaining the 500 mL 0.9% Sodium Chloride Injection, USP IV bag, 0.9% Sodium Chloride Injection, USP in single use vial, sterile syringes and other supplies required for preparation of RMD and Placebo for RMD study product infusion.

5.3.2 Study Product Acquisition/Distribution

RMD (Istodax®) will be available through the NIAID Clinical Research Products Management Center (CRPMC). The ACTG site pharmacist can obtain the study product for this protocol by following the instructions in the manual, *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks,* in the section entitled Study Product Control.

After the pre-entry visit is completed, the site investigator must provide the site pharmacist with the participant's PID number and BSA. The site pharmacist must include the PID number and BSA when ordering study product from the CRPMC.

5.3.3 Study Product Accountability

The ACTG pharmacist is required to maintain complete records of RMD study product received from the NIAID CRPMC and subsequently dispensed. As the 0.9% Sodium Chloride for Injection, USP will be obtained locally by the site, the continuous inventory is not required, but all other information must be completed (including the lot number for the vial and IV solution used). All unused RMD study product must be returned to the NIAID CRPMC after the study is completed or terminated. The procedures to be followed are in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*, in the section entitled, Study Product Management Responsibilities.

5.4 RMD Pharmacokinetic Samples

Per section 10.2, post-infusion whole blood samples will be collected from the opposite side of the body (e.g., infuse in right arm, draw PK or other samples from left arm).

5.5 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent's most recent package insert, Investigator Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the updated ACTG Drug Interactions Database located at: http://tdm.pharm.buffalo.edu/home/di_search/Search.

5.5.1 Required Medications

In Cohorts 1 – 3, two or more nucleoside or nucleotide reverse transcriptase inhibitors with raltegravir, dolutegravir, or efavirenz. In Cohort 4, two or more nucleoside or nucleotide reverse transcriptase inhibitors with raltegravir or dolutegravir. None of these will be supplied through the study.

5.5.2 Prohibited Medications

A table of prohibited medications can be found in the A5315 MOPS. Note that the table includes the duration of time prior to study entry that use of these medications is also prohibited.

5.5.3 Precautionary Medications

There are no precautionary medications listed for this protocol.

NOTE: RMD is a competitive inhibitor of estradiol and thus inhibits estrogen receptor function.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedules of **Evaluations**

6.1.1 **Table 6.1.1-.1:** Cohorts 1 and 2

Valuation	Screen (see section 6.2.1 for rescreen)	Pre-Entry			Entry		Post-Entry Evaluations												Confirmation of HIV-1 RNA ≥ 200 copies/ml	Discontinuation Evaluations
					Week 1											Wk 2	Wk 4	Wk 8		
					Day 1								Day 2	Day 7		Day 14	Day 28	Day 56 (see 6.2.4)		
					Hour															
					Hour 0		2	4	6	8	12	24	48							
					Pre-Infusion	Infusion Start														
Window	-90 to -50 Days unless otherwise specified	-35 to -30 Days	-21 to -7 Days	-7 Days to 0 hr	±15 minutes for blood draws and +60 minutes for ECG							±2 hrs	±4 hrs	±2 Days			-1 to +2 Days	±4 Days		
Documentation of HIV-1	X																			
Medical History	X				X															
Medication History	X				X															
Clinical Assessments	X		X		X							X	X	X	X	X	X			X
Complete Physical Exam			X																	
Targeted Physical Exam	X				X	X	X	X	X	X	X	X	X	X	X	X	X			X
Hematology	X		X										X	X	X	X				X
Liver Function Tests	X		X											X	X	X				X
Blood Chemistries	X		X											X	X	X				X
Urinalysis	X																			

Valuation	Screen (see section 6.2.1 for rescreen)	Pre-Entry			Entry		Post-Entry Evaluations											Confirmation of HIV-1 RNA ≥ 200 copies/ml	Discontinuation Evaluations
					Week 1										Wk 2	Wk 4	Wk 8		
					Day 1								Day 2	Day 7	Day 14	Day 28	Day 56 (see 6.2.4)		
					Hour														
					Hour 0		2	4	6	8	12	24	48						
					Pre-Infusion	Infusion Start													
Window	-90 to -50 Days unless otherwise specified	-35 to -30 Days	-21 to -7 Days	-7 Days to 0 hr	±15 minutes for blood draws and +60 minutes for ECG							±2 hrs	±4 hrs	±2 Days		-1 to +2 Days	±4 Days		
Pregnancy Testing	X		X		X								X	X	X	X			X
Hepatitis Screen	X																		
ECG			X					X					if indicated		X	if indicated			
CD4+/CD8+	X																		
Stored Plasma/PBMC for Immunology Studies					X								X*	X*		X*			
D-dimer					X									X*		X*			
Plasma HIV-1 RNA Real-Time	X													X (see 6.2.4)			X	X	
Plasma HIV-1 RNA by SCA	X	X			X				X		X	X	X*	X*	X*	X*			X
Resting CD4+T-Cells for Cell-associated Total HIV-1 DNA and RNA				X								X			X*				
Histone Acetylation Assay					X						X	X	X*	X*	X*	X*			
Stored PBMC for Virology Studies	X	X			X				X		X	X	X*	X*	X*	X*			X

Valuation	Screen (see section 6.2.1 for rescreen)	Pre-Entry			Entry		Post-Entry Evaluations											Confirmation of HIV-1 RNA ≥ 200 copies/ml	Discontinuation Evaluations
					Week 1											Wk 2	Wk 4	Wk 8		
					Day 1								Day 2	Day 7	Day 14	Day 28	Day 56 (see 6.2.4)		
					Hour														
					Hour 0		2	4	6	8	12	24	48						
					Pre-Infusion	Infusion Start													
Window	-90 to -50 Days unless otherwise specified	-35 to -30 Days	-21 to -7 Days	-7 Days to 0 hr	±15 minutes for blood draws and +60 minutes for ECG							±2 hrs	±4 hrs	±2 Days		-1 to +2 Days	±4 Days		
Resting CD4+T-Cells for Ex Vivo PMA/Ionomycin & RMD Inducible HIV-1 RNA Expression, i.e., TVR assay				X											X*				
Leukapheresis				X								X			X*				
PK for RMD, RAL, EFV, DTG					X -15 mins to RMD (see 10.2)			X	X		X	X							
RMD/Placebo Infusion						X	X	X											
ART Adherence Assessment	X		X		X									X	X	X	X		X

* These evaluations are not required if participant does not undergo the Hour 24 leukapheresis.

6.1.2 **Table 6.1.2-1:** Cohort 3

Evaluation (Cohort 3)	Screen (see section 6.2.1 for rescreen)	Pre-Entry			Entry		Post-Entry Evaluations											Confirmation of HIV-1 RNA ≥ 200 copies/ml	Discontinuation Evaluations
					Week 1											Wk 2	Wk 4	Wk 8		
					Day 1								Day 2	Day 7	Day 14	Day 28	Day 56 (see 6.2.4)		
					Hour														
					Hour 0														
					Pre-Infusion	Infusion Start	2	4	6	8	12	24	48						
Window	-90 to -50 Days unless otherwise specified	-35 to -30 Days	-21 to -7 Days	-7 Days to 0 hr	±15 minutes for blood draws and +60 minutes for ECG							±2 hrs	±4 hrs	±2 Days		-1 to +2 Days	±4 Days		
Documentation of HIV-1	X																		
Medical History	X				X														
Medication History	X				X														
Clinical Assessments	X		X		X							X	X	X	X	X	X		X
Complete Physical Exam			X																
Targeted Physical Exam	X				X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology	X		X										X	X	X	X			X
Liver Function Tests	X		X											X	X	X			X
Blood Chemistries	X		X											X	X	X			X
Urinalysis	X																		
Pregnancy Testing	X		X		X								X	X	X	X			X
Hepatitis Screen	X																		
ECG			X					X					if clinically indicated		X	if indicated			

Evaluation (Cohort 3)	Screen (see section 6.2.1 for rescreen)	Pre-Entry			Entry	Post-Entry Evaluations											Confirmation of HIV-1 RNA ≥ 200 copies/ml	Discontinuation Evaluations
						Week 1									Wk 2	Wk 4	Wk 8	
						Day 1							Day 2	Day 7	Day 14	Day 28	Day 56 (see 6.2.4)	
						Hour												
					Hour 0													
					Pre-Infusion	Infusion Start	2	4	6	8	12	24	48					
Window	-90 to -50 Days unless otherwise specified	-35 to -30 Days	-21 to -7 Days	-7 Days to 0 hr	±15 minutes for blood draws and +60 minutes for ECG							±2 hrs	±4 hrs	±2 Days		-1 to +2 Days	±4 Days	
CD4+/CD8+	X																	
Stored Plasma/PBMC for Immunology Studies					X								X*	X*		X*		
D-dimer					X									X*		X*		
Plasma HIV-1 RNA Real-Time	X													X (see 6.2.4)			X	X
Plasma HIV-1 RNA by SCA	X	X			X				X		X	X	X*	X*	X*	X*		X
Resting CD4+T-Cells for Cell-associated Total HIV-1 DNA and RNA				X								X			X*			
Histone Acetylation Assay					X						X	X	X*	X*	X*	X*		
Stored PBMC for Virology Studies	X	X			X				X		X	X	X*	X*	X*	X*		X

Evaluation (Cohort 3)	Screen (see section 6.2.1 for rescreen)	Pre-Entry			Entry	Post-Entry Evaluations										Confirmation of HIV-1 RNA ≥ 200 copies/ml	Discontinuation Evaluations
						Week 1								Wk 2	Wk 4	Wk 8	
						Day 1							Day 2	Day 7	Day 14	Day 28	Day 56 (see 6.2.4)		
						Hour													
					Hour 0														
					Pre-Infusion	Infusion Start	2	4	6	8	12	24	48						
Window	-90 to -50 Days unless otherwise specified	-35 to -30 Days	-21 to -7 Days	-7 Days to 0 hr	±15 minutes for blood draws and +60 minutes for ECG							±2 hrs	±4 hrs	±2 Days		-1 to +2 Days	±4 Days		
Resting CD4+T-Cells for Ex Vivo PMA/Ionomycin & RMD Inducible HIV-1 RNA Expression, i.e., TVR assay				X											X*				
PK for RMD, RAL, EFV, DTG					X -15 mins to RMD (see 10.2)			X	X		X	X							
RMD/Placebo Infusion						X	X	X											
ART Adherence Assessment	X		X		X									X	X	X	X		X

*These evaluations are not required if participant does not undergo the Hour 24 blood collection.

6.1.3 Table 6.1.3-1: Cohort 4 Screening through Step 2

Evaluation (Cohort 4, Screening through Step 2; standard)	Screening	Pre-Entry	Pre-Entry	Step 1					Step 2					Prem. Tx and Study D/C
									Step 2 Reg.					
	Day -60 to Day -36	Day -35 to Day -28	Day -14 to Day -3	Entry/ Hour 0 Pre-Infusion/Infusion	Week 1 / Day 1 (24 hr post-infusion)	Week 1/ Day 3 (72 hr post-infusion)	Week 1 / Day 7 (7 days post-infusion)	Weeks 2 to **9** (conditional)[1]	Week 2 / Day 14 (+/- 48hr)	Week 3 / Day 15 (24 hr post-infusion)	Week 3 / Day 17 (72 hr post-infusion)	Week 3 / Day 21 (7 days post-infusion)	Weeks 4 to 11 (conditional) [1]	
Documentation of HIV-1	X													
Medical and Medication History	X			X										
Clinical Assessments	X	X	X	X	X	X	X	Once each week	X	X	X	X	Once each week	X
Complete Physical Exam		X												
Karnofsky Performance Score			**X**											
Targeted Physical Exam	**X**		X	X	X	X	X	Once each week	X	X	X	X	Once each week	X
Hematology			X		X	X	X	**Wk 4, 8 (Weekly – see 6.2.3)**		X	X	X	Wk 6, 10 **(Weekly – see 6.2.3)**	X

Evaluation (Cohort 4, Screening through Step 2; standard)	Screening	Pre-Entry	Pre-Entry	Step 1					Step 2					Prem. Tx and Study D/C
									Step 2 Reg.					
	Day -60 to Day -36	Day -35 to Day -28	Day -14 to Day -3	Entry/ Hour 0 Pre-Infusion/Infusion	Week 1 / Day 1 (24 hr post-infusion)	Week 1/ Day 3 (72 hr post-infusion)	Week 1 / Day 7 (7 days post-infusion)	Weeks 2 to **9** (conditional)[1]	Week 2 / Day 14 (+/- 48hr)	Week 3 / Day 15 (24 hr post-infusion)	Week 3 / Day 17 (72 hr post-infusion)	Week 3 / Day 21 (7 days post-infusion)	Weeks 4 to 11 (conditional) [1]	
Potassium and Magnesium (see section 6.3.7 for timing at Pre-entry)			X				X	**Wk 4, 8 (Weekly – see 6.2.3)**				X	Wk 6, 10 **(Weekly – see 6.2.3)**	
LFTs/Blood Chemistries (see section 6.3.7)			X				X	Wk 2, 6				X	Wk 6, 10	X
[1] These "conditional" evaluation weeks are only for participants whose infusions will be delayed for the next Step. (See section 6.2.3). If infusion will be delayed, go to the delayed infusion SOE (section 6.1.4).														
Urinalysis	X													
Urine Pregnancy Testing	X	X	X	X					X					
CD4+ cell count	**X**													
HBV/HCV screening	X													
ECG		X		X Hr 4	As clinically indicated				X Hr 4	As clinically indicated				

Evaluation (Cohort 4, Screening through Step 2; standard)	Screening	Pre-Entry	Pre-Entry	Step 1					Step 2					Prem. Tx and Study D/C
									Step 2 Reg.					
	Day -60 to Day -36	Day -35 to Day -28	Day -14 to Day -3	Entry/ Hour 0 Pre-Infusion/Infusion	Week 1 / Day 1 (24 hr post-infusion)	Week 1/ Day 3 (72 hr post-infusion)	Week 1 / Day 7 (7 days post-infusion)	Weeks 2 to **9** (conditional)[1]	Week 2 / Day 14 (+/- 48hr)	Week 3 / Day 15 (24 hr post-infusion)	Week 3 / Day 17 (72 hr post-infusion)	Week 3 / Day 21 (7 days post-infusion)	Weeks 4 to 11 (conditional) [1]	
CD4%			X	X	X	X			X	X	X			X
Stored Plasma and PBMC for immunology testing (see section 6.3.9)		X	X		X					X				X
Plasma HIV-1 RNA real time	X		X											X
Plasma HIV-1 RNA expedited							X	**Wk 4, 8 (Weekly – see 6.2.3)**				X	**Wk 6, 10 (Weekly – (see 6.2.3)**	
Plasma HIV-1 RNA by SCA		X	X	X	X	X			X	X	X			X
[1] These "conditional" evaluation weeks are only for participants whose infusions will be delayed for the next Step. (See section 6.2.3). If infusion will be delayed, go to the delayed infusion SOE (section 6.1.4).														
PBMCs (see section 6.3.10)		X	X	X	X	X			X	X	X			X

Evaluation (Cohort 4, Screening through Step 2; standard)	Screening	Pre-Entry	Pre-Entry	Step 1					Step 2					Prem. Tx and Study D/C
									Step 2 Reg.					
	Day -60 to Day -36	Day -35 to Day -28	Day -14 to Day -3	Entry/ Hour 0 Pre-Infusion/Infusion	Week 1 / Day 1 (24 hr post-infusion)	Week 1/ Day 3 (72 hr post-infusion)	Week 1 / Day 7 (7 days post-infusion)	Weeks 2 to **9** (conditional)[1]	Week 2 / Day 14 (+/- 48hr)	Week 3 / Day 15 (24 hr post-infusion)	Week 3 / Day 17 (72 hr post-infusion)	Week 3 / Day 21 (7 days post-infusion)	Weeks 4 to 11 (conditional) [1]	
Stored PBMC for virology testing (see section 6.3.10)		X	X	X	X	X			X	X	X			X
Histone Acetylation				Hr 0	X	X			Hr 0	X	X			
Stored PBMC for **qVOA** (see section 6.3.10)		X												
RMD/Placebo Infusion				X					X					
ART Adherence Assessment	X		X	X					X					X

[1] These "conditional" evaluation weeks are only for participants whose infusions will be delayed for the next Step. (See section 6.2.3). If infusion will be delayed, go to the delayed infusion SOE (section 6.1.4).

Table 6.1.3-2: Cohort 4 Screening through Steps 3 and 4

Evaluation (Cohort 4, Steps 3 and 4; standard)	Step 3					Step 4								Prem. Tx and/or Study D/C
	Step 3 Reg.					Step 4 Reg.				Post-Infusion 4 Follow Up				
	Week 4 / Day 28 (+/- 48hr)	Week 5 / Day 29 (24 hr post-infusion)	Week 5 / Day 31 (72 hr post-infusion)	Week 5 / Day 35 (7 days post-infusion)	Weeks 6 to 13 (conditional[1]	Week 6 / Day 42 (+/- 48hr)	Week 7 / Day 43 (24 hr post-infusion)	Week 7 / Day 45 (72 hr post-infusion)	Week 7 / Day 49 (7 days post-infusion)	Week 8 / Day 56	Week 11 (±3 days)	Week 16 (± 7 days)	Week 24 (± 7 days)	
Clinical Assessments	X	X	X	X	Once each week	X	X	X	X	X	X	X	X	X
Targeted Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology		X	X	X	Wk 8, 12 **(Weekly – see 6.2.3)**		X	X		X	X	X	X	X
Potassium and Magnesium (see section 6.3.7 for timing at Pre-entry)				X	Wk 8, 12 **(Weekly – see 6.2.3)**				X					
LFTs/Blood Chemistries (see section 6.3.7)				X	Wk 8, 12				X				X	X
Urine Pregnancy Testing	X					X				As clinically indicated				

Evaluation (Cohort 4, Steps 3 and 4; standard)	Step 3					Step 4								Prem. Tx and/or Study D/C
	Step 3 Reg.					Step 4 Reg.				Post-Infusion 4 Follow Up				
	Week 4 / Day 28 (+/- 48hr)	Week 5 / Day 29 (24 hr post-infusion)	Week 5 / Day 31 (72 hr post-infusion)	Week 5 / Day 35 (7 days post-infusion)	Weeks 6 to 13 (conditional[1]	Week 6 / Day 42 (+/- 48hr)	Week 7 / Day 43 (24 hr post-infusion)	Week 7 / Day 45 (72 hr post-infusion)	Week 7 / Day 49 (7 days post-infusion)	Week 8 / Day 56	Week 11 (±3 days)	Week 16 (± 7 days)	Week 24 (± 7 days)	
ECG	X **Hr 4**	As clinically indicated				X Hr 4	As clinically indicated			X				
[1] These "conditional" evaluation weeks are only for participants whose infusions will be delayed for the next Step. (See section 6.2.3). If infusion will be delayed, go to the delayed infusion SOE (section 6.1.4).														
CD4%	X	X	X			X	X	X		X	X	X	X	X
Stored Plasma and PBMC for immunology testing (see section 6.3.9)		X					X			X	X	X	X	X
Plasma HIV-1 RNA real time									X	X		X		X
Plasma HIV-1 RNA expedited				X	**Wk 8, 12 (Weekly – see 6.2.3)**						X			
Plasma HIV-1 RNA by SCA	X	X	X			X	X	X		X	X	X	X	X

Evaluation (Cohort 4, Steps 3 and 4; standard)	Step 3					Step 4								D/C
	Step 3 Reg.					Step 4 Reg.				Post-Infusion 4 Follow Up				
	Week 4 / Day 28 (+/- 48hr)	Week 5 / Day 29 (24 hr post-infusion)	Week 5 / Day 31 (72 hr post-infusion)	Week 5 / Day 35 (7 days post-infusion)	Weeks 6 to 13 (conditional[1]	Week 6 / Day 42 (+/- 48hr)	Week 7 / Day 43 (24 hr post-infusion)	Week 7 / Day 45 (72 hr post-infusion)	Week 7 / Day 49 (7 days post-infusion)	Week 8 / Day 56	Week 11 (±3 days)	Week 16 (± 7 days)	Week 24 (± 7 days)	Prem. Tx and/or Study
PBMCs (see section 6.3.10)	X	X	X			X	X	X		X	X	X	X	X
Stored PBMC for virology testing (see section 6.3.10)	X	X	X			X	X	X		X	X	X	X	X
Histone Acetylation	**Hr 0**	X	X			**Hr 0**	**X**	**X**						
[1] These "conditional" evaluation weeks are only for participants whose infusions will be delayed for the next Step. (See section 6.2.3). If infusion will be delayed, go to the delayed infusion SOE (section 6.1.4).														
Stored PBMC for **qVOA** (see section 6.3.10)											X		X	
RMD/Placebo Infusion	X					X								
ART Adherence	X					X						X	X	X

Evaluation (Cohort 4, Steps 3 and 4; standard)	Step 3					Step 4								Prem. Tx and/or Study D/C
	Step 3 Reg.					Step 4 Reg.				Post-Infusion 4 Follow Up				
	Week 4 / Day 28 (+/- 48hr)	Week 5 / Day 29 (24 hr post-infusion)	Week 5 / Day 31 (72 hr post-infusion)	Week 5 / Day 35 (7 days post-infusion)	Weeks 6 to 13 (conditional[1]	Week 6 / Day 42 (+/- 48hr)	Week 7 / Day 43 (24 hr post-infusion)	Week 7 / Day 45 (72 hr post-infusion)	Week 7 / Day 49 (7 days post-infusion)	Week 8 / Day 56	Week 11 (±3 days)	Week 16 (± 7 days)	Week 24 (± 7 days)	
Assessment														
PK RMD (Collection times are from the start of the infusion)	X Hr 0 & Hr 4					X Hr 0 & Hr 4								
PK ARVs (Collection time is from the start of the infusion)	X Hr 0	X				X Hr 0	X							

[1] These "conditional" evaluation weeks are only for participants whose infusions will be delayed for the next Step. (See section 6.2.3). If infusion will be delayed, go to the delayed infusion SOE (section 6.1.4).

6.1.4 Table 6.1.4-1: Cohort 4 Delayed Infusion SOE, Steps 2 and 3

Evaluation (Cohort 4, Steps 2 and 3; delayed infusion)	Step 2 Infusion 2					Step 3 Infusion 3					D/C
	Reg. to Step 2 [1]	R + 1 day (24 hr post-infusion)	R + 3 days (72 hr post-infusion)	Week R + 1 (7 days post-infusion)	Weeks R+2 to R+ **9** (conditional) (See section 6.2.3)	Reg. to Step 3 [1]	R + 1 day (24 hr post-infusion)	R + 3 days (72 hr post-infusion)	Week R + 1 (7 days post-infusion)	Weeks R+2 to R+ **9** (conditional) (See section 6.2.3)	Prem. Tx and/or Study
Clinical Assessments	X	X	X	X	Once each week	X	X	X	X	Once each week	X
Targeted Physical Exam	X	X	X	X	Once each week	X	X	X	X	Once each week	x
Hematology	X	X	X		R+**4** & R+**8** **(Weekly)**	X	X	X		R+**4** & R+**8** **(Weekly)**	X
Potassium and Magnesium (see section 6.3.7 for timing at Pre-entry)				X	R+**4** & R+**8** **(Weekly)**				X	R+**4** & R+**8** **(Weekly)**	
LFTs/Blood Chemistries (see section 6.3.7)				X	R+2 & R+6				X	R+2 & R+6	X
Urine Pregnancy Testing	X					X					
ECG	X **Hr 4**	As clinically indicated				X Hr 4	As clinically indicated				
CD4%	X	X	X			X	X	X			X

[1] Registration to step week (R) is defined as one week past the week of the last visit on the previous step.

Evaluation (Cohort 4, Steps 2 and 3; delayed infusion)	Step 2 Infusion 2					Step 3 Infusion 3					D/C
	Reg. to Step 2 [1]	R + 1 day (24 hr post-infusion)	R + 3 days (72 hr post-infusion)	Week R + 1 (7 days post-infusion)	Weeks R+2 to R+ **9** (conditional) (See section 6.2.3)	Reg. to Step 3 [1]	R + 1 day (24 hr post-infusion)	R + 3 days (72 hr post-infusion)	Week R + 1 (7 days post-infusion)	Weeks R+2 to R+ **9** (conditional) (See section 6.2.3)	Prem. Tx and/or Study
Stored Plasma and PBMC for immunology testing (see section 6.3.9)		X					X				X
Plasma HIV-1 RNA real time											X
Plasma HIV-1 RNA expedited				X	**R+4 & R+8 (Weekly)**				X	**R+4 & R+8 (Weekly)**	
Plasma HIV-1 RNA by SCA	X	X	X			X	X	X			X
PBMCs (see section 6.3.10)	X	X	X			X	X	X			X
Stored PBMC for virology testing (see section 6.3.10)	X	X	X			X	X	X			X
Histone Acetylation	X Hr 0	X	X			**X Hr 0**	X	X			
RMD / Placebo Infusion	X					X					

Evaluation (Cohort 4, Steps 2 and 3; delayed infusion)	Step 2 Infusion 2					Step 3 Infusion 3					D/C
	Reg. to Step 2 [1]	R + 1 day (24 hr post-infusion)	R + 3 days (72 hr post-infusion)	Week R + 1 (7 days post-infusion)	Weeks R+2 to R+ **9** (conditional) (See section 6.2.3)	Reg. to Step 3 [1]	R + 1 day (24 hr post-infusion)	R + 3 days (72 hr post-infusion)	Week R + 1 (7 days post-infusion)	Weeks R+2 to R+ **9** (conditional) (See section 6.2.3)	Prem. Tx and/or Study
ART Adherence Assessment	X					X					X
[1] Registration to step week (R) is defined as one week past the week of the last visit on the previous step.											
PK RMD (Collection times are from the start of the infusion)						X Hr 0 & Hr 4					
PK ARVs (Collection time is from the start of the infusion)						X Hr 0	X				
[1] Registration to step week (R) is defined as one week past the week of the last visit on the previous step.											

Table 6.1.4-2: Cohort 4 Delayed Infusion SOE, Step 4

Evaluation (Cohort 4, Step 4; delayed infusion)	Step 4								
	Infusion 4				Post-Infusion 4 Follow Up				Prem. Tx or Study D/C
	Reg. to Step 4 [1]	R + 1 day (24 hr post-infusion)	R + 3 days (72 hr post-infusion)	Week R + 1 (7 days post-infusion)	Week R + 2	Week R + 5	WeekR + 10	Week R + 18	
Clinical Assessments	X	X	X	X	X	X	X	X	X
Targeted Physical Exam	X	X	X	X	X	X	X	X	x
Hematology	X	X	X	X	X	X	X	X	X
LFTs/Blood Chemistries (see section 6.3.7)								X	X
Urine Pregnancy Testing	X				As clinically indicated				
ECG	X **Hr 4**	As clinically indicated			X				
CD4%	X	X	X		X	X	X	X	X
Stored Plasma and PBMC for immunology testing (see section 6.3.9)		X			X	X	X	X	X
Plasma HIV-1 RNA real time					X	X	X		X
Plasma HIV-1 RNA expedited				X					

[1] Registration to step week (R) is defined as one week past the week of the last visit on the previous step.

Evaluation (Cohort 4, Step 4; delayed infusion)	Step 4								Prem. Tx or Study D/C
	Infusion 4				Post-Infusion 4 Follow Up				
	Reg. to Step 4 [1]	R + 1 day (24 hr post-infusion)	R + 3 days (72 hr post-infusion)	Week R + 1 (7 days post-infusion)	Week R + 2	Week R + 5	WeekR + 10	Week R + 18	
Plasma HIV-1 RNA by SCA	X	X	X		X	X	X	X	X
CD4+ T cells (see section 6.3.10)	X	X	X		X	X	X	X	X
Stored PBMC for virology testing (see section 6.3.10)	X	X	X		X	X	X	X	X
Histone Acetylation	**X Hr 0**	**X**	**X**						
Stored PBMC for **qVOA** (see section 6.3.10)						X		X	
RMD/ Placebo Infusion	X								
ART Adherence Assessment	X						X	X	X
PK RMD (Collection times are from the start of the infusion)	Hr 0 & Hr 4								
PK ARVs (Collection time is from the start of the infusion)	Hr 0	X							
[1] Registration to step week (R) is defined as one week past the week of the last visit on the previous step.									

6.2 Timing of Evaluations

6.2.1 Screening and Pre-Entry Evaluations

Screening and pre-entry evaluations must occur prior to the participant's starting any study medications, treatments, or interventions.

Screening, Cohorts 1-3
Screening evaluations to determine eligibility must be completed between 50 and 90 days prior to study entry unless otherwise specified.

The screening Plasma HIV-1 RNA by Single Copy Assay (SCA) will be collected between 50 and 90 days prior to entry and shipped for real-time testing. See section 6.3.10.

In addition to data being collected on candidates who enroll into the study, demographic, clinical, and laboratory data on candidates who do not enroll will be captured in a Screening Failure Results form and entered into the ACTG database. Due to blood volume restrictions, candidates who fail screening can only be rescreened 60 days after their previous screening visit.

The following data will also be collected on an additional CRF from candidates who do not enroll in the study: screening CD4+ cell count, screening HIV-1 RNA level, pre-ART HIV-1 RNA level, pre ART nadir CD4 (if documentation is not available participant recall can be used), date of first undetectable HIV-1 RNA level prior to sustained viral load suppression (may be estimated if exact date not available), antiretroviral regimen at the time of screening and the start date of this regimen, the start date of the first antiretroviral regimen and the date(s) of any previous virologic failure on ART (if known) as determined by the investigator.

Pre-Entry, Cohorts 1 – 3
The timing for each pre-entry evaluation is noted in the SOE. The window ranges for their completion are: between 30 and 35 days, between 7 and 21 days, or between 7 days prior to study entry and hour 0 of the study entry day. Sites must ensure that each evaluation occurs within the appropriate pre-entry window of time.

Screening, Cohort 4
Screening evaluations to determine eligibility must be completed between 36 and 60 days prior to study entry unless otherwise specified.

In addition to data being collected on candidates who enroll into the study, demographic, clinical, and laboratory data on candidates who do not enroll will be captured in a Screening Failure Results form and entered into the ACTG database.

The following data will also be collected on an additional CRF from candidates who do not enroll in the study: screening CD4+ cell count, screening HIV-1 RNA level, pre-ART HIV-1 RNA level, pre-ART nadir CD4 (if documentation is not available participant recall can be used), date of first undetectable HIV-1 RNA level prior to sustained viral load suppression (may be estimated if exact date not available), antiretroviral regimen at the time of screening and the start date of this regimen, the start date of the first antiretroviral regimen and the date(s) of any previous virologic failure on ART (if known) as determined by the investigator.

Pre-Entry, Cohort 4
Pre-entry evaluations must be performed per SOE **section** 6.1.3, between 35 and 28 days or between 14 and 3 days prior to entry.

6.2.2 Entry Evaluations

Cohorts 1 – 3
Entry/Hour 0 evaluations must occur within 24 hours after randomization and at least 7 days after the second pre-entry visit (-21 to -7 days) evaluations, unless otherwise specified.

All entry/Hour 0 specimens must be obtained and pregnancy test reported before initiating RMD or placebo infusion.

Cohort 4
Entry evaluations must occur within 24 hours after randomization.

All entry/Hour 0 specimens must be obtained and pregnancy test reported before initiating the first RMD or placebo infusion.

6.2.3 Post-Entry Evaluations

The RMD/placebo infusion should be completed in 4 hours. In the event that the infusion requires more than 4 hours, the time of infusion completion is still to be considered Hour 4.

Post-Treatment Evaluations, Cohorts 1 – 3
Hour 4 evaluations begin immediately following completion of RMD/placebo infusion. All subsequent evaluation time points are to be calculated from the infusion completion time which is considered Hour 4 regardless of whether the actual time from infusion start to completion took less or more time than 4 hours (ie, Hour 6 is 2 hours after the infusion has finished, Hour 8 is 4 hours after the infusion has finished, etc.).

Post-Treatment Visit Schedule, Cohorts 1 – 3
Study visits and collection time points must be scheduled as indicated in the Schedule of Events (SOE) ± 15 minutes for Hour 2, 4 (except for ECG which has a window of +0-60 minutes), 6, 8, 12; ± 2 hours for Hour 24; ± 4 hours for Hour

48/Day 2; ± 2 days for Day 7 and Week 2/Day 14, and -1 day to +2 days for Week 4/Day 28. Per sections 6.2.4 and 7.1, participants may be required to return for a Week 8/Day 56 visit ± 4 days.

Study Completion Evaluations, Cohorts 1 – 3
Week 4/Day 28 evaluations will serve as the study completion evaluations for participants who have maintained an HIV-1 RNA level of < 200 copies/mL by standard ultrasensitive assay since the Day 7 visit. See **section** 6.2.4 for participants who have an HIV-1 RNA level of ≥200 copies/mL at the Day 7 visit.

Also, these evaluations will be the study completion evaluations for participants who did not experience any ≥Grade 3 AE or clinical event (per section 7.1).

Post-Entry Visit Schedule, Cohort 4
Study visits and collection time points must be scheduled as indicated in the Cohort 4 SOE, section 6.1.3. **The windows are ±6 hours for day 1 (24 hours post-infusion), ±1 day for day 3 (72 hours post-infusion), and ±1 day for day 7 (7 days post infusion).** For participants whose second, third, and/or fourth infusion must be delayed for any reason, the Delayed Infusion SOE, section 6.1.4, must be followed until the end of the study follow-up for that participant. Participants' visits will be scheduled per this SOE beginning with the first delayed infusion.

Sites should notify the A5315 core team if any infusion will be delayed (actg.corea5315@fstrf.org).

Conditional Evaluation Weeks, Cohort 4
Conditional evaluation weeks are only for participants whose next infusion will be delayed. The evaluations are performed weekly, unless otherwise specified, until the participant meets the criteria for the next infusion. If the participant does not meet the criterial for the next infusion by the last conditional evaluation week visit, then the participant will have the premature discontinuation evaluations performed per the SOE and then be taken off study.

Evaluations for hematology, potassium, magnesium, and/or plasma HIV-1 RNA expedited must be performed weekly as needed to meet the eligibility criteria for the next infusion. Otherwise, these evaluations should only be performed at the specific weeks indicated on the SOE.

6.2.4 Event-Driven Evaluations

Cohorts 1 – 3
Participants with HIV-1 RNA levels ≥ 200 copies/mL detected at the Day 7 visit (real-time HIV-1 RNA level) should be contacted immediately upon receipt of the Day 7 HIV-1 RNA results and asked to return as soon as possible (preferably within 72 hours) for a repeat HIV-1 RNA real-time PCR. If the repeat HIV-1 RNA

PCR level after Day 7 is ≥200 copies/mL, the participant will complete both the Week 4/Day 28 and Week 8/Day 56 visits per section 6.1.1 or 6.1.2

Also, per section 7.1, participants who experience any ≥Grade 3 AE or clinical event, regardless of their Day 7 HIV-1 RNA level, will be seen at Week 8/Day 56.

Cohort 4
Participants with plasma HIV-1 RNA levels ≥50 copies/mL detected 7 days after any of the first three infusions should be contacted immediately upon receipt of the results by site staff and asked to return as soon as possible (preferably within 72 hours) for additional real-time testing. While this testing is being performed, the next infusion should be postponed. The participant should have weekly HIV-1 RNA levels tested, in addition to the other evaluations per the SOE, until the HIV-1 RNA level is <50 copies/mL, after which infusions and/or blood collections can continue per the Delayed Infusion SOE, section 6.1.4. Sites must promptly advise the A5315 core team upon initial receipt of any elevated HIV-1 RNA level (actg.corea5315@fstrf.org).

Also, per section 7.1, participants who experience any ≥ Grade 3 AE or clinical event during an infusion will be followed as indicated in section 6.2.5**.**

6.2.5 Discontinuation Evaluations

Evaluations for Randomized Participants Who Do Not Start Study Treatment
No further evaluations are required for participants who do not initiate RMD/placebo infusion.

Cohorts 1 – 3
All CRFs must be completed and keyed for the period up to and including entry/Hour 0.

Cohort 4
All CRFs must be completed and keyed for the period up to and including Entry/Hour 0.

Premature Treatment and Study Discontinuation Evaluations
Cohorts 1 – 3
Participants who receive RMD/placebo infusion but from whom blood is not collected at the 24-hour time point should remain on study for safety monitoring through Day 28.

Participants who prematurely discontinue study participation after receiving RMD/placebo or prior to the completion of RMD/placebo infusion, will have the premature study discontinuation evaluations performed per the SOE and recorded on CRFs.

Cohort 4
Participants who prematurely discontinue study treatment **due to a ≥ Grade 3 AE or clinical event or for any other reason** will not have any further infusions but **will be followed on study/off study treatment**. Participants will **remain on their current step and complete the following visits: 24-hour post-infusion, 72-hour post-infusion, 7-day (1 week) post-infusion, and premature treatment/study discontinuation evaluations 4 weeks post-infusion** and **will** then be taken off study.

Participants from whom the blood collection is not performed at more than one of the 24-hour time points after a RMD/placebo infusion will not have any further infusions but will be followed on study/off study treatment. Participants will remain on their current step and complete the following visits: 72-hour post-infusion, 7-day (1 week) post-infusion, and premature treatment/study discontinuation evaluations 4 weeks post-infusion and then will be taken off study.

Participants who prematurely discontinue study participation after receiving four RMD/placebo infusions or prior to the completion of four RMD/placebo infusions, will have the premature study discontinuation evaluations performed per the SOE and then will be taken off study. A replacement participant may be enrolled for each participant who prematurely discontinues the study, including participants who receive all four infusions but discontinue study participation prior to the week 11 visit.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS Web site for information about what must be included in the source document: http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/sourcedocappndx.pdf

All stated evaluations are to be recorded on the CRF and keyed into the database unless otherwise specified. This includes events that meet the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) definitions for a serious adverse event.

- Results in death
- Life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other important medical event (may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above).

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009), which can be found on the DAIDS RSC Web site: **http://rsc.tech-res.com/clinical-research-sites/safety-reporting**.

6.3.1 Documentation of HIV-1

Sections 4.1.1 and 4.3.1 specify assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the CRF.

6.3.2 Medical History

In addition to recording all diagnoses that occurred within 30 days prior to study entry, the following diagnoses should be recorded and keyed within 2 business days, regardless of when the diagnosis was made:

- Immunologic including AIDS-defining conditions and HIV- associated opportunistic infection (OI)
- Bone fractures (verbal history accepted)
- Cardiovascular including coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis (TB)
- Chronic hepatitis C
- Chronic hepatitis B
- Gastrointestinal including cholecystectomy, peptic ulceration, and inflammatory bowel disease
- Allergies to any medications and their formulations

Document the pre-ART HIV-1 RNA level and nadir CD4 count if available. If nadir documentation is not available, then collect and record participant recall. Record the date of the first undetectable HIV-1 RNA level prior to sustained viral load suppression (may be estimated if exact date not available). Record date(s) of any previous virologic failure on ART (if known) as determined by the investigator.

6.3.3 Medication History

At study entry, record in source documentation only, the treating physician's confirmation that a viable alternate ART regimen can be constructed for the participant, should a single dose of RMD lead to virologic failure (ie, 2 consecutive HIV-1 RNA levels $\geq$ 200 copies/mL) and resistance to the current ART regimen.

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history.

Table 6.3.3-1: Medication History

Medication Category	Complete History or Timeframe
Antiretroviral therapy	Complete history
Immune-based therapy	Complete history
Blinded study treatment	Complete history
HIV-1-related vaccines	Complete history
Prescription drugs (other)	Current use (within 30 days prior to entry)
Potassium & Magnesium Supplements	Current use (within 21 days prior to entry)

6.3.4 Clinical Assessments

Height
Height (cm) will be measured and recorded at the pre-entry visit only.

Weight
Cohorts 1 – 3
Weight in kilograms (kg) should be assessed at the screening, pre-entry, entry, and Days 7, 14, and 28 study visits.

Cohort 4
Weight (in kg) should be assessed at screening, the first pre-entry visit, entry, **at Days 7, 21, and 35**, and at Days 14, 28, and 42. For participants following the Delayed Infusion SOE, weight will be assessed at the following visits: Registration to Step 2, Registration to Step 3, and Registration to Step 4. If at least 8 weeks have elapsed since the dose of study treatment (RMD or placebo for RMD) was calculated, then the site pharmacist must recalculate the dose using the participant's most recently documented weight.

Signs and Symptoms
At entry, all grades of signs and symptoms that occurred 30 days prior to study entry must be recorded and keyed within 2 business days. Post-entry, all signs and symptoms Grade $\geq$ 2 must be recorded and keyed within two business days. Further evaluation will be required for signs and symptoms, regardless of grade, that led to a change in study treatment and/or Grade ≥ 3 and/or meet EAE or ICH reporting requirements, which must also be recorded and keyed within 2 business days.

Diagnoses
Record all diagnoses identified by the ACTG criteria for clinical events and other diseases since the last visit and key within 2 business days.

Concomitant Medications
Record, all new or discontinued prescription medications, and potassium and magnesium supplements, since the last visit.

Antiretroviral Medications
During the study, all modifications to the participant's ARV regimen, including any ARV interruptions (there is no minimum number of days of interruption needed for report), dose modifications, formulation modifications, starts, and permanent discontinuations since the last study visit or at the study visit must be recorded.

If the site decides to have the participant stay overnight at a Clinical and Translational Research Center or similar facility, they should remind participant to bring his/her own antiretroviral medications for the inpatient stay or overnight stay elsewhere.

Study Treatment Modifications
Record and key within 2 business days, the RMD/placebo infusion, including dose administered, whether administration was temporarily halted for any reason, duration of infusion, and whether the full dose was administered. If the infusion is temporarily halted, the schedule of evaluations should resume following completion of the RMD/placebo infusion (referred to as Hour 4, regardless of whether the actual time from infusion start to completion took more time than 4 hours). See sections 6.2.3 and 6.3.11. Record any unscheduled discontinuation of RMD or placebo for RMD.

6.3.5 Complete Physical Exam

A complete physical examination will be conducted at the pre-entry visit indicated on the appropriate SOE and is to include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; examination of the lower extremities for edema; and calculation of Karnofsky performance score. The complete physical exam will also include signs and symptoms, diagnoses, and vital signs (temperature, pulse, respiration rate, and blood pressure).

Note: For Cohort 4, a Complete Physical Exam will be performed at the first pre-entry visit (Day -35 to Day -28) with the exception of the calculation for the Karnofsky performance score, which will be performed at the second pre-entry visit (Day -14 to Day -3).

6.3.6 Targeted Physical Exam

A targeted physical examination will be performed **at the visits** indicated in the SOE; at a minimum, it will include vital signs (temperature, pulse, respiration rate, and blood pressure) and, beginning at entry, is to be driven by any previously

identified or new signs or symptoms and diagnoses that the participant has experienced since the last study visit.

Vital signs must be obtained prior to the RMD/placebo infusion, at Hour 2 (+/- 15 minutes) during the RMD/placebo infusion, at any time during the RMD/placebo infusion if clinically indicated, and following completion of the RMD/placebo infusion.

6.3.7 Laboratory Evaluations

Refer to the A5315 MOPS and lab processing chart (LPC), located on the A5315 PSWP, for the specific procedures for the collection, preparation, and storage of specimens.

NOTE: All post-infusion blood collections must be performed on the opposite side of the body from the infusion.

At screening, pre-entry, and entry, all laboratory values, regardless of grade, must be recorded and keyed within 2 business days of study enrollment. The entry laboratory values must be obtained and reviewed prior to initiating RMD/placebo infusion. For post-entry assessments, record and key all Grade ≥2 laboratory values within 2 business days.

Further evaluation will be required for laboratory values and toxicities, regardless of grade, that led to a change in RMD or placebo for RMD infusion and/or Grade ≥ 3 and/or meet EAE or ICH reporting requirements and must be recorded within 2 business days.

Hematology
Cohorts 1 – 3
Hemoglobin, hematocrit, red blood cells [RBC], mean corpuscular volume [MCV], white blood cell count [WBC], differential WBC, absolute neutrophil count (ANC), and platelets will be evaluated.

The pre-entry window for hematology testing is -21 days to 0 hour on Day 0.

Cohort 4
Hemoglobin, hematocrit, RBC, MCV, WBC, ANC, and platelets.

NOTE: On the days that infusions are scheduled, the results from the previous visit must be available before the infusion begins and must **meet the step's eligibility criteria (refer to sections 4.5.4, 4.7.4, 4.9.4)** for the infusion to proceed. **Notify the study's core team (actg.corea5315@fstrf.org) if an infusion must be delayed.**

Liver Function Tests
Cohorts 1 – 3
Total bilirubin, AST [SGOT], ALT [SGPT], alkaline phosphatase, indirect bilirubin, and γ-glutamyl transaminase [GGT] will be evaluated.

Cohort 4
Total bilirubin, AST [SGOT], ALT [SGPT], alkaline phosphatase, indirect bilirubin, and GGT will be evaluated.

The pre-entry window for blood chemistries and liver function tests is -14 days to **-3 days (i.e., day -14 to day -3 pre-entry visit)**.

Potassium and Magnesium
Prior to the Step 1 infusion, potassium and magnesium levels will be assessed at the day -14 to day -3 pre-entry visit, as indicated in the SOE.

Potassium and magnesium levels will be assessed 7 days prior to **the Steps 2, 3, and 4** infusion**s**. Blood potassium and magnesium values must be within normal limits. If the potassium and/or magnesium value is below the site's clinical laboratory's limit of normal, the participant should be supplemented as medically indicated, retested, and evaluated again within 3 days prior to the infusion. The repeated potassium and/or magnesium values must be within normal range for the site's limit of normal for the infusion to take place.

Given blood volume constraints in this study, sites should use pediatric volume tubes for checking potassium and magnesium levels whenever feasible.

Prior to the Steps 2, 3, and 4 infusions, if the potassium and magnesium levels are still out of range after retest, **c**onsultation with the core team is required before a decision about discontinuation is made (actg.corea5315@fstrf.org).

Blood Chemistries
All Cohorts
Electrolytes [sodium, potassium, chloride, phosphate, bicarbonate], calcium, magnesium, creatinine, blood urea nitrogen (BUN), and uric acid will be evaluated.

Calculated creatinine clearance estimated by the Cockcroft-Gault equation will be evaluated.

NOTE: A program for calculating creatinine clearance by the Cockcroft-Gault method is available on www.fstrf.org.

Urinalysis
Urinalysis with microscopic exam will be done at screening only.

Pregnancy Test
Pregnancy testing will be done per the SOE. For women of reproductive potential: Serum or urine β-HCG (urine test must have a sensitivity of ≤ 25 mIU/mL).

For Cohort 4, only urine pregnancy testing is permitted.

Refer to section 7.2 for details on pregnancy and pregnancy outcome reporting.

Hepatitis Screen
HBsAg and HCV antibody testing will be done per the SOE. HCV RNA testing is required if HCV antibody positive. See sections 4.1.9, 4.1.10, 4.3.7, and 4.3.8 for details.

6.3.8 ECG

Resting ECG results, including heart rate and measured QTc interval, must be recorded per the SOE. For the ECG done during pre-entry, the QTc interval must be read by a cardiologist and signed off by the site investigator prior to the start of the RMD/placebo infusion and should ideally be taken from limb lead II.

For the ECGs that are performed at the completion of the RMD/placebo infusion (Hour 4) and 2 weeks later, the QTc interval must be read by a cardiologist but this reading may be done at a later time and QTc interval will be recorded. See section 7.1.5 for clinical management directions for participants with a prolonged QTc interval on study.

NOTE: Should ECGs be performed for any reason at visits after entry, the site is responsible for recording any change in QTc interval relative to the baseline value.

A program for calculating QTc by Fridericia's correction is available on the DMC website at www.fstrf.org.

6.3.9 Immunologic Studies

CD4+/CD8+ (Cohorts 1 – 3 only)
For Cohorts 1-3 only, obtain absolute CD4+/CD8+ T cell count and percentages within 90 days prior to entry from a laboratory that possesses a CLIA (Clinical Laboratory Improvement Amendments) certification or equivalent.

CD4+ (Cohort 4 only)
At screening, obtain absolute CD4+ cell count between 36 and 60 days prior to study entry performed at a laboratory that possess CLIA certification or equivalent.

CD4+ percentages
At the time points indicated **in the SOE**, obtain CD4 percentages only **performed at** a laboratory that possess CLIA certification or equivalent.

During the study, all laboratories must possess a CLIA certification or equivalent and must be qualified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program.

Stored Plasma/PBMC for Immunology Studies
Cryopreserved PBMC obtained by blood draw will be stored for T cell analysis per the SOE. Specific lymphocyte marker testing will include the following:
- Proportion of CD4+ and CD8+ T cells co-expressing CD38/HLA-DR or CD25/CD69
- Percentage of CD3+ lymphocytes that are CD4+ and CD8+
- Proportion of CD4+ and CD8+ T cells that are in cell cycle (Ki-67+)
- Percent of total lymphocytes expressing Annexin V alone and those expressing both Annexin V and 7-AAD

Plasma samples will be obtained to test for the levels of soluble markers of inflammation including IL-6 and hsCRP.

D-dimer (Cohorts 1 – 3 only)
Citrated plasma samples will be obtained per the SOE to test for the levels of D-dimer.

6.3.10 Virologic Studies

See the LPC for processing, shipping, and storage information.

Plasma HIV-1 RNA Real-Time
Screening, Cohorts 1 – 3
Screening HIV-1 RNA (real-time) by standard ultrasensitive assay must be obtained between 50 and 90 days prior to study entry.

Screening, Cohort 4
Screening HIV-1 RNA (real-time) by standard ultrasensitive assay must be obtained between 36 and 60 days prior to entry.

Pre-entry and post-entry, all cohorts
After the screening visit, plasma HIV-1 RNA will be performed real time per the SOE at the protocol-designated laboratory. See section 6.2.4. See the LPC for processing, shipping, and storage information.

Day 7 post-infusion, Cohorts 1 – 3
The HIV-1 RNA level sample obtained at the Day 7 visit must be processed and shipped in real-time, preferably on the day the sample is obtained to ensure results are available prior to the Week 4/Day 28 visit.

Plasma HIV-1 RNA Expedited
Day 7 post-infusion, Cohort 4
The HIV-1 RNA level plasma sample obtained 7 days after each infusion must be processed and shipped overnight. See the LPC for overnight shipping instructions.

Conditional Evaluation Weeks, Cohort 4
HIV-1 RNA level plasma samples obtained at conditional evaluation weeks per the SOE must be processed and shipped overnight per the LPC. Refer to section 6.2.4, Event-Driven Evaluations for Cohort 4.

Plasma HIV-1 RNA by SCA
Screening, entry, and post-entry, Cohorts 1 – 3
The plasma samples for the screening SCA will be collected between 50 and 90 days prior to entry and shipped to a central laboratory for real-time testing. Pre-entry SCA must be obtained between 30 and 35 days prior to entry. Other plasma for SCA will be obtained per the SOE and stored for batched analyses.

Entry and post-entry SCA evaluations will be performed by the designated ACTG Virology Specialty Laboratory on stored plasma samples collected per SOE.

Pre-entry, entry, and post-entry, Cohort 4
Plasma for HIV-1 RNA by SCA will be collected per the SOE and stored for batched analysis by the designated ACTG Virology Specialty Laboratory.

PMBC (Cohort 4)
In Cohort 4, histone acetylation assay will be performed real-time in total CD4+ cells isolated from PBMC per the SOE.

Resting CD4+T-Cells for Cell-associated HIV-1 DNA and HIV-1 RNA
Cohorts 1 – 3
Cell-associated HIV-1 RNA will be measured in resting CD4+ cells from blood collected on Day 0 prior to RMD/placebo infusion and then about 24 hours after the start of the infusion and about 14 days following infusion.

Cell-associated HIV-1 DNA will be measured in resting CD4+ cells from blood collected within 7 days prior to RMD/placebo infusion and then about 24 hours after the start of the infusion and about 14 days following infusion; see section 6.2.3 for timing.

Cohort 4
Cell-associated total HIV-1 RNA will be measured in **PBMCs** cells from blood collected at pre-entry visits, on Day 0 prior to RMD/placebo infusion, and then about 24 and 72 hours after the start of each infusion.

Cell-associated HIV-1 DNA will be measured in **PBMCs** from blood collected prior to RMD/placebo infusion and then about 24 and 72 hours after the start of each infusion.

Stored PBMC for Virology Studies
Stored PBMCs will be used for:

- Future virology studies
- Total CD4+ T-cells for Histone Acetylation and PTEF-b Phosphorylation Assays: Positive transcription elongation factor-b (PTEF-b) phosphorylation will be assessed in total CD4+ cells isolated from cryopreserved stored PBMC per the SOE.

Stored PBMC for **qVOA** (Cohort 4 only)
At the time points indicated in section 6.1.3 SOE, a separate blood collection will be made and PBMCs will be stored for a **quantitative viral outgrowth** assay.

Resting CD4+ T-cells for Ex vivo PMA/Ionomycin and RMD Inducible HIV-1 RNA Expression
Cohorts 1 – 3
Resting CD4+ T cells will be isolated from blood collected per the SOE. Cells will be cultured in the presence of RMD or PMA/Ionomycin. At various times post-stimulation, HIV-1 RNA levels will be measured in culture supernatants by Abbott real-time assay.

6.3.11 Pharmacokinetic (PK) Studies (Refer to Section 10.0)

NOTE: For PK collections, blood must be drawn from the opposite side of the body from that used for the RMD infusion.

Refer to the LPC for collection, processing, storage, and shipping details.

Cohorts 1 – 3
Blood will be drawn following completion of the RMD infusion for determination of RMD and ARV (RAL, EFV, or DTG) plasma levels per the SOE and section 10.2. The date and time of the last three doses of ARV taken immediately prior to the pre-infusion blood sample must be recorded.

Cohort 4
Blood will be collected immediately prior to the third and fourth infusions and then again at Hour 4 (for RMD PK) and at Hour 24 (for ARV PK) after the third and fourth infusions. The date and time of the last three doses of ARV taken immediately prior to the pre-infusion blood sample must be recorded.

6.3.12 RMD or Placebo for RMD Infusion

For correct RMD dosing calculate BSA per section 5.1. See section 6.3.4, Clinical Assessments, Study Treatment Modifications.

Cohorts 1 – 3
RMD will be administered as a single 4-hour intravenous infusion starting at entry/Hour 0. Potassium and magnesium levels will be assessed prior to infusion at the pre-entry visit (day -21 to -7). Blood potassium and magnesium values must be within normal limits. If the pre-entry potassium and/or magnesium value(s) is below the site's clinical laboratory's limit of normal, the participant should be supplemented as medically indicated, retested, and evaluated prior to study entry. If the pre-entry potassium and/or magnesium value(s) is high, the value(s) should be retested, and evaluated prior to study entry. The repeated pre-entry potassium and/or magnesium values must be within normal range for the site's limit of normal for study entry. Given blood volume constraints in this study, sites should use pediatric volume tubes whenever feasible.

Cohort 4
RMD will be administered as a 4-hour intravenous infusion at four time points, as indicated in the Cohort 4 SOE, section 6.1.3 or, as warranted, in the Cohort 4 - Delayed Infusion SOE, section 6.1.4, . See section 6.3.7 for pre-infusion safety testing.

6.3.13 ART Adherence Assessment

Participants will be asked to complete a brief ART adherence questionnaire per the SOE.

7.0 CLINICAL MANAGEMENT ISSUES

Criteria for participant management, dose interruption and discontinuation changes in drug treatment will be mandated only for toxicities attributed to RMD. Toxicities due to drugs in the antiretroviral regimen should be managed according to standard clinical practice, with the goal of maintaining continuous therapy, if possible.

The grading system for drug toxicities is located in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification, August 2009), which can be found on the DAIDS RSC Web site: **http://rsc.tech-res.com/clinical-research-sites/safety-reporting**.

NOTE: The core team must be notified within 24 hours by email at actg.corea5315@fstrf.org regarding toxicities thought to be associated with RMD that result in the discontinuation of the infusion.

7.1 Toxicity

7.1.1 Grade 1 or 2 Toxicity **(All Cohorts)**

Participants who develop a Grade 1 or 2 AE or toxicity during infusion may complete the infusion at the discretion of the site investigator, and will be followed carefully. If a participant chooses to discontinue the infusion, the site should notify the A5315 Core Team at actg.corea5315@fstrf.org and encourage the participant to complete safety visits for the study. Grade 1 or 2 AEs that may be related to RMD should be handled according to standard clinical practice and documented.

7.1.2 Grade 3 Toxicity

Cohorts 1 – 3
Participants who develop a Grade 3 AE or toxicity during infusion should have the infusion discontinued and the A5315 Core Team should be notified. Grade 3 AEs or toxicities that occur following infusion should be handled according to standard clinical practice and the A5315 Core Team should be notified. Participants who experience a Grade 3 AE or clinical event must return for a Week 8/Day 56 visit.

Cohort 4
Participants who develop a Grade 3 AE or toxicity during infusion should have the infusion discontinued. The A5315 Core Team should be notified within 48 hours (preferably within 24 hours). No further infusions will be performed. Refer to section 6.2.5 for required evaluations.

Grade 3 AEs or toxicities that occur following an infusion should be handled according to standard clinical practice, and the A5315 Core Team should be notified.

7.1.3 Grade 4 Toxicity

Cohorts 1 – 3
Participants who develop a Grade 4 AE or toxicity during infusion will have the infusion discontinued. Participants experiencing Grade 4 AEs should be followed closely until the resolution of the AE to < Grade 2 and the A5315 Core Team must be consulted within 72 hours (preferably within 24 hours). Participants who experience a Grade 4 AE or clinical event must return for a Week 8/Day 56 visit.

Cohort 4
Participants who develop a Grade 4 AE or toxicity during infusion should have the infusion discontinued. The A5315 Core Team should be notified within 48 hours (preferably within 24 hours). No further infusions will be performed. Refer to section 6.2.5 for required evaluations.

Grade 4 AEs or toxicities that occur following an infusion should be handled according to standard clinical practice, and the A5315 Core Team should be notified.

7.1.4 Nausea/Vomiting

Nausea/vomiting may be treated symptomatically with oral antiemetics or antiemetic suppositories per standard clinical practice.

7.1.5 Cardiac Toxicity

Refer to the A5315 MOPS for the DAIDS Toxicity Table to grade QTc prolongation.

Grade 1: Infusion should continue without interruption, at the discretion of the site investigator.

Grade 2: Infusion should continue without interruption, at the discretion of the site investigator. A repeat ECG should be performed at the 7 and 14 days following the infusion.

Grade 3 and 4: The infusion should be interrupted. If the Grade 3 QTc prolongation is considered to be most likely due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, should be undertaken. A repeat ECG should be performed 7 and 14 days after the infusion.

Several treatment-emergent changes in ECGs (including T-wave and ST-segment changes) have been reported in clinical studies of RMD. The clinical significance of these changes is unknown. In this study, electrolytes and ECGs are monitored at Pre-Entry and then again after each infusion. The use of strong CYP3A4 inhibitors that may increase RMD concentrations is prohibited during the study. ECG changes observed in participants may be multifactorial. Clinicians should evaluate participants with ECG changes for other possible contributing factors and address any that are identified. Sites should contact the core team (actg.corea5315@fstrf.org) to help determine whether additional infusions should be cancelled.

7.2 Pregnancy

If a female participant becomes pregnant during study follow-up, the site staff should request permission to contact her regarding pregnancy outcomes at the end of pregnancy. A visit 6 months following the end of pregnancy will be conducted to assess for evidence of adverse events (AEs) in the participant and infant and an outcome case report form (CRF) will be completed. Sites must collect and record information on

pregnancy complications and outcome for all pregnancies that occur during study follow-up and within 180 days after an infusion.

Intrapartum complications and/or pregnancy outcome will be recorded on the CRFs. Pregnancies that occur on study must be reported prospectively to The Antiretroviral Pregnancy Registry which collects information about ART exposure and adverse pregnancy outcomes. More information is available at www.apregistry.com. Phone: 800-258-4263; Fax: 800-800-1052.

Pregnancy Outcomes
Pregnant women will be asked to provide pregnancy outcome data. The outcome and the AEs for the participant and infant will be recorded on an outcome CRF. Site staff must request permission to contact her regarding pregnancy and infant outcomes at the end of pregnancy. Pregnancy outcomes for the participant and infant will be submitted on a CRF at the end of the pregnancy.

Procedures in the Event of Contraceptive Failure
In the event of contraceptive failure, the use of an emergency contraceptive is an option. A levonorgestrel-only emergency contraceptive (ie, Plan B) is preferred to minimize the occurrence of nausea. The use of EFV with an emergency contraceptive containing both ethinyl estradiol and levonorgestrel may cause significantly increased ethinyl estradiol levels (Stocrin package insert, 2014), thereby increasing the incidence of nausea and vomiting. Combined ethinyl estradiol/levonorgestrel emergency contraceptive is, however, an acceptable option if a levonorgestrel-only emergency contraceptive is unavailable.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Permanent and Premature Treatment Discontinuation

- Grade 3 or higher drug-related toxicity (see section 7.1 Toxicity).
- Requirement for prohibited concomitant medications (see section 5.5).
- Request by participant to terminate treatment.
- Clinical reasons believed to be serious or life-threatening by the physician, even if not addressed in the toxicity section of the protocol.
- Temperature >101.5 degrees Fahrenheit during **an** infusion.
- Development of an allergic reaction (such as difficulty breathing, wheezing, symptomatic hypotension, hives) which is thought by the site investigator to be related to the study drug.
- Development of a symptomatic cardiac arrhythmia.

8.2 Premature Study Discontinuation

- Participant does not receive any RMD or placebo.
- Participant lacks adequate venous access.
- In Cohort 4, participant does not receive all four infusions of RMD or placebo for RMD.
- In Cohort 4, participant misses more than one of the 24-hour post-infusion blood collections.
- In Cohort 4, participant does not complete the week 11 visit.
- Pregnancy or breastfeeding.
- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- Participant 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 ACTG, IRB, Food and Drug Administration (FDA), NIAID, Office for Human Research Protections (OHRP), other government agency as part of their duties, investigator, or industry supporter.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a dose-escalation study in which cohorts will open sequentially based on the safety of the previous cohort. Up to three dose levels of single-dose RMD (0.5 mg/m^2, 2 mg/m^2, 5 mg/m^2) may be assessed in the first three cohorts. Multiple doses of RMD (at 5mg/m^2) may be assessed in Cohort 4 if safety is established in Cohort 3, ie, if dose-escalation criteria are met. Each cohort of 15 participants consists of 12 evaluable participants receiving RMD and 3 receiving placebo (single dose in Cohorts 1 – 3, and multiple doses in Cohort 4).

The study is double-blinded, placebo-controlled and randomized. There are three participants receiving placebo at each dose cohort. Inclusion of a placebo group in each cohort, albeit small, may help assess treatment-related events by allowing blinded assessment of events in relation to treatment. Also, the efficacy of RMD among those receiving RMD in Cohorts 1 – 3 can be compared to those of placebo participants pooled from Cohorts 1 – 3.

Accrual of the first five participants in any cohort will be limited to one participant in a 3-day period.

Analyses and dissemination of study results from Cohorts 1 – 3 will commence after Cohort 3 follow-up is completed. Analyses and dissemination of Cohort 4 results will commence after Cohort 4 follow-up is completed.

9.2 Outcome Measures

NOTE: Due to insufficient numbers of resting CD4+ T-cells available from some Cohort 4 participants to perform all the planned assays (e.g., cell-associated HIV-1 RNA, total HIV-1 DNA, histone acetylation, PTEF-b activation), those assays will be performed using peripheral blood mononuclear cells (PBMCs). The team carefully reassessed the priorities for the use of these cells based on advances in the field since the prior protocol version. Accordingly, the relevant objectives and outcomes measures sections have been updated.

9.2.1 Primary Endpoints

9.2.1.1 Safety

Occurrence of Grade ≥ 3 AE including signs/symptoms, lab toxicities, and /or clinical events that is probably, possibly or definitely related to study treatment (as judged by the core team, blinded to treatment arm) any time from the time of study treatment administration until 28 days after the administration.

9.2.1.2 Efficacy

9.2.1.2.1 Change in plasma HIV-1 RNA levels from baseline (average of pre-entry and entry values) as detected by single copy assay at 24 and 48 hours (average) after the single administration of RMD or placebo in Cohorts 1 – 3.

9.2.1.2.2 Change in plasma HIV-1 RNA levels from baseline (average of pre-entry and entry values) as detected by single copy assay before and 24 hours after each administration of RMD or placebo in Cohort 4.

9.2.1.2.**3** Change in cell-associated HIV-1 RNA levels in resting CD4+ T-cells from baseline to 24 hours after the single administration of RMD or placebo in Cohorts 1 – 3.

9.2.1.2.**4** Change in cell-associated HIV-1 RNA levels in **PBMCs** before and **24 hours** after each administration of RMD or placebo in Cohort 4.

9.2.2 Secondary Outcome Measures

9.2.2.1 Changes in plasma HIV-1 RNA levels as detected by single copy assay from baseline to after the single administration of RMD or placebo in Cohorts 1 – 3 and after each **administration** of RMD or placebo in Cohort 4.

9.2.2.2 Change in cell-associated HIV-1 RNA levels in resting CD4+ T-cells from baseline to 14 days after the administration of RMD or placebo **in Cohorts 1-3, and in PBMCs after each administration of RMD or placebo in Cohort 4**.

9.2.2.**3** Changes in histone acetylation in CD4+ **and CD8+** T-cells from baseline to after the single administration of RMD or placebo in Cohorts 1-3 and after each administration of RMD or placebo in Cohort 4.

9.2.2.**4** Changes in total HIV-1 DNA in resting or total CD4+ T-cells from baseline to after the single administration of RMD or placebo in Cohorts 1 – 3 and **in PBMCs** after each administration of RMD or placebo in Cohort 4.

9.2.2.**5** Pharmacokinetic parameters for RMD and co-administered antiretroviral drugs (EFV, DTG, or RAL).

9.2.2.**6** Number/percent of participants in Cohorts 1 – 3 with HIV-1 RNA levels ≥200 copies at the Day 7 visit

9.2.2.**7** Number/percent of participants in Cohort 4 with HIV-1 RNA levels ≥200 copies/mL at scheduled post-infusion 4 visits.

9.2.2.**8** All reported Grade 2-4 AEs.

9.2.2.9 Change in CD4+ T cell percent from baseline to after each administration of RMD or placebo in Cohort 4.

9.2.2.10 Change in CD4+ and CD8+ T cell percent from baseline to after the single administration of RMD or placebo in Cohorts 1 – 3 and after each administration of RMD or placebo in Cohort 4.

9.2.2.11 Changes in the percentage of CD3+ CD4+ and CD3+ CD8+ lymphocytes and cellular markers of immune activation (CD38/HLA-DR or CD69/CD25 expression on CD4+ and CD8+ T-cells) from baseline to after the single administration of RMD or placebo in Cohorts 1 – 3 and after each administration of RMD or placebo in Cohort 4.

9.2.2.12 Change in percentage of total lymphocytes expressing annexin V and/or 7 amino-actinomycin D (7-AAD) from baseline to after the single administration of RMD or placebo in Cohorts 1 – 3 and after each administration of RMD or placebo in Cohort 4.

9.2.2.13 Changes in P-TEFb and HIV-1 expression; changes in PTEF-b phosphorylation in CD4+ and CD8+ T-cells from baseline to after

the single administration of RMD or placebo in Cohorts 1 – 3 and after each administration of RMD or placebo in Cohort 4.

9.2.3 Exploratory Outcome Measures

9.2.3.1 Change in quantitative viral outgrowth assay (qVOA) from baseline to after administration of all doses of RMD or placebo in Cohort 4.

9.2.3.**2** Changes in proportion of cycling CD4+ and CD8+ T-cells (Ki67 expression) from baseline to after the single administration of RMD or placebo in Cohorts 1 – 3 and after each administration of RMD or placebo in Cohort 4.

9.2.3.**3** Changes in the levels of soluble markers IL-6, C-reactive protein (CRP), and D-dimer from baseline to after the single administration of RMD or placebo in Cohorts 1 – 3 and after each administration of RMD or placebo in Cohort 4.

9.2.3.4 Changes in HIV-specific immune responses from baseline to after the first and fourth administration of RMD or placebo in Cohort 4.

9.2.3.5 Changes in host RNA expression profiles by RNAseq of PBMC from after the first and fourth administration of RMD or placebo in Cohort 4.

9.3 Randomization and Stratification

Each cohort will open sequentially. Within each cohort, 15 participants will be randomized to receive RMD (12 participants) or placebo (3 participants). Randomization will use a permuted block method without institutional balancing or stratification. After each cohort enrollment is complete, study enrollment will be suspended until a decision on the subsequent cohort is made, based on the dose escalation criteria.

9.4 Sample Size and Accrual

The total sample size of this study will be 60 evaluable participants (12 evaluable active plus 3 evaluable placebo controls, per dosing cohort) if all four cohorts are enrolled. For Cohorts 1 – 3, participants who do not receive study drug (RMD or placebo) and/or complete the pre-infusion blood collection and/or the 24-hour blood collection will be replaced. For Cohort 4, participants who do not complete all 4 doses of study drug (RMD or placebo) and/or who miss more than one of the 24-hour post-infusion blood collections or the week 11 blood collection will be replaced.

9.4.1 Safety

Dose escalation criteria for consideration by the SMC are defined as:

a) No more than three participants have experienced a Grade 3 AE that is probably or possibly related to study treatment (as judged by the core team, blinded to treatment arm) prior to or on Day 14 after the treatment administration; and

b) None of the participants has experienced a Grade ≥ 3 AE that is definitely related to study treatment or that is Grade ≥ 4 and probably or possibly related to study treatment (as judged by the core team, blinded to treatment arm) prior to or on Day 14 after the treatment administration.

Note: The occurrence of a Grade 3 infusion site pain or tenderness that is sustained for less than 48 hours will be excluded from the dose escalation evaluation.

The tables below show the probabilities of dose escalation under various assumed true rates for two types of AEs as described above and under various enrollment projections (i.e., if at least 12 but fewer than 15 participants are enrolled into a cohort).

In the tables, the column “True rate of Grade 3 AE probably or possibly related to study Rx” is the probability conditional on not having the “Grade 3 or higher AE definitely related or Grade 4 or higher AE probably or possibly related to study Rx”. The column “True rate of Grade 3 or higher AE definitely related or Grade 4 or higher AE probably or possibly related to study Rx” is the unconditional probability of the event. The calculations in these tables assume there is negligible probability that a participant in the placebo arm will experience a Grade ≥ 3 AE.

The proposed sample size provides a reasonably high probability of dose escalation when the true event rates are, in fact, acceptable. For example, if the probability of a participant in the active treatment arm of a given dose cohort experiencing a Grade 3 AE as described above that is possibly or probably due to study treatment is 0.012 (ie, 1.2%), and the corresponding probability of experiencing such an AE that is definitely due to study treatment is 0.10 (ie, 1%), then the probability that the study will dose escalate to the next higher dose is 0.89 (ie, 89%). Given that this is an acceptable safety profile, this means that the probability of incorrectly concluding the current dose unsafe is 11%. On the other hand, the proposed sample size provides a low probability of dose escalation when the true event rates are unacceptable. For example, if the true rate of Grade 3 AE that is probably or possibly related to study treatment is 0.180 (ie, 18%), and the true rate of Grade 3 AE that is definitely related or Grade 4 or higher AE that is probably or possibly related to study treatment is 0.150 (ie, 15%), then the probability of dose escalation is only 0.12 (ie, 12%), and the corresponding probability of not dose escalating and correctly concluding the dose unsafe is high at 0.88 (1-0.12).

Table **9.4.1-1:** Probabilities of dose escalation under various assumed true rates (n=12 on RMD).

True rate of Grade 3 AE probably or possibly related to study Rx	True rate of Grade 3 or higher AE definitely related or Grade 4 or higher AE probably or possibly related to study Rx	Probability of Dose Escalation
0.006	0.005	0.94
0.012	0.010	0.89
0.024	0.020	0.78
0.036	0.030	0.69
0.048	0.040	0.61
0.060	0.050	0.54
0.120	0.100	0.27
0.180	0.150	0.12
0.240	0.200	0.05
0.360	0.300	**<0.01**

The randomization of study participants to either RMD or placebo uses a permuted block design. With a ratio of 4:1, a block size of 5 has been used. Based on this method, with a total of 12 participants enrolled in Cohort 3, there will be 9 or 10 participants randomized to receive RMD. The following calculations of probabilities of dose escalation using the same criteria are based on N=9 or 10 on RMD.

Table **9.4.1-2:** Probability of dose escalation under various assumed true rates (n=10 on RMD)

True rate of Grade 3 AE probably or possibly related to study Rx	True rate of Grade 3 or higher AE definitely related or Grade 4 or higher AE probably or possibly related to study Rx	Probability of Dose Escalation
0.006	0.005	0.95
0.012	0.010	0.90
0.024	0.020	0.82
0.036	0.030	0.74
0.048	0.040	0.66
0.060	0.050	0.60
0.120	0.100	0.34
0.180	0.150	0.18
0.240	0.200	0.09
0.360	0.300	0.01

With N=10, the study still provides a low probability (although higher than with N=12) of dose escalation when the true event rates are unacceptable. For example, for the same assumed rates as above, the probability of dose escalation is 0.18 (ie, 18%) vs. 0.12 with N=12, and the corresponding probability of not dose escalating and correctly concluding the dose unsafe is high at 0.82 (1-0.18) vs. 0.88.

Table **9.4.1-3:** Probability of dose escalation under various assumed true rates (n=9 on RMD)

True rate of Grade 3 AE probably or possibly related to study Rx	True rate of Grade 3 or higher AE definitely related or Grade 4 or higher AE probably or possibly related to study Rx	Probability of Dose Escalation
0.006	0.005	0.96
0.012	0.010	0.91
0.024	0.020	0.83
0.036	0.030	0.76
0.048	0.040	0.69
0.060	0.050	0.63
0.120	0.100	0.38
0.180	0.150	0.22
0.240	0.200	0.11
0.360	0.300	0.02

With N=9, the probabilities of dose escalation are larger than in the setting with N=12 as expected. For example, for the same assumed rates as above, the probability of dose escalation is 0.22 (ie, 22%) vs. 0.12 with N=12, and the corresponding probability of not dose escalating and correctly concluding the dose unsafe is high at 0.78 (1-0.22) vs. 0.88.

9.4.2 Efficacy

For evaluating primary efficacy endpoints in Cohorts 1 – 3, the study will use the results from the placebo arms combined across Cohorts 1 – 3 as a control. If all three cohorts are fully enrolled and treated and followed per protocol, there will be n=9 participants in the combined placebo control group and n=36 participants in the combined RMD group.

The study is powered on the change of HIV-1 RNA by SCA from baseline (average of pre-entry and entry values) to the 24 and 48 hour measurements (averaged) after RMD administration. Under the assumptions that the standard deviation of $\log_{10}$ change is 0.32 (derived from A5244 SCA measurements) and there will be no change in HIV-1 RNA in the placebo group, with a sample size of n=36 in the combined RMD group and n=9 in the combined placebo group, the study will have 80% power to detect a 0.42 $\log_{10}$ increase in HIV-1 RNA by SCA using a two-sided Wilcoxon rank sum test at 5% level.

For the secondary comparison of a given RMD dose group (n=12) with the combined placebo group (n=9), the study will have 80% power to detect a 0.52 $\log_{10}$ increase in RNA by SCA.

The sample size estimation includes an adjustment of 15% for the potential loss of efficiency due to left censoring of SCA results below assay limit.

The following table presents the detectable effect size based on various sample sizes and standard deviations:

Table **9.4.2-1:** Detectable effect sizes based on various sample sizes and assumed standard deviations.

Estimated standard deviation of $\log_{10}$ change	Sample size per cohort: RMD/ placebo	Detectable Effect size ($\log_{10}$) with 80% power for comparison between combined RMD group and combined placebo group	Detectable Effect size ($\log_{10}$) with 80% power for comparison between a given RMD dose group and combined placebo group
SD=0.29	15/5	0.29	0.37
	12/3	0.38	0.47
SD=0.32	15/5	0.32	0.41
	12/3	0.42	0.52
SD=0.35	15/5	0.35	0.44
	12/3	0.46	0.56

For comparison of the change of cell-associated viral RNA in resting CD4+ T-cells from baseline, assuming that the standard deviation (SD) of $\log_{10}$ change is 0.33 [39] and there will be no change in HIV-1 RNA in the placebo group, with 36 active and 9 placebos combined in Cohorts 1 – 3, the study will have 80% power to detect a difference of 0.38 $\log_{10}$ copies/million CD4 cells in the cell-associated viral RNA between the two combined groups, using a two-sided 5% level Wilcoxon rank sum test. For Cohort 4, with 12 in the RMD group and 3 in the placebo group, the study will have 80% power to detect a difference of 0.79 $\log_{10}$ copies/million CD4 cells.

For Cohort 4, a quantitative viral outgrowth assay (qVOA) will be performed instead of the modified TVR assay [41]. The team opted to perform the qVOA

since it is the current gold-standard assay for quantifying the latent reservoir.

9.4.3 Accrual

Accrual and screening will be suspended when the current cohort is fully enrolled and until the cohort is evaluated. Screening will reopen for enrollment once the decision to open the next cohort is made.

Participants who do not receive study treatment or complete the pre-infusion and hour 24 blood collection will be replaced in Cohorts 1 – 3; in Cohort 4, any participant who misses an infusion, more than one of the 24-hour post-infusion blood collections, or the week 11 blood collection will be replaced. Any participant who prematurely discontinues the 4 hour study treatment infusion for reasons other than the study treatment-attributed Grade ≥ 3 events will be replaced with a participant assigned to the same dose cohort and the same arm.

Expected accrual per month is 2 to 4 participants.

In the unlikely event that dose escalation to all three doses is not undertaken due to the stopping rules noted in section 9.5, the enrollment will be expanded in the lower dose cohort(s) to maintain power for efficacy comparisons. Details and implementation of the enrollment expansion plan will be discussed in consultation with the SMC.

9.5 Monitoring

Accrual, baseline characteristics, conduct of the study, all toxicities, and AEs will be monitored during the trial with reports pooled over treatment arms and broken down by dose cohort sent to the core team on a regular basis. The protocol core safety team will review the individual safety data frequently to assess relation of all reported toxicities and AEs to the study treatment in blinded assessments, incorporating the site investigator's opinion on their relation to the treatment reported on the CRFs.

It will be the responsibility of the core safety team to interpret the toxicity data, make decisions needed to protect participants from undue risk, and determine whether or not participant replacements are needed.

If at any time within a given dose cohort,

a) four or more participants experience a primary safety endpoint (section 9.2.1.1) that is possibly or probably related to study treatment (as judged by the core safety team, blinded to treatment arm); or

b) one or more participants experience a primary safety endpoint (section 9.2.1.1) that is definitely related to study treatment or that is Grade 4 or death and possibly or probably related to study treatment (as judged by the core safety team, blinded to

treatment arm) then enrollment into the study will be temporarily suspended and an independent SMC, unblinded to treatment assignment, will be asked to review all safety data; review the relation to study treatment of the event(s) thought by the blinded core safety team to be a primary safety endpoint; and recommend how the study should proceed with respect to resuming enrollment, continuing study treatment and dose escalation.

After the last enrolled participant in a given cohort completes 14 days after the study treatment and the blinded data become available for review, all safety data, including the decisions on the relationships between AEs and study treatment, will be reviewed by the SMC to determine whether to dose escalate or modify the study. In addition, the SMC will review the study at least yearly while the study is ongoing. Furthermore, the core safety team, at any time it thinks appropriate, may ask for the SMC to independently review all available safety data (unblinded to treatment arms) and make a recommendation to the HIV Reservoirs and Eradication Transformative Science Group on whether to modify or stop the study.

The DAIDS clinical representative will receive the standard toxicity summary report according to the schedule for phase I/II studies.

9.6 Analyses

For the primary safety analysis, Grade ≥ 3 AEs attributed to the study treatment will be described separately for the treatment arm of each dose cohort, and for the combined placebo arms. All participants who have been exposed to the study treatment/placebo will be included in this analysis. As secondary analyses, all reported Grade ≥ 2 AEs on all enrolled participants will be summarized for the treatment arm of each dose cohort, and combined placebo arms.

For the primary efficacy outcome measures of changes in plasma HIV-1 RNA level and cell-associated viral RNA levels in resting memory CD4+ T-cells **in Cohorts 1-3**, the analyses will be “as-treated” based only on participants who completed study treatment/placebo administration. Changes from baseline to scheduled study visits will be summarized with appropriate median plots, separately for the combined RMD and the combined placebo groups. A Wilcoxon rank sum test will be used for the comparison between the two combined groups for Cohorts 1 – 3. Analysis for the primary efficacy outcome measures in Cohort 4 will use the same approach between RMD and placebo.

Secondary outcome measures will be explored in a similar fashion. Additionally, a generalized Wilcoxon test will be used to compare the changes in plasma HIV-1 RNA by SCA in Cohort 4 between RMD and placebo to account for potential censoring due to undetectable SCA value at baseline. If proportions of undetectable SCA values are high, changes in SCA levels may also be analyzed as categorical data (increase from baseline vs. decrease from baseline vs. undetermined). Furthermore, longitudinal SCA levels per participant will be plotted.

As exploratory secondary analyses, the comparison of a given RMD dose group with the combined placebo group will be made using the same approach. Furthermore, the relationship between dose level and changes in plasma HIV-1 RNA level and cell-associated viral RNA levels will be explored using a Wilcoxon rank sum test (comparison between two dose levels) or Jonckheere-Terpstra test (comparison among three dose levels), depending on the actual study cohorts that open. In addition, comparisons will be made with non-parametric repeated measures test (Wei-Johnson test with Xu-Tian-Wei method with a Wilcoxon-type kernel function) between the combined RMD and placebo groups for Cohorts 1 – 3 and between RMD and placebo for Cohort 4. Each test will be a 2-sided with a type I error rate of 5%. As exploratory analyses, no adjustment for multiple tests will be made in the type I error rate.

10.0 PHARMACOLOGY PLAN

The pharmacology plan described in this section applies primarily to Cohorts 1-3. In Cohort 4, similar PK testing will be performed before and after the third and fourth RMD infusion from samples collected at appropriate time points.

10.1 Pharmacology Objectives

The primary objective is to evaluate RMD pharmacokinetics in HIV-infected participants on ART at three different single dose levels in Cohorts 1 – 3 and at a single dose level after multiple administrations in Cohort 4. The secondary objective is to assess the effect of efavirenz, dolutegravir, or raltegravir on RMD exposure in Cohorts 1 – 3 and of dolutegravir or raltegravir on RMD exposure in Cohort 4. The third objective is to determine whether there is an association between RMD PK parameters (AUC, C_{min}, C_{max}, etc.) and induction of HIV-1 transcription in CD4+ T-cells of HIV-infected participants receiving suppressive ART.

10.2 Pharmacology Study Design

This is a dose-finding trial of RMD at dose levels of 0.5, 2.0, and 5.0 mg/m^2. Participants in Cohorts 1 – 3 will be receiving an EFV-, DTG-, or RAL-based regimen that includes two N(t)RTIs. In Cohort 4, participants will be receiving a DTG- or RAL-based regimen that includes twp N(t)RTIs. PIs are not permitted in any cohort nor are other ARVs that are eliminated by or induce CYP3A4 (e.g., maraviroc, etravirine, rilpivirine).

Cohorts 1 – 3
The last ARV dosing taken prior to infusion will be recorded as a part of the entry/Hour 0 evaluation. A baseline whole blood sample (4 mL) will be drawn at pre-infusion entry/Hour 0 (within 15 minutes prior to RMD administration). RMD/placebo will be administered intravenously over a 4 hour infusion. Post infusion whole blood samples will be collected following completion of the RMD-infusion from the opposite side of the body, at 4, 6, 12, and 24 hours after initiation of RMD dosing. RAL, EFV, or DTG plasma levels will also be quantitated from these samples.

Cohort 4
The last ARV dosing taken prior to infusion will be recorded as a part of the Hour 0 evaluation for Steps 3 and 4. In each of these two steps, a whole blood sample will be drawn at pre-infusion /Hour 0 (within 15 minutes prior to RMD/placebo administration). RMD/placebo will be administered intravenously over a 4-hour infusion. Post-infusion whole blood samples will be collected from the opposite side of the body, at 4 and 24 hours after initiation of the infusion. **RMD plasma levels will be quantified from the 4-hours post-infusion sample and** DTG or RAL plasma levels will be quantitated from the **24-hours post-infusion** sample.

10.3 Primary and Secondary Data, Modeling, and Data Analysis

The primary analysis will be non-compartmental (WinNonlin 5.3, Pharsight). The area under the plasma concentration time curve (AUC_τ) will be calculated using the linear-up/log-down trapezoidal rule. Maximum plasma concentration (C_{max}) and time to maximum concentration (T_{max}) will be taken directly from the observed concentration-time data. Clearance (CL/F) is calculated as dose/$AUC\tau$. Terminal apparent distribution volume (V_z/F) is calculated as dose divided by the product of the elimination rate constant (λ_z) and AUC_τ. The elimination rate constant will be determined by linear regression of the terminal elimination phase concentration-time points; elimination half-life ($t_{1/2}$) is calculated as $\ln(2)/\lambda_z$.

RMD PK parameters will be compared across participants receiving RAL, DTG, or EFV to determine the magnitude of any interactions. Relationships between RMD PK parameters and biomarkers of HIV-1 reactivation will be explored using maximum effect models. These biomarkers include, but are not limited to, plasma viremia using a single copy HIV-1 RNA assay, changes in cell-associated viral RNA levels in resting memory CD4+ T-cells, changes in total HIV-1 DNA, and other immunologic and inflammatory biomarkers.

10.4 Anticipated Outcomes

We anticipate full description of RMD pharmacokinetic parameters in this patient population. Since this drug is metabolized by CYP3A4, we also anticipate a potential interaction with EFV (a CYP3A4 inducer) (for Cohorts 1 – 3), but not RAL or DTG. The RMD concentration range should be large enough to establish relationships with biomarkers, but these analyses will be exploratory.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

Case report forms (CRF) will be provided for each participant. Participants must not be identified by name on any CRFs. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon (randomization/registration).

11.2 Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

11.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

11.3 Clinical Site Monitoring and Record Availability

11.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

11.3.2 The site investigator will make study documents (eg, consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, the NIAID, the OHRP, **other local, US, and international regulatory entities,** and the industry supporter(s) or designee for confirmation of the study data.

11.4 Expedited Adverse Event Reporting to DAIDS

11.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at **http://rsc.tech-res.com/clinical-research-sites/safety-reporting.**

The DAIDS Adverse Events Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: **http://rsc.tech-res.com/clinical-research-sites/safety-reporting.** For questions about expedited reporting, please contact DAIDS RSC (DAIDSRSCSafetyOffice@tech-res.com).

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

The study agents for which relationship assessments are required: Romidepsin or Placebo for Romidepsin.

The Division of AIDS Table for Grading the Severity of Adult and Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009), must be used and is available on the DAIDS at **http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables**.

The protocol-defined expedited event reporting period for this protocol is 3 months for an individual participant in Cohorts 1, 2, or 3 (beginning at study enrollment) and 6 months for an individual participant in Cohort 4 (beginning at study enrollment). If the site becomes aware of an event after the reporting period**,** it should be reported in a timely fashion.

After the end of the protocol-defined EAE Reporting Period stated above, sites must report serious, unexpected, clinical suspected adverse drug reactions if the study site staff becomes aware of the event on a passive basis, ie, from publicly available information.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: **http://rsc.tech-res.com/clinical-research-sites/safety-reporting**. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

11.4.2 Grading Severity of Events

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, August 2009), must be used and is available on the DAIDS RSC Web site at **http://rsc.tech-res.com/clinical-research-sites/safety-reporting.**

11.4.3 Expedited AE Reporting Period

- The expedited AE reporting period for this study is 3 months for an individual participant in Cohorts 1, 2, or 3 (beginning at study enrollment) and 6 months for an individual participant in Cohort 4 (beginning at study enrollment).

- After the protocol-defined AE reporting period, unless otherwise noted, only SAEs, as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

12.0 HUMAN PARTICIPANTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent documents (Appendices IV, V, and VI) and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study. A signed consent form will be obtained from the participant (or parent, legal representative, or person with power of attorney for participants who cannot consent for themselves, such as those below the legal age of consent). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, parent, or legal representative, and this fact will be documented in the participant's record.

12.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, other **local, US, and international regulatory entities** as part of their duties, or the industry supporter or designee.

12.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, or the industry supporter, or other government agencies as part of their duties to ensure that research participants are protected.

13.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

14.0 BIOHAZARD CONTAINMENT

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 will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

15.0 REFERENCES

1. Finzi D, Hermankova M, Pierson T, et al. Identification of a reservoir for HIV-1 patients on highly active antiretroviral therapy. Science 1997; 278:1295-1300.
2. Finzi D, Blankson J, Siliciano JD, et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. Nat Med 1999; 5(5):512-7.
3. Siliciano JD, Kajdas J, Finzi D, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. Nat Med 2003;9(6):727-8.
4. Chun TW, Stuyver L, Mizell SB, et al. Presence of an inducible HIV-1 latent reservoir for HIV-1 in patients on highly active antiretroviral therapy. Proc Natl Acad Sci USA. 1997;94:13193-7.
5. Palmer S, Maldarelli F, Wiegand A, et al. Low-level viremia persists for at least seven years in patients on suppressive antiretroviral therapy. Proc Natl Acad Sci USA 2008;105:3879-84.
6. Dinoso JB, Kim SY, Wiegand AM, et al. Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy. Proc Natl Acad Sci USA 2009; 106 (23):9403-8. Epub 2009.
7. McMahon D, Jones J, Wiegand A, et al. Raltegravir intensification does not reduce persistent low level viremia in patients suppressed on combination therapy. CID 2010; 50:912-9.
8. Gandhi RT, Zheng L, Bosch RJ, et al, AIDS Clinical Trials Group A5244 team. The effect of raltegravir intensification on low-level residual viremia in HIV-infected patients on antiretroviral therapy: a randomized controlled trial. PLoS Med 2010 Aug;10;7(8).
9. Shan L, Deng K, Shroff NS, et al. Stimulation of HIV-1-specific cytolytic T lymphocytes facilitates elimination of latent viral reservoir after virus reactivation. Immunity 2012 Mar; 23;36(3):491-501.
10. Chun TW, Engel D, Mizell SB, et al. Effect of interleukin-2 on the pool of latently infected, resting CD4+ T cells in HIV-1-infected patients receiving highly active antiretroviral therapy. Nat Med. 1999 Jun;5(6):651-5.
11. Prins JM, Jurriaans S, van Praag RM, et al. Immuno-activation with anti-CD3 and recombinant human IL-2 in HIV-1-infected patients on potent antiretroviral therapy AIDS. 1999;13:2405.
12. Scripture-Adams DD, Brooks DG, Korin YD, Zack JA. Interleukin-7 induces expression of latent human immunodeficiency virus type 1 with minimal effects on T-cell phenotype. J Virol 2002 76;13077-082.
13. Chomont N, El-Far M, Ancuta P, et al. HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation. Nat Med 2009;15(8):893-900.
14. Bosque A, Famigliette M, Weyrich AS, Goulston C, Planelles V. Homeostatic proliferation fails to efficiently reactivate HIV-1 latently infected central memory CD4+ T cells. Plos Pathog 2011;7(10):e1002288.

15. Katlama C, Lambert S, Assoumou L, et al. Impact of interleukin-7 and raltegravir plus maraviroc intensification on total HIV DNA reservoir: results from ERAMUNE 01 (Abstract 170). Presented at 20th Conference on Retroviruses and Opportunistic Infections; 2013 Mar 3-6; Atlanta, GA.
16. Ylisastiqui L, Archin NM, Lehrman G, Bosch RJ, Margolis DM. Coaxing HIV-1 from resting CD4 T cells: histone deacetylase inhibition allows latent viral expression. AIDS 2004;18: 1101-8.
17. Lehrman G, Hogue IB, Palmer S, et al. Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. Lancet 2005;366(9485):549-55.
18. Siliciano JD, Lai J, Callender M, et al. Stability of the latent reservoir for HIV-1 in patients receiving valproic acid. J Infect Dis 2007 Mar 15;195:833-6.
19. Routy J, Tremblay C, Angel J, et al. Valproic acid in association with highly active antiretroviral therapy for reducing systemic HIV-1 reservoirs: results from a multicentre randomized clinical study. HIV Med 2012. May;13(5):291-6.
20. Archin NM, Espeseth A, Parker D, et al. Expression of latent HIV induced by the potent HDAD inhibitor suberoylanilide hydroxamic acid. AIDS Res Hum Retroviruses 2009;25(2):207-12.
21. Edelstein LC, Micheva-Viteva S, Phelan BD, Dougherty JP. Short communication: activation of latent HIV type 1 gene expression by suberoylanilide hydroxamic acid (SAHA), an HDAC inhibitor approved for use to treat cutaneous T cell lymphoma. AIDS Res Hum Retroviruses 2009;25(9):883-7.
22. Contreras X, Schweneker M, Ching-Shih C, et al. Suberolyanilide hydroxamic acid reactivates HIV from latently infected cells. J Biol Chem 2009;284(11):6782-9.
23. Archin NM, Liberty AL, Kashuba AD, et al. Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. Nature 2012;487(7408):482-5.
24. Piekarz RL, Frye R, Prince HM, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood 2011;117:5827-34.
25. Subramanian S, Bates SE, Wright JJ, et al. Clinical toxicities of histone deacetylase inhibitors. Pharmaceuticals 2010;3(9):2751-2767.
26. Bosque A, Planelles V. Induction of HIV-1 latency and reactivation in primary memory CD4+ T cells. Blood 2009;113:58-65.
27. Reuse S, Calao M, Kabeya K, et al. Synergistic activation of HIV-1 expression by deacetylase inhibitors and prostratin: implications for treatment of latent infection. PLoS One 2009; 4(6):e6903.
28. Neves P, Lampropoulou V, Calderon-Gomez E, et al. Signaling via the MyD88 adaptor protein in B cells suppresses protective immunity during Salmonella typhimurium infection. Immunity. 2010 Nov 24;33(5):777-90.
29. Children's Oncology Group, Fouladi M, Furman WL, et al. Phase I study of depsipeptide in pediatric patients with refractory solid tumors: a Children's Oncology Group report. J Clin Oncol 2006 Aug 1;24(22):3678-85.

30. Klimek VM, Fircanis S, Maslak P, et al. Tolerability, pharmacodynamics, and pharmacokinetics studies of depsipeptide (romidepsin) in patients with acute myelogenous leukemia or advanced myelodysplastic syndromes. Clin Cancer Res 2008 Feb 1;14(3):826-32.
31. Marshall JL, Rizvi N, Kauh J, et al. A phase I trial of depsipeptide (FR901228) in patients with advanced cancer. J Exp Ther Oncol 2002 Nov-Dec;2(6):325-32.
32. Sandor V, Bakke S, Robey RW, et al. Phase I trial of the histone deacetylase inhibitor, depsipeptide (FR901228, NSC 630176), in patients with refractory neoplasms. Clin Cancer Res 2002 Mar;8(3):718-28.
33. Hilldorfer BB, Cillo AR, Besson GJ, et al. New tools for quantifying HIV-1 reservoirs: plasma RNA single copy assays and beyond. Curr HIV/AIDS Rep 2012 Jan 4. Mar; 9(1):91-100.
34. International Conference on Harmonisation; guidance for industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Food and Drug Administration, US Department of Health and Human Services. Fed Regist 2005 Oct 20;70(202):61134-5.
35. Søgaard OS, Graversen ME, Leth S, et al. The depsipeptide romidepsin reverses HIV-1 latency in vivo. PLoS Pathog 2015;11(9):e1005142.
36. Jones RB, O'Connor R, Mueller S, et al. Histone deacetylase inhibitors impair the elimination of HIV-infected cells by cytotoxic T-lymphocytes. PLoS Pathog 2014; 10(8):e1004287.
37. Leth S, Schleimann MH, Nissen SK, et al. Combined effect of Vacc-4x, recombinant human granulocyte macrophage colony-stimulating factor vaccination, and romidepsin on the HIV-1 reservoir (REDUC): a single-arm, phase 1B/2A trial. Lancet HIV 2016 Jul 7;10(16)30055-8.
38. Crooks AM, Bateson R, Cope AB, et al. Precise quantitation of the latent HIV-1 reservoir: implications for eradication strategies. J Infect Dis. 2015 Nov 1;212(9):1361-5.
39. Hong F, Aga E, Cillo A, et al. Novel assays to measure total cell-associated HIV-1 DNA and RNA. J Clin Microbiol. 2016 Apr;54(4):902-11.
40. Elliott JH, Wightman F, Solomon A, et al. Activation of HIV transcription with short-course vorinostat in HIV-infected patients on suppressive antiretroviral therapy. PLoS Pathogens. 2014;10(10):e1004473.
41. Wang Z, Simonetti FR, Siliciano RF, et al. Measuring replication competent HIV-1: advances and challenges in defining the latent reservoir. Retrovirology. 2018:15:21.

APPENDIX I: A5315 STUDY VISITS – COHORT 3

The study staff can answer any questions you have about individual study visits, the evaluations that will occur, or how long each visit will be. The table below can be used as a quick reference for you, along with the explanations that follow.

Appendix I, Table 1: Study Schedule

Evaluation	Screen[1]	Pre-Entry[2]			Entry[3]						On Study Visits[4]						HIV-1 RNA ≥200	Early Disc[5]
	-90 to -50 Days	-35 to -30 Days	-21 to -7 Days	-7 Days to -0 Hours	Hour						Day							
					0	2	4	6	8	12	1	2	7	14	28	56		
Consent Signed	X																	
HIV Confirmed	X																	
Medical/Medication History	X				X													
Physical Exam	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood Collected	X	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X
Urine Collected	X																	
Pregnancy Test	X		X		X							X	X	X	X			X
Electrocardiogram (ECG)			X				X					if required		X	if required			
Study Drug Infusion					X	X	X											
ART Adherence Assessment	X		X		X								X	X	X	X		X

[1] Screening Visit: Between 50 and 90 days before entry and after you have read and signed the consent form, you will have several evaluations done to make sure that you meet the requirements for joining the study. These evaluations may be scheduled in more than one visit.

[2] Pre-Entry Visits: You will come to the clinic for about three pre-entry visit evaluations. The first pre-entry evaluations will be done between 30 and 35 days before the entry visit. The second pre-entry evaluations will be done between 7 and 21 days before the entry visit. The third pre-entry evaluations will be done at any time between 7 days before the entry visit and up to the same day as the entry visit.

[3] Entry Visit: If you are eligible to join the study, you will be admitted to the clinic in the morning. You will have blood collected for some study-specific tests either on the day of study entry or up to 7 days before. On the day of entry, the study treatment (RMD or placebo) will be given to you via an infusion. This should take about 4 hours. Then, over the next 24 hours, you will have blood collected about five times. You may be asked to stay overnight at a clinic in the hospital or another facility close by. You will return to the clinic the next morning for one more blood collection.

[4] On Study Visits: You will have study visits at days 7, 14, and 28. If your viral load at day 7 is less than 200 copies/mL by the standard test, day 28 will be your final study visit. If your viral load at day 7 is more than 200 copies/mL, you will be asked to return for an additional visit before day 28; if the repeat HIV-1 RNA PCR level (viral load) after day 7 is more than 200 copies/mL, you will be asked to return for a day 56 (+/- 4 days) visit.

[5] Early Discontinuation: If you stop participating in this study before completing the study drug infusion or after receiving the study drug infusion before the end of the study, you will be asked to come in for a special visit.

II. Explanation of Evaluations

Consent signed and contact information collected
After you read the consent and have had a chance to ask questions about the study, you will sign the consent form if you want to continue to be evaluated for study participation. You will also be asked how to be contacted in case you miss a visit or there are problems with your tests, and whether you give the study team permission to contact you.

HIV infection confirmed
If an HIV test has to be done, you may have to sign a separate consent form. You will be told the results of the HIV test as soon as it is available.

Medical/medication history
You will be asked about the medications you have taken and your medical history.

Physical examination
You will have a physical exam which will include being weighed and you will be asked questions about your health and about any medicines you have taken or are taking now.

Blood collected
Blood will be collected from you for various tests during the study. These include routine safety lab tests to check your red and white blood cell counts and the health of your liver and kidneys, to test for hepatitis B and hepatitis C, measure levels of study drug, measure CD4+/CD8+ cell counts (cells that fight infection), and measure HIV viral load. In addition, some of your blood will

be stored for future tests of the immune system and HIV virus. The total amount of blood collected at any one visit and across multiple visits is within clinical guidelines. *(Sites may insert total volumes by study visit using information from the LPC.) (Sites to use this next sentence only if applicable:* If the hepatitis B or hepatitis C test is positive, the results may be reported to the local or state department of health per local standards.*)*

Urine collected
To check the health of your kidneys

Pregnancy test
If you are a woman who is able to become pregnant, you will be asked to give a small urine or blood sample for a pregnancy test.

Electrocardiogram (ECG)
An ECG is a test to measure heart activity. Small adhesive pads connected to wires from the ECG machine will be painlessly placed on your chest and arms. You will be asked to lie down, remain still, and breathe normally during the test.

Study drug infusion
A small thin tube called an indwelling catheter will be placed into a vein in your arm. The catheter will be connected with a long tube to the bag of study drug solution, and then the study drug solution will be infused over 4 hours.

ART adherence assessment
You will be asked to complete a brief questionnaire about how you are taking your HIV drugs.

APPENDIX II: A5315 STUDY VISITS – COHORT 4

The study staff can answer any questions you have about individual study visits, the evaluations that will occur, or how long each visit will be. The table below can be used as a quick reference for you, along with the explanations that follow.

I. Appendix II, Table 1: Study Schedule, Part 1

Evaluation	Screening Visit[1]	Pre-Entry/Entry Visits[2]		
	36-60 days before entry	28-35 days before entry	3-14 days before entry	Entry, Pre-Infusion
Consent Signed	X			
HIV Confirmed	X			
Physical Exam	X	X	X	X
Blood Collected	X	X	X	X
Urine Collected	X			
Pregnancy Test (females able to become pregnant)	X	X	X	X
Electrocardiogram (ECG)		X		
ART Adherence Assessment	X		X	X

[1]Screening Visit: Between 36 and 60 days before entry and after you have read and signed the consent form, you will have several evaluations done to make sure that you meet the requirements for joining the study. These evaluations may be scheduled in more than one visit.

[2]Pre-Entry/Entry Visits: You will come to the clinic for two pre-entry visits. The first pre-entry evaluations will be done between 28 and 35 days before the entry visit. The second pre-entry evaluations will be done between 3 and 14 days before the entry visit. If you are eligible to join the study, you will be admitted to the clinic in the morning. You will have blood collected for some study-specific tests either on the day of study entry or up to 7 days before.

Appendix II, Table 2: Study Schedule, Part 2

Evaluation	Day of infusion[1]	Days after each infusion[1]			Weeks after the last infusion[2]				Extra Visits[3]	Early Disc[4]
	0	1	3	7	2	5	10	18		
Physical Exam	X	X	X	X	X	X	X	X	X	X
Blood Collected	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X				if required					
Electrocardiogram (ECG)	X	if required			X	if required			if required	
Study Drug Infusion	X									
ART Adherence Assessment	X						X	X		X

[1]Days of the infusion and days after each infusion:
You will have four infusions in this study. For every infusion, there will be a visit on the day of the infusion (day 0, in the table above), and then a visit 1 day, 3 days, and 7 days later. Then there will be 1 week with no visits before the next infusion or, in the case of the fourth infusion, before the next study visit.

[2]Weeks after the last infusion:
There will be visits 2, 5, 10, and 18 weeks after your last infusion.

[3]Extra Visits:
If your viral load (VL) increases or if you are not eligible for the next infusion, you will be asked to return to the clinic for more testing. The study staff can tell you how your schedule will be adjusted if this happens.

[4]Early Discontinuation:
If you want or are asked to stop participating in this study before completing any or all four of the infusions**, you will be asked to come in for 24-hour post-infusion, 72-hour post-infusion, 7 day (1 week) post-infusion, and 4-weeks post-infusion premature treatment/study discontinuation visits. If you want or are asked to stop participating in this study** after receiving all of the infusions but before the end of the study, you will be asked to come in for one more study visit.

II. Explanation of Evaluations

Consent signed
After you read the consent and have had a chance to ask questions about the study, you will sign the consent form if you want to continue to be evaluated for study participation. You will also be asked how to be contacted in case you miss a visit or there are problems with your tests, and whether you give the study team permission to contact you.

HIV infection confirmed
If an HIV test has to be done, you may have to sign a separate consent form before this is done. You will be told the results of the HIV test as soon as it is available.

Physical examination
You will have a physical exam which will include being weighed and asked questions about your health and about any medicines you have taken or are taking now. At the screening and entry visits, you will also be asked about the medications you have taken and your medical history.

Blood collected
Blood will be collected from you for various tests during the study. These include routine safety lab tests to check your blood cell counts and the health of your liver and kidneys, test for hepatitis, measure levels of study drug, measure CD4+/CD8+ cell counts (cells that fight infection), and measure HIV viral load. In addition, some of your blood will be stored for future tests of the immune system, HIV virus, and drug levels.

The total amount of blood collected at any one visit and across multiple visits is within clinical guidelines. *(Sites may insert total volumes by study visit using information from the LPC.) (Sites to use this next sentence only if applicable:* If the hepatitis B or hepatitis C test is positive, the results may be reported to the local or state department of health per local standards.)

Urine collected
You will be asked to provide a small amount of urine during the study visit to check the health of your kidneys.

Pregnancy test
If you are a woman who is able to become pregnant, you will be asked to provide a small amount of urine for a pregnancy test.

Electrocardiogram (ECG)
An ECG is a test to measure heart activity. Small adhesive pads connected to wires from the ECG machine will be placed on your chest and arms. You will be asked to lie down, remain still, and breathe normally during the test. The study staff will tell you about how long each ECG might take.

Study drug infusion
A small thin tube called an indwelling catheter will be placed into a vein in your arm. The catheter will be connected with a long tube to the bag of study drug solution, and then the study drug solution will be infused (or delivered directly into your vein) over 4 hours.

ART adherence assessment
You will be asked to complete a brief questionnaire about how you are taking your anti-HIV drugs.

APPENDIX III: A5315 BENEFITS AND RISKS

A. Benefits

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

B. Risks of Study Drug

Listed below are the most common side effects experienced when taking romidepsin, as well as the more serious side effects. The staff will be able to tell you which are the most serious side effects. They will also be able to tell you what to do if you have any of these side effects.

Romidepsin (Istodax)
The most common side effects associated with the use of RMD are

- Nausea
- Fatigue (tiredness)
- Vomiting
- Anorexia (loss of appetite)
- Infection

Other serious side effects that are associated with higher doses of RMD include:

- Thrombocytopenia (a drop in platelets that help blood to clot)
- Leukopenia (a drop in blood white cells that fight infection)
- Anemia (low red blood cell count)
- Electrocardiographic (ECG) changes in heart rate and rhythm
- Serious infections and fatal infections:
  - These have been reported rarely in clinical trials of RMD in people who were not infected with HIV.
  - These infections can occur at the time of treatment and up to 30 days after treatment.
  - The infections have included the following:
    - Pneumonia
    - Sepsis (a severe illness caused by a bacterial infection of the bloodstream)
    - Reactivation (recurrence) of viruses in people who previously had an Epstein Barr virus infection or a hepatitis B infection.
  - Life-threatening infections have also been reported in people who were treated with RMD for bone marrow disease.

Some of these side effects are potentially serious. The study staff will discuss them with you and will tell you what to do if you have any of them.

C. Risks Associated with Procedures

Intravenous infusion and indwelling catheter
Rarely, sepsis (a severe illness caused by a bacterial infection of the bloodstream), blood clots, and localized infection may occur. Common risks that may occur include discomfort, bleeding, or bruising at the catheter site.

Blood draw
Taking blood may cause some discomfort, lightheadedness, bleeding, swelling, or bruising where the needle enters the body, and in rare cases, fainting or infection. At some visits, the amount of blood collected is very close to the maximum amount under these guidelines. You should not plan to have blood collected for other testing while you are on this study without first discussing the collection with the study staff. If you must have blood collected between study visits, you should tell the study staff.

Electrocardiogram (ECG)
You may have local skin irritation and redness where the adhesive patches are placed on your skin.

APPENDIX IV: SAMPLE INFORMED CONSENT, COHORTS 1 & 2

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)

For Cohorts 1 and 2 in protocol A5315 Final Version 4.0, dated 06/07/18

A Phase I/II Study of Romidepsin in HIV-Infected Adults
with Suppressed Viremia on Antiretroviral Therapy to Assess
Safety, Tolerability, and Activation of HIV-1 Expression

NOTE: Cohorts 1 and 2 are closed. No further enrollment will be possible into either of these cohorts.

Cohort 3 and Cohort 4 have separate sample informed consent forms (APPENDICES V and VI, respectively)

INTRODUCTION

You are being asked to take part in this research study because you are infected with human immunodeficiency virus (HIV), the virus that causes acquired immune deficiency syndrome (AIDS) and:

1) You have been taking a combination of antiretroviral drugs that does not include a protease inhibitor for at least the past 3 months; and
2) Your HIV-1 RNA level (viral load, the amount of HIV in your blood) has been less than 50 copies/mL plasma, or below the limit of detection, for the past 24 months.

This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

WHY IS THIS STUDY BEING DONE?

HIV medications can reduce HIV virus to very low levels in the blood and partially repair the immune system. However, these medications do not cure (remove) the HIV infection and a small amount of the virus continues to live in the body even when the viral load is measured below the limit of detection. This explains why the virus levels rebound or come back when these medications are stopped. The source of this rebounding HIV is likely coming from cells that live for a long time after becoming infected with HIV. These cells are thought to carry the HIV virus in a latent or hidden form (like they are “asleep”). As long as the virus exists in this sleeping state, HIV medications, that block only multiplying (awake) virus, cannot eliminate the HIV, and infected persons cannot be cured.

Romidepsin [RMD] (Istodax) is a drug approved by the Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma, a serious type of skin cancer. In laboratory studies with HIV-infected cells, RMD can awaken HIV from its sleeping state and this is thought to be an

important step in getting rid of the virus that remains in your body. But RMD's ability to do this in people with HIV has not been studied.

This study is being done to see if RMD is safe in HIV-infected persons and whether it can awaken the latent (sleeping) HIV. Once the virus is awakened it should reproduce, and the new HIV that is produced will hopefully kill the cell that is hiding it. If any of the awakened virus escapes the cell, no other cells should become infected because you will be continuing to take your HIV medications. The overall goal of this exploratory study is to identify single doses of RMD that are safe and well-tolerated in HIV-infected persons on antiretroviral therapy (ART), and that can awaken the latent or sleeping HIV allowing it to be targeted by your HIV medications.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Study Visits
If you join this study, you will be seen in the clinic approximately 8 times; most people will complete the study in 1 month; some people may need to come back for a visit 2 months after starting the study. The study staff will tell you about how long each visit could be. You may need to come to the clinic for additional visits if you develop side effects. The study drug, all tests, and strategies are for research purposes; antiretroviral medications are part of routine clinical care and not covered by the study. Details of the study visits and procedures are in Attachment A.

If you do not enroll into the study
If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count, viral load) information is being collected from you so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study.

Study medication
If you qualify to be in this study, you will be randomized (by chance, like the flip of a coin) to receive either the study medication, RMD or the placebo (a salt solution that does not contain RMD).

At study entry, RMD or placebo will be given as a single intravenous (IV) infusion over 4 hours through a small plastic flexible tube placed into a vein in your arm.

Depending on when you enter this study, you will be placed in one of three groups. Each group will have a total of 15 participants: 12 will receive RMD and 3 will receive the placebo salt solution that does not contain RMD. You cannot choose which group you are in.

- The first 15 study participants will be in Group 1. They will receive 0.5 mg/m^2 of RMD or placebo. By chance, 12 participants will receive RMD and 3 will receive placebo. If this amount of RMD solution is found to be safe, then the next 15 participants will enter into Group 2.

- The 15 participants in Group 2 will receive 2 mg/m^2 of RMD or placebo. By chance, 12 participants will receive RMD and 3 will receive placebo. If this amount of RMD solution is found to be safe, then the next 15 participants will enter into Group 3.
- The 15 participants in Group 3 will receive 5 mg/m^2 of RMD or placebo. By chance, 12 participants will receive RMD and 3 will receive placebo.

Neither you nor the study staff will know whether you will receive RMD or the placebo. You will be notified if you received RMD or placebo once the entire study is completed and all of the information from the study has been reviewed.

Blood will be drawn before the infusion, during the infusion, and 4, 6, 12, 24, and 48 hours afterward and on Days 7, 14, and 28 in order to measure the amount of study drug in your blood and**/or** to measure your viral load using a new investigational test called a single copy assay, or SCA, that can measure viral load down to 1 copy/mL. The SCA is not approved by the FDA for routine medical care, and you will not be given the results of this test. You will be given the results of other study tests as soon as they are available, including all standard viral loads, safety blood tests, and pregnancy tests. If required, blood will also be drawn on Day 56 to measure your viral load.

Even the highest dose of RMD used in this study is only 35% of the dose used for cancer treatment. Also, only one infusion will be given in this study instead of three infusions over a 28 day period usually given for cancer treatment. Furthermore, participants will first receive the lowest doses being tested and only when safety is assured will the next higher dose be given. RMD has not been shown to cause mutations or changes in the genetic material in cells like some other cancer drugs.

RMD does not persist for a long time in the body; it has a half-life of about 3 hours (half of the drug remaining in the blood is removed or broken down over this time period).

If the RMD does awaken the inactive HIV, it may become detectable in the blood. Since the effect of one dose of RMD is short-lived and because you will continue to receive your HIV therapies, this viral load increase is expected to last a brief time if it should occur. Nevertheless, your viral load will be monitored repeatedly, and if it does not become undetectable quickly you could possibly require an addition of another anti-HIV medication. The chance of this being necessary is thought to be highly unlikely.

<u>What if I have to permanently stop the study-provided infusion before completion?</u>
During the study:

If you must permanently stop the study-provided infusion before completion, the study doctor may ask you to return for a study visit and some procedures, and the study staff will discuss other options that may be available to you.

After the study:

After you have completed your study participation, the study will not be able to continue to provide you with RMD you received on the study.

Use of Your Samples for this Study
Some of your blood samples will be stored and used for testing that is required for this study. No one will know just from looking at the labels of your stored samples that they came from you.

Use of Your Stored Samples
If you agree, some of your blood samples that are left over after all required study testing is done may be stored for future research that is not yet planned, including future ACTG-approved HIV-related research. No one will know just from looking at the labels of your stored samples that they came from you. Although researchers will not be given your name or any other personally identifying information about you, some information about your medical condition, your race, ethnicity, gender, and age may be shared.

These samples will be kept frozen for an indefinite length of time. We cannot ensure that you will be told of the results of the research done on these samples.
Allowing your samples to be stored for this use is optional. Please indicate below if you agree to this storage for later use. No matter what you decide, it will not affect your participation in the study.

_____ (initials) YES, I agree _____ (initials) NO, I do not agree

If you decide now that your samples can be stored for research to be done at a later date, you may change your mind at any time. If you change your mind, you must contact your study doctor or nurse and let them know that you do not want your samples used for research to be done at a later date. Every effort will then be made to destroy your left-over samples.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 45 men and women 18 years of age and older will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 4 to 8 weeks.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- you are not able to attend the study visits as required by the study
- you become pregnant or are breast-feeding

- the study is stopped or cancelled
- A study monitoring committee (SMC) of the ACTG, or the IRB/EC, FDA, NIAID, the Office for Human Research Protections (OHRP), or another government agency with the duty to ensure that research participants are protected, or Gilead Sciences (the industry supporter), recommends that the study be stopped early. A SMC is an outside group of experts who monitor the study. An IRB is a committee that watches over the safety and rights of research participants.

The study doctor may also need to take you off the study drug without your permission if:

- continuing the study drug infusion may be harmful to you
- you need a treatment that you may not take while on the study
- you are not able to receive the study drug infusion as required by the study

If you must stop participating in this study before completing the study drug infusion or after receiving the study drug before the study is over, the study doctor may ask you to return for a study visit and some procedures.

WHAT ARE THE RISKS OF THE STUDY?

The drug used in this study may have side effects, some of which are listed in Attachment B. These lists include only the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects please ask the medical staff at your site. Safety data from the lower dose level will be carefully reviewed before higher doses are administered. If needed, side effects will be treated with use of anti-nausea medication and electrolyte supplements. An ECG (electrocardiogram) will be performed before and following RMD administration.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drug. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

ARE THERE RISKS RELATED TO PREGNANCY?

The drug in this study may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a woman pregnant while participating in this study. Because of the risk involved, we will ask for written or oral documentation if you report you are not able to become pregnant. If you can possibly get pregnant, you must use two non-estrogen methods of birth control that you discuss with the study staff for 180 days (6 months) after receiving the RMD infusion. You may choose two of the birth control methods listed below although not all contraceptives recommended can prevent HIV transmission.

• Non-estrogen containing formulations of hormonal birth control drugs that prevent pregnancy given by pills, shots, or placed under the skin, for at least 90 days prior to study entry
• Condoms (male or female) with or without a spermicide (cream or gel that kills sperm)
• Diaphragm or cervical cap with spermicide
• Plan B or emergency contraceptive may be used in case of contraceptive failure
• Intrauterine device (IUD)
• Tubal ligation

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. Pregnancy tests will also be performed at most study visits. If you think you may be pregnant at any time during the study or up to 180 days of receiving the study medication, tell your study staff right away. The study staff will talk to you about your choices. You will be followed on study until study completion. You will be asked to return to the clinic 6 months after the end of your or your partner's pregnancy to follow up on any side effects. Pregnancies will be reported to the Antiretroviral Pregnancy Registry.

Based on long-term studies in animals (rats), male and female fertility may be compromised by treatment with RMD.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

This is the first use of RMD in humans to awaken latent HIV in an attempt to decrease the HIV reservoir, and no guarantee of any benefit can be made. It is possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:
- continuing the antiretrovirals you are currently prescribed by your HIV provider or changing to other FDA- approved antiretroviral drugs
- talking with your doctor about other studies for which you may be eligible

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you

personally. A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the web site will include a summary of the results. You can search this website at any time.

People who may review your records include the ACTG, OHRP, FDA, (insert name of site) IRB/EC, National Institutes of Health (NIH), your country's national health agency, or **other local, US, and international regulatory entities** with the duty to ensure that research participants are protected, study staff, study monitors, Gilead Sciences, the drug company supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for the study drug, RMD or placebo, study-related visits, physical examinations, required laboratory tests or other procedures. This study will not provide you with antiretroviral drugs. You, your insurance company, or your health care system may need to assume the cost of drugs not provided by the study. In some cases, it is possible that your insurance company or health care system will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

[Insert site-specific information on compensation to study participants.]

WHAT IF I AM INJURED?

If you are injured as a result of your being in this study, you will be given immediate treatment for injuries and be referred for further treatment, if necessary. However, you may/may not *(per site/country policy)* have to pay for this care. There is no program for compensation either through (*this institution)* or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT HAPPENS IF I BECOME PREGNANT, MY BABY IS INJURED?

If you or your baby is injured as a result of your being in this study, you or your baby will be given immediate treatment for injuries and be referred for further treatment, if necessary. However, you may/may not (per site/country policy) have to pay for this care. There is no program for compensation either through (this institution) or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. The care that you would normally receive will not be affected if you decide not to take part. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.
We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research participant, contact:

- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE ACTG Study A5315, Cohorts 1 or 2 only

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Participant's Legal Representative (print) (As appropriate)	Legal Representative's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date

APPENDIX V: SAMPLE INFORMED CONSENT, COHORT 3

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT

For Cohort 3 in protocol A5315 Final Version 4.0, dated 06/07/18

A Phase I/II Study of Romidepsin in HIV-Infected Adults
with Suppressed Viremia on Antiretroviral Therapy to Assess
Safety, Tolerability, and Activation of HIV-1 Expression

NOTE: A separate consent form, APPENDIX IV, was used for Cohorts 1 and 2. The consent form for Cohort 4 is APPENDIX VI.

INTRODUCTION

You are being asked to take part in this research study because you are infected with human immunodeficiency virus (HIV), the virus that causes acquired immune deficiency syndrome (AIDS) and:

1) You have been taking a combination of antiretroviral drugs that does not include a protease inhibitor for at least the past 3 months; and
2) Your HIV-1 RNA level (viral load, the amount of HIV in your blood) has been less than 50 copies/mL plasma, or below the limit of detection, for the past 24 months.

This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

WHY IS THIS STUDY BEING DONE?

HIV medications can reduce HIV virus to very low levels in the blood and partially repair the immune system. However, these medications do not cure (remove) the HIV infection and a small amount of the virus continues to live in the body even when the viral load is measured below the limit of detection. This explains why the virus levels rebound or come back when these medications are stopped. The source of this rebounding HIV is likely coming from cells that live for a long time after becoming infected with HIV. These cells are thought to carry the HIV virus in a latent or hidden form (like they are “asleep”). As long as the virus exists in this sleeping state, HIV medications, **which** block only multiplying (awake) virus, cannot eliminate the HIV, and infected persons cannot be cured.

Romidepsin [RMD] (Istodax) is a drug approved by the Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma, a serious type of skin cancer. In laboratory studies with HIV-infected cells, RMD can awaken HIV from its sleeping state and this is thought to be an

important step in getting rid of the virus that remains in your body. But RMD's ability to do this in people with HIV has not been studied.

This study is being done to see if RMD is safe in HIV-infected persons and whether it can awaken the latent (sleeping) HIV. Once the virus is awakened it should reproduce, and the new HIV that is produced will hopefully kill the cell that is hiding it. If any of the awakened virus escapes the cell, no other cells should become infected because you will be continuing to take your HIV medications. The overall goal of this exploratory study is to identify single doses of RMD that are safe and well-tolerated in HIV-infected persons on antiretroviral therapy (ART), and that can awaken the latent or sleeping HIV allowing it to be targeted by your HIV medications.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Study Visits
If you join this study, you will be seen in the clinic approximately 8 times; most people will complete the study in 1 month; some people may need to come back for a visit 2 months after starting the study. The study staff will tell you about how long each visit could be. You may need to come to the clinic for additional visits if you develop side effects. The study drug, all tests, and strategies are for research purposes; antiretroviral medications are part of routine clinical care and not covered by the study. Details of the study visits and procedures may be provided in a separate document.

If you do not enroll into the study
If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count, viral load) information is being collected from you so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study.

Study medication
If you qualify to be in this study, you will be randomized (by chance, like the flip of a coin) to receive either the study medication, RMD or the placebo (a salt solution that does not contain RMD).

At study entry, RMD or placebo will be given as a single intravenous (IV) infusion (putting the drug slowly into your blood) over 4 hours through a small plastic flexible tube placed into a vein in your arm.

Depending on when you enter this study, you will be placed in one of three groups. Each group will have a total of 15 participants: 12 will receive RMD and 3 will receive the placebo salt solution that does not contain RMD. You cannot choose which group you are in.

- The first 15 study participants will be in Group 1. They will receive 0.5 mg/m^2 of RMD or placebo. By chance, 12 participants will receive RMD and 3 will receive placebo. If this

amount of RMD solution is found to be safe, then the next 15 participants will enter into Group 2.

- The 15 participants in Group 2 will receive 2 mg/m^2 of RMD or placebo. By chance, 12 participants will receive RMD and 3 will receive placebo. If this amount of RMD solution is found to be safe, then the next 15 participants will enter into Group 3.
- The 15 participants in Group 3 will receive 5 mg/m^2 of RMD or placebo. By chance, 12 participants will receive RMD and 3 will receive placebo.

Neither you nor the study staff will know whether you will receive RMD or the placebo. You will be notified if you received RMD or placebo once the entire study is completed and all of the information from the study has been reviewed.

Blood will be drawn before the infusion, during the infusion, and 4, 6, 12, 24, and 48 hours afterward and on days 7, 14, and 28 in order to measure the amount of study drug in your blood and**/or** to measure your viral load using a new investigational test called a single copy assay, or SCA, that can measure viral load down to 1 copy/mL. The SCA is not approved by the FDA for routine medical care, and you will not be given the results of this test. You will be given the results of other study tests as soon as they are available, including all standard viral loads, safety blood tests, and pregnancy tests. If required, blood will also be drawn on day 56 to measure your viral load.

Even the highest dose of RMD used in this study is only 35% of the dose used for cancer treatment. Also, only one infusion will be given in this study instead of three infusions over a 28 day period usually given for cancer treatment. Furthermore, participants will first receive the lowest doses being tested and only when safety is assured will the next higher dose be given. RMD has not been shown to cause mutations or changes in the genetic material in cells like some other cancer drugs.

RMD does not persist for a long time in the body; it has a half-life of about 3 hours (half of the drug remaining in the blood is removed or broken down over this time period).

If the RMD does awaken the inactive HIV, it may become detectable in the blood. Since the effect of one dose of RMD is short-lived and because you will continue to receive your HIV therapies, this viral load increase is expected to last a brief time if it should occur. Nevertheless, your viral load will be monitored repeatedly, and if it does not become undetectable quickly you could possibly require an addition of another anti-HIV medication. The chance of this being necessary is thought to be highly unlikely.

<u>What if I have to permanently stop the study-provided infusion before completion?</u>
During the study:

If you must permanently stop the study-provided infusion before completion, the study doctor may ask you to return for a study visit and some procedures, and the study staff will discuss other options that may be available to you.

After the study:

After you have completed your study participation, the study will not be able to continue to provide you with RMD you received on the study.

Use of your samples for this study
Some of your blood samples will be stored and used for testing that is required for this study. No one will know just from looking at the labels of your stored samples that they came from you.

Use of your stored samples
If you agree, some of your blood samples that are left over after all required study testing is done may be stored for future research that is not yet planned, including future ACTG-approved HIV-related research. No one will know just from looking at the labels of your stored samples that they came from you. Although researchers will not be given your name or any other personally identifying information about you, some information about your medical condition, your race, ethnicity, gender, and age may be shared.

These samples will be kept frozen for an indefinite length of time. We cannot ensure that you will be told of the results of the research done on these samples.
Allowing your samples to be stored for this use is optional. Please indicate below if you agree to this storage for later use. No matter what you decide, it will not affect your participation in the study.

_____ (initials) YES, I agree _____ (initials) NO, I do not agree

If you decide now that your samples can be stored for research to be done at a later date, you may change your mind at any time. If you change your mind, you must contact your study doctor or nurse and let them know that you do not want your samples used for research to be done at a later date. Every effort will then be made to destroy your left-over samples.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About **60** men and women 18 years of age and older will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 4 to 8 weeks.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- You are not able to attend the study visits as required by the study

- You become pregnant or are breast-feeding.
- The study is stopped or cancelled.
- A study monitoring committee (SMC) of the ACTG, or the IRB/EC, FDA, NIAID, the Office for Human Research Protections (OHRP), or another government agency with the duty to ensure that research participants are protected, or Gilead Sciences (the industry supporter), recommends that the study be stopped early. A SMC is an outside group of experts who monitor the study. An IRB is a committee that watches over the safety and rights of research participants.

The study doctor may also need to take you off the study drug without your permission if:

- Continuing the study drug infusion may be harmful to you.
- You need a treatment that you may not take while on the study.
- You are not able to receive the study drug infusion as required by the study.

If you must stop participating in this study before completing the study drug infusion or after receiving the study drug before the study is over, the study doctor may ask you to return for a study visit and some procedures.

WHAT ARE THE RISKS OF THE STUDY?

The drug used in this study may have side effects, some of which are listed in a separate document. These lists include only the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects please ask the medical staff at your site. Safety data from the lower dose level will be carefully reviewed before higher doses are administered. If needed, side effects will be treated with use of anti-nausea medication and electrolyte supplements. An ECG (electrocardiogram) will be performed before and following RMD administration.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drug. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

ARE THERE RISKS RELATED TO PREGNANCY?

The drug in this study may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a woman pregnant while participating in this study. Because of the risk involved, we will ask for written or oral documentation if you report you are not able to become pregnant. If you can possibly get pregnant, you must use two non-estrogen methods of birth control that you discuss with the study staff for 180 days (6 months) after receiving the RMD infusion. You may choose two of the birth control methods listed below although not all contraceptives recommended can prevent

HIV transmission.

- Non-estrogen containing formulations of hormonal birth control drugs that prevent pregnancy given by pills, shots, or placed under the skin, for at least 90 days prior to study entry
- Condoms (male or female) with or without a spermicide (cream or gel that kills sperm)
- Diaphragm or cervical cap with spermicide
- Plan B or emergency contraceptive may be used in case of contraceptive failure
- Intrauterine device (IUD)
- Tubal ligation

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. Pregnancy tests will also be performed at most study visits. If you think you may be pregnant at any time during the study or up to 180 days of receiving the study medication, tell your study staff right away. The study staff will talk to you about your choices. You will be followed on study until study completion. Pregnancies will be reported to The Antiretroviral Pregnancy Registry.

Based on long-term studies in animals (rats), male and female fertility may be compromised by treatment with RMD.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

This is the first use of RMD in humans to awaken latent HIV; there should be no expectation of any benefit. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- Not being in a study.
- Talking with your doctor about other studies for which you may be eligible.

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally. A description of this clinical trial will be available on ClinicalTrials.gov, as required by

U.S. law. This website will not include information that can identify you. At most, the web site will include a summary of the results. You can search this website at any time.

People who may review your records include the ACTG, OHRP, FDA, *(insert name of site)* institutional review board (IRB)/ethics committee (EC), National Institutes of Health (NIH), or **other local, US, and international regulatory entities** with the duty to ensure that research participants are protected, study staff, study monitors, the pharmaceutical companies supporting this study, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about you and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will be required to tell the proper authorities.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for the study drug, RMD or placebo, study-related visits, physical examinations, required laboratory tests or other procedures. This study will not provide you with anti-HIV medications. You, your insurance company, or your health care system may need to assume the cost of drugs not provided by the study. In some cases, it is possible that your insurance company or health care system will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

(Insert site-specific information on compensation to study participants.)

WHAT IF I AM INJURED?

If you are injured as a result of your being in this study, you will be given immediate treatment for injuries and be referred for further treatment, if necessary. However, you may/may not *(per site/country policy)* have to pay for this care. There is no program for compensation either through (*this institution)* or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT HAPPENS IF I BECOME PREGNANT, MY BABY IS INJURED?

If you or your baby is injured as a result of your being in this study, you or your baby will be given immediate treatment for injuries and be referred for further treatment, if necessary. However, you may/may not (per site/country policy) have to pay for this care. There is no program for compensation either through (this institution) or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. The care that you would normally receive will not be affected if you decide not to take part. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, tell the study staff.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- Name of the investigator or other study staff
- Telephone number of above

For questions about your rights as a research participant, contact:

- Name or title of person on the IRB/EC or other organization appropriate for the site
- Telephone number of above

SIGNATURE PAGE for Cohort 3, ACTG Study A5315

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Participant's Legal Representative (print) (As appropriate)	Legal Representative's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date

APPENDIX VI: SAMPLE INFORMED CONSENT, COHORT 4

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
SAMPLE INFORMED CONSENT

For Cohort 4 of protocol A5315 Final Version 4.0, dated 06/07/18

A Phase I/II Study of Romidepsin in HIV-Infected Adults with Suppressed Viremia on Antiretroviral Therapy to Assess Safety, Tolerability, and Activation of HIV-1 Expression

Short title: Romidepsin to Awaken HIV

INTRODUCTION

This study involves research. Research is not the same as medical care. Research answers scientific questions. These answers can help find new medicines, treatments, vaccines, and even knowledge on how the human body works. Only people who want to participate will be part of this study. You can discuss the study with others before deciding to join. No matter what your decision is, any other care that you get at this clinic will not change.

You are being asked to take part in this research study because:

1) you are infected with human immunodeficiency virus (HIV), the virus that causes acquired immune deficiency syndrome (AIDS),
2) you have been taking a combination of anti-HIV drugs that does not include a protease inhibitor for at least the past 3 months, and
3) your HIV-1 RNA level (viral load, the amount of HIV in your blood) has been less than 50 copies/mL, or below the limit of detection, for the past 24 months.

This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: *(insert name of site Principal Investigator)*. Before you decide if you want to be a part of this study, we want you to know about the study. This is a consent form; it provides you with information about the study. This consent form is for the second part of this two-part study.

WHY IS THIS STUDY BEING DONE?

Anti-HIV drugs can reduce HIV virus to very low levels in the blood of an HIV-infected person. But these drugs do not cure (or completely remove) the HIV infection. A small amount of HIV can still be in a person's body even though it cannot be measured in their blood. Some cells that are infected with HIV can live for a long time, and they are able to keep the virus latent (as if it were asleep). As long as the virus is in this sleeping state, anti-HIV drugs, which attack only active (awake) virus, cannot completely remove HIV.

In laboratory studies with HIV-infected cells, romidepsin [RMD] (Istodax) can "awaken" latent HIV. This is thought to be an important step in completely removing HIV from an infected person's body. RMD is a drug approved by the Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma, a serious type of skin cancer. RMD's ability to awaken HIV has only been studied in a very small number of people, and the results of these studies are not available.

This study is being done to see if there is a safe and well-tolerated dose of RMD that can awaken latent HIV in HIV-infected persons who are taking anti-HIV drugs.

Once the virus is awakened, it should reproduce, and the new HIV that is produced should kill the cell that is hiding it. If any of the awakened virus escapes the cell, the anti-HIV drugs that a person is taking should kill it.

WHY IS THIS PART OF THIS STUDY BEING DONE?

In the first part of this study, we tested three doses of RMD in each of three groups of 12-15 people. These people received a one-time infusion of one of three doses of RMD or a placebo (a solution that does not contain any medicine). An infusion is a way of slowly delivering liquid (in this case, RMD or placebo) into a person's bloodstream through a thin tube that is placed into a vein in the arm. In this study, the infusion takes about 4 hours.

The doses that have been tested so far appear safe. This second part is being added to this study to see if multiple doses of RMD are safe and to test whether multiple doses are able to awaken latent HIV better than a single dose. If this is the case, then the study might be able to see if awakening these cells can lower the number of them in your body.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Study Visits

If you join this study, you will be seen in the clinic at least 3 times before the study starts; these visits will be for screening and pre-entry tests to see if it is safe and appropriate for you to be in this study. Once you enter the study, you will be seen in the clinic approximately 16-20 times over 24 weeks (or about 6 months.)

The study staff will tell you about how long each study visit could be. You may need to come to the clinic for additional visits if you develop side effects. Details of the study visits and procedures are in a separate document *(Appendix II)*. If you have to come for extra visits, then you could be in the study for up to 48 weeks (or almost 1 year)

If you do not enroll into the study

If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, some demographic (for example, age, sex, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count, viral load) information is being collected from you so that ACTG

researchers can help determine whether there are patterns or common reasons why people do not join a study.

Study treatment
If you meet all the requirements to be in this study, you will be randomized (assigned by chance, as if by the flip of a coin) to receive either the study medication, RMD, or the placebo.

Fifteen people will enter this part of the study: 12 will receive RMD and 3 will receive the placebo. You cannot choose which product you receive and neither you nor the clinic staff will know which product you are receiving. You will be told whether you received RMD or placebo once the entire study is completed and all of the information from the study has been reviewed.

At study entry, and again every 2 weeks for a total of four times, RMD or placebo will be given as an infusion over about 4 hours through a small plastic flexible tube placed into a vein in your arm. An ECG (electrocardiogram) will be performed immediately following each infusion.

You must continue to take your anti-HIV drugs throughout the study.

Study tests
Blood will be collected from you before each infusion, and then 1 day and 3 days and then 1 week after each infusion. This blood will be used for safety tests, viral load, drug levels, and study-specific testing. You will be given the results of some tests, including all standard viral loads, safety blood tests, and pregnancy tests, as soon as they are available. Blood will also be collected from you 2, 5, 10, and 18 weeks after the last infusion.

If the RMD does awaken latent HIV, then HIV may become detectable in your blood (your viral load will become measurable). Because you will continue taking your anti-HIV drugs while on this study, this increase in your viral load is only expected to last a brief time. Your viral load will be monitored frequently; if it does not become undetectable within a few weeks you might need another anti-HIV drug. The chance of this being necessary is thought to be very small.

What if I have to permanently stop the infusion before completion?
During the study:

If you **are unable to complete** all four **infusions**, **you will be asked to complete the follow-up visits for any infusion that was interrupted and to return for premature treatment/discontinuation evaluations 4 weeks after the infusion**.

After the study:

After you have completed your study participation, the study will not provide you with RMD or placebo.

Use of your blood for this study
Some of your blood will be stored and used for testing that is required for this study. No one will know just from looking at the labels of your stored blood that it came from you.

Use of your stored blood

If you agree, some of your blood that is left over after all required study testing is done may be stored for future research that is not yet planned, including future ACTG-approved HIV-related research. No one will know just from looking at the labels of your stored blood that it came from you. Although researchers will not be given your name or any other personally identifying information about you, some information about your medical condition, your race, ethnicity, sex, and age may be shared.

Stored blood will be kept frozen for an indefinite length of time. We cannot ensure that you will be told of the results of the research that is done on this blood.

Allowing your blood to be stored for this use is optional. Please indicate below if you agree to this storage for later use. No matter what you decide, it will not affect your participation in the study.

_____ (initials) YES, I agree _____ (initials) NO, I do not agree

If you decide now that your blood can be stored for research to be done at a later date, you may change your mind at any time. If you change your mind, you must contact your study doctor or nurse and let them know that you do not want your blood used for research to be done at a later date. Every effort will then be made to destroy your left-over blood.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 60 men and women 18 years of age and older will take part in this study: about 45 in the first part and 15 in the part of the study that you are now reading about.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 24 weeks (almost 6 months). If one of your infusions has to be delayed for any reason, you could be on the study for an extra 6 weeks. If more than one of your infusions has to be delayed for any reason, then you could be on the study for an extra 6 weeks each time. The maximum length of time that you could be on the study would be 48 weeks (about 11 months).

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- You are not able to attend the study visits as required by the study.
- The staff is not able to start one of your infusions because there is trouble finding a vein in one of your arms.

- You are not able to complete one of the infusions.
- You are not able to have blood collected 24 hours after one of the infusions.
- You are not able to complete the study visit that is about 5 weeks after the 4th infusion.
- You become pregnant or are breast-feeding.
- The study is stopped or cancelled.
- A study monitoring committee (SMC) of the ACTG, or your site's institutional review board (IRB)/ethics committee (EC), FDA, NIAID, the Office for Human Research Protections (OHRP), or another government agency with the duty to ensure that research participants are protected, or an industry supporter recommends that the study be stopped early. A SMC is an outside group of experts who monitor the study. An IRB or EC is a committee that watches over the safety and rights of research participants.

The study doctor may also need to take you off the study treatment without your permission if:

- Continuing the treatment may be harmful to you.
- You need a treatment that you may not take while on the study.
- You are not able to receive the infusion as required by the study.

If you must stop participating in this study before completing the infusion or before the study is over, the study doctor may ask you to return for a study visit and some procedures.

WHAT ARE THE RISKS OF THE STUDY?

The drug used in this study may have side effects, some of which are listed below *(and in a separate document - Appendix III)*. These lists include only the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects please ask the medical staff at your site.

Safety data from the lower dose levels and from a single infusion of the dose level to be used in this part of the study have been carefully reviewed. If needed, side effects will be treated with use of anti-nausea medication and electrolyte supplements.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drug. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

IS THERE OTHER INFORMATION I SHOULD KNOW ABOUT?

In earlier groups or cohorts of this study, three different single dose levels of RMD were studied to see if they were safe and well-tolerated in HIV-infected persons receiving HIV treatment. Based on information from these cohorts, a safe and well-tolerated dose was chosen to be used in this cohort.

It may be that a single dose of RMD cannot activate or 'wake up' all the HIV in the HIV reservoir. In this part of the study, we will test how much HIV is activated after each infusion and after all infusions have been completed. This study will provide important information regarding the role that drugs like RMD may have in awakening HIV.

The dose of RMD being used in this part of the study is about one-third of the dose used for cancer treatment. The dosing schedule in this study (one infusion every 2 weeks over a 6-week period) is different from what is followed for cancer treatment: one infusion a week for 3 weeks, followed by a 1-week pause and then a repeat of one infusion per week for 3 weeks.

RMD will not stay in your blood system for a long time; it has a half-life of about 3 hours (this means that half of the drug that entered your blood will have been broken down or otherwise removed within 3 hours; every 3 hours, another half of what is remaining is removed until none is left).

ARE THERE RISKS RELATED TO PREGNANCY?

RMD may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make a woman pregnant while participating in this study.

Because of the risk involved, we will ask for written or oral documentation if you report you are not able to become pregnant.

If you can possibly get pregnant, you must use two non-estrogen methods of birth control that you discuss with the study staff for 180 days (6 months) after your last RMD infusion. You may choose two of the birth control methods listed below.

- Non-estrogen containing formulations of hormonal birth control drugs that prevent pregnancy given by pills, shots, or placed under the skin, for at least 90 days prior to study entry
- Condoms (male or female) with or without a spermicide (cream or gel that kills sperm)
- Diaphragm or cervical cap with spermicide
- Plan B or emergency contraceptive may be used in case of contraceptive failure
- Intrauterine device (IUD)
- Tubal ligation

Note that some but not all of these contraceptive methods can also prevent HIV transmission.

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. Pregnancy tests will also be performed at most study visits. If you think you may be pregnant at any time during the study or up to 180 days (about 6 months) after the last time that you received the study medication, tell your study staff right away. The study staff will talk to you about your choices. You will be followed on study until study completion. Pregnancies will be reported to The Antiretroviral Pregnancy Registry.

Based on long-term studies in animals (rats), male and female fertility may be compromised by treatment with RMD.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

There is no expectation of any benefit to you. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- Not entering a study
- Talking with your doctor about other studies for which you may be eligible

Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally. A description of this clinical trial will be available on ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the web site will include a summary of the results. You can search this website at any time.

People who may review your records include employees of the ACTG, OHRP, FDA, *(insert name of site)* IRB/EC, National Institutes of Health (NIH), or **other local, US, and international regulatory entities** with the duty with the duty to ensure that research participants are protected, as well as study staff, study monitors, employees of the pharmaceutical and laboratory testing companies supporting this study, or their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for the study drug, RMD or placebo, study-related visits, physical examinations, required laboratory tests or other procedures. This study will not provide you with

anti-HIV drugs. You, your insurance company, or your health care system may need to assume the cost of drugs not provided by the study. In some cases, it is possible that your insurance company or health care system will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

(Insert site-specific information on compensation to study participants.)

WHAT IF I AM INJURED?

If you are injured as a result of your being in this study, you will be given immediate treatment for injuries and be referred for further treatment, if necessary. However, you may/may not *(per site policy)* have to pay for this care. There is no program for compensation either through (*this institution)* or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT HAPPENS IF I BECOME PREGNANT AND MY BABY IS INJURED?

If you or your baby is injured as a result of your being in this study, you or your baby will be given immediate treatment for injuries and be referred for further treatment, if necessary. However, you *may/may* not *(per site policy)* have to pay for this care. There is no program for compensation either through *(this institution)* or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. The care that you would normally receive will not be affected if you decide not to take part. Your decision will not have any impact on your participation in other studies conducted by the NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, tell the study staff.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- *Name of the investigator or other study staff*
- *Telephone number of above*

For questions about your rights as a research participant, contact:

- *Name or title of person on the IRB/EC or other organization appropriate for the site*
- *Telephone number of above*

SIGNATURE PAGE ACTG Study A5315, Cohort 4

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Participant's Legal Representative (As appropriate) (print)	Legal Representative's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness' Signature and Date