# A Phase I-II Pilot Study to Assess the Safety and Efficacy of Combined Administration with Pegylated Interferon-α2a and the Histone Deacetylase Inhibitor (HDACi) Panobinostat for Reducing the Residual Reservoir of HIV-1 Infected Cells in cART-Treated HIV-1 Positive Individuals

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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.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

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## 1.0 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| ATI | analytical treatment interruption |
| AUC | area under the curve |
| bpm | beats per minute |
| β-HCG | β-human chorionic gonadotropin |
| cART | combination antiretroviral therapy |
| CDC | Centers for Disease Control and Prevention |
| CFR | Code of Federal Regulations |
| CMV | cytomegalovirus |
| CP | clinical pharmacology |
| CRF | Case report form |
| CTU | Clinical trial unit |
| CyTOF | cytometry-by-time-of-flight assays |
| DAIDS | Division of AIDS |
| DNA | Deoxyribonucleic acid |
| EAE | Expedited Adverse Event |
| ECG | Electrocardiogram |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| eGFR | estimated glomerular filtration rate |
| GT | genotype |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HGB | Hemoglobin |
| HIV-1 | Human Immunodeficiency Virus-1 |
| HDAC | Histone deacetylase |
| HDACi | Histone deacetylase inhibitor |
| HLA | human leukocyte antigen |
| HR | heart rate |
| IC50 | Inhibitory Concentration at which 50% of viruses are inhibited |
| ICH | International Council on Harmonization |

| | |
|---|---|
| IFA | immunofluorescent antibody |
| IFN | Interferon |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| ISRC | Internal Safety Review Committee |
| ISG | Interferon-stimulated gene |
| IUPM | infectious viral units per million |
| i.v. | intravenous |
| KIR | killer cell immunoglobulin-like receptor |
| LLN | lower limit of normal |
| LTR | long terminal repeat |
| MMRM | mixed models with repeated measures |
| NK | Natural killer |
| NRTI | Nucleoside Reverse Transcriptase Inhibitor |
| NNRTI | Non-Nucleoside Reverse Transcriptase Inhibitor |
| PBMC | peripheral blood mononuclear cells |
| PBT | panobinostat |
| PCR | Polymerase Chain Reaction |
| PEG | pegylated |
| pDC | plasmacytoid dendritic cells |
| PK | pharmacokinetics |
| PI | Protease Inhibitor |
| p.o. | per os (by mouth) |
| PLT | platelets |
| PPD | purified protein derivative |
| PTT | partial Thromboplastin time |
| QOW | every second week |
| QOD | every second day |
| RNA | Ribonucleic acid |
| SAE | severe adverse event |
| s.c. | subcutaneous |
| SCA | single copy assay |
| SMC | Safety monitoring committee |
| SNP | single nucleotide polymorphisms |
| TCP | Thrombocytopenia |

| | |
|---|---|
| TSH | Thyroid stimulating hormone |
| TIW | Three time per week |
| TILDA | Tat/rev Induced Limiting Dilution Assay |
| ULN | upper limit of normal |

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## 3.0 SCHEMA

**A Phase I-II pilot study to assess the safety and efficacy of combined administration with pegylated IFN-α2a and the histone deacetylase inhibitor (HDACi) panobinostat for reducing the reservoir of HIV-1 infected cells in cART-treated HIV-1 positive individuals.**

DESIGN: This study is a prospective, open-label, randomized, two-arm, dose-escalation exploratory pilot clinical trial involving HIV-1 infected participants treated with suppressive combination antiretroviral therapy (cART).

DURATION: One month of pre-treatment observation, one week of treatment, three weeks of post-treatment observation. The total duration per patient will be 2 months.

SAMPLE SIZE: n=8 participants for stage 1 and stage 2; n=18 in stage 3 (total of 34 individuals)

POPULATION: Participants (18-65 years of age) with HIV-1 infection who have received antiretroviral therapy (ART) with HIV RNA levels <50 copies/mL for at least two years and a CD4 T cell count >400 cells/$mm^3$. Patients who started antiretroviral treatment in early HIV-1 infection (within <12 months of HIV-1 transmission), and patients who started antiretroviral treatment in chronic infection (⩾12 months after HIV-1 transmission) are eligible for this study.

REGIMEN: All study patients will receive the histone deacetylase (HDAC) inhibitor panobinostat administered as an oral tablet three times every other day (TIW) during the treatment week.

In stage 1, each panobinostat dose will be 5 mg; in stage 2, each panobinostat dose will be 10 mg; in stage 3, each panobinostat dose will be 15 mg.

In each stage, participants will be randomized to one of the following regimens:

**Arm A**: Treatment with panobinostat alone at stage-specific dose (n=2 participants in stages 1 and 2; n=4 participants in stage 3).

**Arm B**: Combined treatment with panobinostat (at the stage-specific dose) and pegylated IFN-α2a (Pegasys, 180 micrograms, administered by s.c. injection simultaneously with the first dose of panobinostat during the treatment week (n=6 participants in stages 1 and 2; n=10 participants in stage 3).

**Arm C**: Treatment with pegylated IFN-α2a only (Pegasys, 180 micrograms, administered by s. c. injection; n=0 in stage 1/2, n=4 in stage 3)

Progression to stages 2 and 3 will depend on satisfactory safety reviews of data from the preceding stage.

ART will be continued throughout the entire treatment course in the entire study population.

OBJECTIVES: The primary objectives of this study are (i) to evaluate the safety and tolerability of combined treatment with panobinostat and pegylated IFN-α2a in individuals with well-controlled HIV-1 infection on suppressive cART, and (ii) to evaluate effects of combined treatment with panobinostat and pegylated IFN-α2a on the reservoir of HIV-1 infected cells in comparison to effects of treatment with panobinostat only or with Interferon-α2a only.

ENDPOINTS: The two co-primary study endpoints will be (i) the cumulative frequency and intensity of any (grade ≥ 1) adverse event and serious adverse event during the one week treatment

period (primary safety endpoint) and (ii) change from baseline in the number of latently infected CD4 T cells, as assessed by CD4 T cell-associated proviral HIV-1 DNA levels, after completion of study treatment (primary efficacy endpoint) in arm B vs. arm A or C.

## 4.0 STUDY OBJECTIVES

4.1 Primary Objectives

4.1.1 To evaluate the safety and tolerability of combined treatment with panobinostat and PEG-IFN-α2a in individuals with well-controlled HIV-1 infection on suppressive cART.

4.1.2 To evaluate effects of combined treatment with panobinostat and PEG-IFN-α2a on the reservoir of HIV-1 infected cells in comparison to effects of treatment with panobinostat alone. For this primary efficacy objective, the reservoir measurements will be CD4 T cell-associated proviral HIV-1 DNA levels.

4.2 Secondary Objectives

4.2.1 To evaluate levels of CD4 T cells harboring replication-competent HIV-1 during treatment with the study medication in the different treatment arms.

4.2.2 To evaluate acetylation of histone proteins in CD4 T cells during treatment with the study medication in the different treatment arms.

4.2.3 To evaluate levels of CD4 T cell-associated HIV-1 RNA during treatment with the study medication in the different treatment arms.

4.2.4 To analyze levels of plasma HIV-1 RNA by standard and single-copy assay (SCA) during treatment with the study medication in the different treatment arms.

4.2.5 To evaluate effects of the study medication on chromosomally integrated proviral HIV-1 DNA and 2-LTR HIV-1 DNA in CD4 T cells in the different treatment arms.

4.2.6 To assess effects of the study medication on levels of proviral HIV-1 DNA in CD4 T cell subsets (naïve, T memory stem cells, central-memory, effector-memory, terminally-differentiated) in the different treatment arms.

4.2.7 To identify expression patterns of interferon-stimulated genes (ISG) that are associated with changes in viral reservoir size during treatment with the study medication in the different treatment arms.

4.2.8 To identify innate and adaptive immune responses that are associated with a change in the reservoir of HIV-1 infected cells during treatment with the study medication in the different treatment arms.

4.2.9 To analyze changes in cellular and soluble immune activation markers in response to the study treatment in the different treatment arms.

## 5.0 INTRODUCTION

5.1 HIV-1 Eradication and Cure

Current combination antiretroviral therapy (cART) is extremely effective at suppressing HIV-1 viremia, and substantially reduces HIV-1 associated morbidity and mortality[1]. The major weakness of current ART is its inability to fully eliminate HIV-1. This failure is mainly due to the fact that HIV-1 persists in specific cells in a transcriptionally silent, latent form that is not susceptible to antiretroviral effects of HIV-1 drugs[2,3]. Once treatment is stopped, latently infected cells can become activated and produce new viral virions that fuel rebound viremia, which typically leads to pre-treatment levels of HIV-1 replication within a short time[4-6]. Therefore, ART currently has to be given life-long, which is associated with drug-related adverse reactions, high costs, and the possibility for selecting drug-resistant viruses[7,8]. Moreover, it is now well recognized that despite treatment with ART, abnormal immune activation is detectable in the majority of individuals[9,10], which may be related to HIV-1 persistence and seems to be responsible for increased cardiovascular co-morbidities, accelerated aging and cognitive deficits that can be encountered in

individuals undergoing long-term antiretroviral therapy[11,12]. As such, the development of clinical strategies that can reduce or eradicate the reservoir of latently-infected CD4 T cells and induce a long-term drug-free remission of HIV-1 infection is a high priority for HIV-1 clinicians and scientists and would be of great benefit to infected patients[13].

Hope for successful reduction or elimination of the reservoir of HIV-1 infected cells in ART-treated patients was primarily galvanized by the recent identification of selected patients who appear to have achieved long-term ART-free remission of HIV-1 infection. Such patients include the "Berlin" patient, an HIV-1 infected patient with AML who received an allogeneic hematopoietic stem cell transplant from a CCR5 32-homozygous donor[14], a group of patients who maintained a drug-free remission of HIV-1 infection after initiation of treatment in early HIV-1 infection[15], and a baby with intrauterine HIV-1 infection who was started on ART within 30 hours after birth and maintained undetectable HIV-1 RNA for two years despite interrupting ART[16].

## 5.2 Targeting Latently HIV-1 Infected CD4 T Cells with HDACi

HIV preferentially infects activated CD4 T cells, which do not survive for more than a few days thereafter. On rare occasions, however, the virus infects a CD4 T cell as it transitions to a resting memory T-cell state. The result is stably integrated proviral HIV-DNA in a cell with a very long life span capable of resuming viral replication upon subsequent activation[17-19]. The molecular mechanisms by which HIV establishes latency are manifold and complex and include enzymatic processes that affect the chromatin organization of the HIV-promoter region, one of the key determinants of transcriptional activity[20]. Histone deacetylation by histone deacetylases (HDACs) leads to conformational changes that constrict the chromatin and block transcription. There are 18 known HDACs which are grouped into 4 classes. Of these, the class I HDACs 1, 2, and 3 may be particularly important to maintaining HIV latency[21-23]. Pharmacological HDAC inhibitors (HDACi) have shown the ability to reactivate and induce expression of HIV-1 from latently infected cells[24]. The use of HDACi for pharmacological reactivation of HIV-1 was first tested in a clinical study using the weak HDAC inhibitor valproic acid.[25] Reduction of the latent viral reservoir was seen in 3 of 4 participants, but further studies gave mixed results and the effect could not be confirmed. Newer and more potent HDAC inhibitors include suberoylanilide hydroxamic acid [SAHA] (vorinostat, Merck), PXD101 (belinostat, TopoTarget), ITF2357 (givinostat, Italfarmaco), romidepsin (Celgene) and LBH589 (panobinostat, Novartis). These compounds can induce expression of HIV-1 in chronically infected cell lines and ex vivo in resting CD4 T cells from aviremic ART treated HIV-1 patients[26].

## 5.3 Panobinostat

LBH589 (panobinostat, Novartis) is a novel HDAC inhibitor that exhibits potent HDAC inhibition including powerful activity against HDAC3, the enzyme that appears to be particularly important to disrupting HIV latency. Panobinostat is formulated as an oral capsule and a solution for intravenous (i.v.) injection. Both the oral and i.v. formulations are currently being investigated in on-going phase I-III studies for various oncologic indications. Panobinostat was approved by the US FDA on February 23rd, 2015 for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.

### 5.3.1 Clinical Experience

In clinical studies, both oral and intravenous (i.v.) formulations of panobinostat have been explored for a variety of indications. As of December 31st, 2013, 36 clinical studies, including clinical pharmacology (CP), Phase I and Phase II trials, as well as two randomized Phase III studies have either been completed or are ongoing. A total of 2428 participants were enrolled, 235 for i.v. and 2193 for oral, who received at least one dose of panobinostat either as a single agent or in combination with other agents.

### 5.3.2 Pharmacokinetics (PK)

Panobinostat is rapidly absorbed with a median Cmax reached within 1 h after oral administration. The absolute oral bioavailability of panobinostat is approximately 30%. The compound can be administered

regardless of food intake as the variability and overall systemic exposure remained unchanged in participants taking panobinostat with or without food. AUC increased linearly and proportionally with doses up to 50 mg. The inter-individual variability (CV%) in systemic exposure is 60%. The plasma protein binding of panobinostat (mainly to albumin) is moderate (89.6% at 37°C) and independent of concentration. Elimination half-lives averaged 15 hours. Steady state is achieved by the third dose following days 1, 3, and 5 (TIW) weekly (QW) dosing. The metabolism of panobinostat involves several metabolic pathways including reduction, hydrolysis, oxidation, and glucuronidation processes. It is a substrate of cytochrome P450 3A4 (CYP3A4) with minor involvement of CYP2D6 and 2C19 as well as a weak inhibitor of CYP2D6 in vivo. Panobinostat and its metabolites (~at least 40 metabolites in circulating plasma) were nearly equally excreted in urine and bile/feces of participants. Dose adjustments are not necessary in patients with severe renal impairment.

### 5.3.3 Safety Profile

As of December 31st, 2013, a total of 2428 participants (235 for i.v. & 2193 for oral) were enrolled into the panobinostat clinical development program. A total of 762 (31.3%) participants treated with single agent oral panobinostat with available safety data were included in the pooled safety population described in the Investigator's Brochure. Across all these single agent studies conducted to date, the most common adverse events of all grades are thrombocytopenia (TCP), neutropenia, fatigue, nausea/vomiting and diarrhea. Most common grade 3/4 events reported are TCP, neutropenia and fatigue. TCP appears to be dose-dependent and was identified as the leading cause of dose-reduction/interruption or discontinuation with single agent dosing. Preliminary evidence suggests that switching from the QW to the QOW schedule may be more effective than other dose modifications for reducing the recurrence of TCP. The median time to the first event of grade 3-4 TCP at the dose 40 mg TIW QOW is >15 days. A trend to increased TSH levels from baseline and a slight compensatory decrease in T4 not associated with clinical signs or symptoms have been noted in on-going clinical studies of oral panobinostat. The clinical significance of these observations is unclear. A theoretical risk of HDAC inhibitors is that they will induce activation of other retroviruses, oncogenes and/or DNA viruses, including CMV, hepatitis B virus and JC viruses. To date there is no evidence that the clinical use of HDAC inhibitors is associated with reactivation of DNA viruses[27,28], but the long-term impact is not fully known.

### 5.3.4 Mutagenicity

Panobinostat demonstrated dose-dependent mutagenic potential in bacterial cells and in mouse lymphoma cells, but did not reveal clastogenic potential in a chromosome aberration test in human peripheral blood lymphocytes. However, the assays demonstrated an increased frequency of endoreduplicated cells after panobinostat exposure of human lymphocytes. Endoreduplication is a form of nuclear polyploidization that results in multiple, uniform copies of chromosomes. This physiologic process is common in plants and animals, especially in tissues with high metabolic activity, and it generally occurs in cells that are terminally differentiated. Increased induction of endoreduplicated cells is likely related to the pharmacologic mechanism of panobinostat and contributes to its effects against malignant cells. Evaluation of panobinostat in general toxicity studies in mice and dogs did not reveal any evidence for increased frequencies of malignant diseases during panobinostat treatment. Moreover, there was no evidence for increased risks for malignant diseases in human clinical trials conducted with panobinostat since the initiation of the panobinostat clinical development program in 2004. According to current classification criteria for mutagenicity, panobinostat is classified as a category 4 substance. Therefore, use of contraceptive methods for both female and male study participants is required during the entire study period; this is specified in the inclusion criteria.

### 5.3.5 QTc prolongation and cardiovascular toxicity

As with other HDAC inhibitors, panobinostat, has the potential to prolong the QTc interval[29,30]. In the initial Phase I study utilizing the i.v. formulation of panobinostat administered on consecutive days, significant QTc interval abnormalities were noted, with one patient experiencing Torsades de pointes. Extensive ECG

monitoring has been conducted in all clinical studies of panobinostat. With the intermittent oral dosing (TIW QW and TIW QOW) used in clinical trials, QTc intervals >500 msec are uncommon and only noted with the TIW QW schedule. No cases of Torsades de pointes have been reported in clinical trials with intermittent i.v. or oral dosing regimens[29,31]. Other ECG abnormalities reported from previous clinical studies of panobinostat are asymptomatic T-wave abnormalities and asymptomatic sinus tachycardia. These have been noted frequently, but were generally not associated with clinical symptoms and their clinical significance is unclear. Ischemic heart disease, regardless of causality, was observed in 12 out of 666 study patients (1.8%) who received oral panobinostat as a single agent in the panobinostat development program. 3 of these patients had severe (Grade 3/4) events. In the panobinostat licensing study (a randomized phase III study in which panobinostat was tested in combination with dexamethasone and bortezomib vs. dexamethasone and bortezomib alone in 758 individuals with refractory multiple myeloma), cardiac ischemic events occurred in 4% of the subjects assigned to the panobinostat arm vs 1% of patients assigned to the control arm.

### 5.3.6 Interactions with other drugs

Based on in vitro data, panobinostat is a CYP3A4 and CYP2D6 substrate and a CYP2D6 inhibitor (IC50 0.17 μM). Thus, two clinical DDI studies were conducted using ketoconazole as a potent CYP3A inhibitor [CLBH589B2110] and panobinostat as CYP2D6 inhibitor with dextromethorphan as CYP2D6 substrate [CLBH589B2109]. Study [CLBH589B2110] was conducted in 14 participants with advanced cancer. Multiple ketoconazole doses at 400 mg increased Cmax and AUC of panobinostat by 1.6- and 1.7-fold, respectively, but with no change in Tmax[32]. The less than 2-fold increase in panobinostat AUC upon co-administration suggests that CYP3A contribution to the total clearance is low. The observed effect of ketoconazole on panobinostat CYP3A mediated metabolic pathways is considered weak and not clinically relevant, as doses at least 2-fold greater than 20 mg (i.e. 40 mg and 60 mg) have been safely administered in participants. Clinical monitoring of signs of possibly panobinostat related adverse events is recommended when long-term (≥1 week) concomitant administration of potent CYP3A inhibitors and panobinostat at doses >20 mg is medically indicated. Study [CLBH589B2109] was conducted in 17 participants with advance cancer. Multiple panobinostat doses at 20 mg (TIW) increased Cmax and AUC of dextromethorphan by a mean of 1.8- and 1.6-fold, respectively, but with no change in Tmax. An approximately 2-fold increase in dextromethorphan AUC upon co-administration with panobinostat indicated that in vivo CYP2D6 inhibition of panobinostat is weak. As the study was conducted using a sensitive CYP2D6 substrate resulting in a weak inhibition, drugs with a large therapeutic index such as anti-emetics, antihypertensives, and anti-depressants are generally considered safe to be co-administered with panobinostat. Caution is to be exercised when panobinostat is co-administered with medications that are exclusively metabolized by CYP2D6 and have a narrow therapeutic window (e.g. tamoxifen, anti-arrhythmics). There are known interactions with the following anti-retroviral drugs of the protease inhibitor class: Indinavir/ritonavir, Lopinavir/ritonavir Saquinavir/ritonavir, Tipranavir/ritonavir, Ritonavir. In addition, there are interactions with antiretroviral regimens containing cobicistat. Use of any protease inhibitor or cobicistat will not be permitted during participation in this study. NNRTIs can induce CYP3A, but there was no clinical or laboratory evidence for significant pharmacokinetic interactions between NNRTIs (Efavirenz, Rilpivirine) or Integrase Inhibitors (Raltegravir) with panobinostat in a prior clinical trial with panobinostat in cART-treated HIV-1 participants[33].

## 5.4 Clinical Trials with HDACi in cART-treated HIV-1-Positive Individuals

So far, three different HDACi (vorinostat, romidepsin, panobinostat) have been or are being tested for reactivation of HIV-1 in ART-treated participants. Major findings from these studies are summarized below.

### 5.4.1 Clinical Trials with Vorinostat

Effects of vorinostat on HIV-1 reactivation have so far been tested in two clinical trials, one conducted at the University of North Carolina at Chapel Hill (UNC)[26,34] and one at the University of Melbourne,

Australia[35]. The UNC study administered a single dose of vorinostat to ART-treated HIV-1 patients, which led to significant increase in HIV-1 RNA transcription within hours after drug administration in 8 study participants. Effects of a single dose of treatment on CD4 T cell-associated HIV-1 DNA (as a surrogate marker for the viral reservoir) were not expected in this study and not reported. No clinically significant toxicity was recorded. Repetitive dosing of vorinostat in a subsequent study did not show substantial increases of cell-associated HIV-1 RNA. In the study at the University of Melbourne, vorinostat was administered at 400 mg daily for 14 consecutive days to n=20 cART-treated HIV-1 patients. Enhanced HIV-1 transcription was observed at multiple timepoints during this study, but there were no significant effects on CD4 T cell-associated HIV-1 DNA. No significant toxicity of vorinostat treatment was reported in this study[36].

### 5.4.2 Clinical Trials with Romidepsin

A clinical trial evaluating effects of a single dose of romidepsin on HIV-1 reactivation in ART-treated HIV-1 patients is being conducted by the AIDS Clinical Trials Group (ACTG). Data from this study are expected in early 2016. In a second clinical trial, romidepsin was administered once-weekly in three consecutive i. v. infusions in six cART-treated study participants at Aarhus University Hospital in Denmark. Results from the study demonstrate strong reactivation of CD4 T cell-associated HIV-1 RNA and HIV-1 plasma RNA in six study participants[37].

### 5.4.3 Clinical Trials with Panobinostat

The CLEAR study, conducted at the University of Aarhus in Denmark, was an investigator initiated, single-group, non-randomized phase I/II trial designed to evaluate the safety and ability of oral panobinostat to activate HIV-transcription in latently infected CD4 T cells of HIV-infected patients on suppressive cART. None of the participants received protease inhibitors. The study enrolled 15 participants and included a 4-week pre-treatment observation phase, an 8-week treatment course and a post-treatment follow-up observation period of 24 weeks. Each individual received oral panobinostat at a dose of 20mg three times a week (TIW) every other week (QOW) for a total of eight weeks (12 doses of panobinostat total). Major findings from this study have been published recently [33] and are summarized below.

#### 5.4.3.1 Safety analysis

No serious adverse events related to the study medication were noted during the entire time of observation in the CLEAR study. A total of 15 adverse events were noted that were likely related to the study medication; all of these were Common Terminology Criteria for Adverse Events (CTCAE) grade 1 and included fatigue (7 AEs), diarrhea (2 AEs), nausea (2 AEs), subjective palpitations with an otherwise normal cardiac exam (1 AE), epigastric pain (1 AE), vomiting (1 AE), and insomnia (1 AE). 20 adverse events were recorded that were unlikely to be related to the study medication, 14 of these were CTCAE grade 1 and 6 were CTCAE grade 2. These events included a fracture due to accident (1 AE, grade 2), maxillary sinusitis (1 AE), subclinical TSH increase (1 AE), flu-like symptoms (fever, cough, myalgia, 1 AE), skin excoriation after accident (1 AE, grade 2), identification of sigmoid polyp during colonoscopy (1 AE, colonoscopy was part of study protocol), rash (1 AE), fungal skin infection (1 AE), pharyngitis (1 AE), aphthous stomatitis (1 AE), monosymptomatic fever (1 AE), headache (1 AE, grade 2), post-LP headache (5 AEs, 2 grade 1 and 3 grade 2; LP was part of study protocol), URI symptoms (1 AE). Thrombocyte and neutrophil levels remained within normal limits for all study participants during the entire time of observation.

#### 5.4.3.2 Virologic effects

The degree of histone acetylation is a direct measure of the pharmacodynamic effect of an HDACi on cells. In the CLEAR study, mean histone H3 acetylation increased rapidly (2.5-fold, 95% CI: 1.9-3.4; $p<0.0001$) two hours after the first dose of panobinostat. Overall, panobinostat treatment resulted in significant changes in histone H3 acetylation with increases and decreases corresponding to the cyclic dosing pattern. To investigate changes in CD4 T cell-associated (CA) unspliced (US) HIV-1 RNA during panobinostat

treatment, we used a semi-nested real time quantitative PCR previously described by Pasternak et al[38]. The level of CA US HIV-1-RNA, which represented the primary outcome measure of the CLEAR trial, increased significantly during panobinostat treatment ($p<0.0001$) with statistically significant increases at all assayed time points on-panobinostat as compared to baseline. As with histone H3 acetylation, levels of CA US HIV-1-RNA increased rapidly with a mean 2.4-fold increase (95% CI: 1.8-3.3; $p<0.0001$) two hours after initiating panobinostat. The median maximal fold-increase in CA US HIV-RNA during panobinostat treatment was 3.5-fold (range 2.1–14.4). In conclusion, these data show that panobinostat treatment can lead to significant increases in histone H3 acetylation and HIV-1 transcription in CD4 T cells.

T cell-associated HIV-1 DNA was measured in the CLEAR study as a surrogate marker for the viral reservoir size. Despite increased HIV-1 transcription and virion production during panobinostat dosing, our analyses did not detect cohort-wide reductions in HIV-1 DNA. However, on review of the dynamics of HIV-1 DNA changes in individual patients, we observed a significant and sustained 3-5 fold decline of total HIV-1 DNA in four out of the 15 study patients. This suggests that administration of panobinostat can, under specific circumstances, result in a reduction of the reservoir of HIV-1 infected CD4 T cells in cART-treated patients. Interestingly, three of these four study patients participated in an analytical treatment interruption (ATI) and had delayed rebound kinetics in comparison to the six other study persons who participated in the ATI and for who no change of HIV-1 DNA was observed during panobinostat treatment[33].

#### 5.4.3.3 Immunologic effects

Immunological studies in the CLEAR study included assessments of HIV-1-specific T cells, NK cells, dendritic cells and B cells by flow cytometry. The immunological parameters most closely associated with decline of HIV-1 DNA during treatment with panobinostat were innate effector cell responses, in particular activated CD69+ NK cells. In addition, declining levels of HIV-1 DNA were correlated with proportions of plasmacytoid dendritic cells. Reductions of HIV-1 DNA were also associated with expression patterns of interferon-stimulated genes (ISGs). Together, these data suggest that innate immune activity is critical for a reduction of the viral reservoir during panobinostat treatment.

#### 5.4.3.4 Pharmacokinetics

Plasma levels of panobinostat increased in all 15 participants of the CLEAR study with the highest levels measured two hours after dosing as compared to eight hours after the previous dose, consistent with a Cmax occurring approximately 1-2 hours after oral ingestion as described previously[39]. There was no clinical or laboratory evidence for relevant pharmacological interactions between panobinostat and the antiretroviral drugs used in this study (NRTIs, PIs, NNRTIs).

### 5.5 Pegylated Interferon-α2a

Peginterferon-α2a (Pegasys, Hoffmann-La Roche) is a covalent conjugate of recombinant α-2a interferon (approximate molecular weight [MW] 20,000 daltons) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate MW 40,000 daltons). The PEG moiety is linked at a single site to the interferon alpha moiety via a stable amide bond to lysine. Peginterferon-α2a has an approximate molecular weight of 60,000 daltons. Interferon-α2a is produced using recombinant DNA technology in which a cloned human leukocyte interferon gene is inserted into and expressed in *Escherichia coli*. A chemically modified IFN-α2a has been developed in which a branched methoxy polyethylene glycol moiety has been covalently attached to IFN. PEG-IFN has a decreased systemic clearance and an approximately 10-fold increase in serum half-life compared with IFN-α, leading to PEG-IFN circulating in the blood for a much longer time than the parent compound. The biological activity of PEG-IFN, as measured using serum 2'5'-oligoadenylate synthetase (OAS) activity, was similarly prolonged, resulting in a significantly improved pharmacodynamic response of PEG-IFN compared with IFN.

### 5.5.1 Clinical experience with pegylated IFN-α2a

Pegasys was registered by the US Food and Drug Administration on October 16th, 2002. It is licensed for treatment of Hepatitis C and B infection. In addition, IFN-α2a has an orphan drug status for treatment of chronic myeloid leukemia, renal cancer and melanoma. It has been safely administered to >10,000 patients since approval.

### 5.5.2 Safety and Toxicity

Side effects of pegylated IFN-α2a are usually mild to moderate and include flu-like symptoms such as fatigue, muscle aches, headaches, chills/fever, nausea, vomiting, or diarrhea and injection site irritation. Depression, irritability, insomnia, and anxiety have been seen in a moderate percentage (40%) of participants, but are usually mild. Other reported events include neutropenia and thrombocytopenia, alopecia, and infrequently an abnormal (increased or decreased) thyroid function. A decrease in leukocytes has been reported but is usually within normal range. All of these are usually manageable and reversible upon discontinuation of the drug or decrease in dosage.

### 5.5.3 Effects of IFN-α on active HIV-1 replication

A number of studies in the pre-HAART era have assessed effects of IFN-α on plasma levels of HIV-1 RNA in otherwise untreated patients. These studies demonstrated that IFN-α leads to a 0.5- to 1-log reduction of plasma HIV-1 RNA[40-42]. This effect occurs within several weeks of IFN-α administration and was most pronounced at week 10-15 of therapy. Similar observations were made in SIV-infected rhesus macaques treated with recombinant IFN-α or IFN-α receptor agonists[43]. Antiviral effects of IFN-α likely result from an IFN-α-dependent upregulation of antiviral molecules in HIV-1 target cells[44,45]. In addition, IFN-α can directly activate innate and adaptive effector immune cells[46-48], reduce the expression of inhibitory molecules (PD-1) on antigen-specific T cells, and reduce the frequency of regulatory T cells[49], all of which are assumed to contribute to antiviral effects of IFN-α.

### 5.5.4 Effects of IFN-α on the reservoir of HIV-1 infected cells in ART-treated patients

Effects of IFN-α on the reservoir of HIV-1 infected cells in HIV-1 patients receiving suppressive antiretroviral therapy have been investigated in two prior studies. In a prospective clinical trial, treatment with IFN-α led to moderate, approximately 2-fold reduction of integrated HIV-1 DNA in CD4 T cells in a subset of participants[50]. A retrospective analysis of ART-treated HIV/HCV-co-infected participants receiving treatment with PEG-IFN-α and ribavirin confirmed a moderate, approximately 2-fold decrease of HIV-1 DNA levels; this effect was sustained after treatment discontinuation[51]. Together, these studies suggest that IFN-α is effective in reducing the reservoir of HIV-1 infected cells in ART-treated patients. Given that IFN-α2a can by itself influence viral reservoir dynamics, a control arm of patients receiving IFN-α2a only will be recruited in stage 3 of this study to allow comparisons in reservoir size between patients receiving the combination of IFN-α2a and panobinostat, and those receiving IFN-□2a only.

## 5.6 Rationale and Hypotheses for this Study

Findings from the CLEAR study suggest that the HDACi panobinostat can increase HIV-1 gene expression in CD4 T cells from cART-treated patients in vivo, and that this increased virus production leads to transient increases in residual HIV-1 plasma viremia, indicating that panobinostat can be effective in reactivating HIV-1 gene expression from latently infected cells in vivo. However, these effects were insufficient to substantially reduce the total reservoir of HIV-1-infected cells that persist despite treatment. The immune correlates most strongly associated with a decrease of HIV-1 DNA in participants during panobinostat treatment were the proportion of activated CD69+ NK cells, the proportion of CD57+ NK cells with increased cytotoxic activities, and the proportion of plasmacytoid dendritic cells.

Interestingly, prior studies have shown that treatment with PEG-IFN-α rapidly activates NK cells within hours of administration and induces the exact CD69+ NK cell phenotype that was associated with declining HIV-1 DNA in CD4 T cells during the CLEAR study[46,47]. Treatment with PEG-IFN-α also increases the

frequency of plasmacytoid dendritic cells[52], the second innate immune effector cell population associated with decreasing levels of HIV-1 DNA during panobinostat treatment in the CLEAR study. Moreover, in vitro studies suggest that treatment with IFN-α can support cell-autonomous pro-apoptotic immune recognition of HIV-1 RNA that is reactivated by treatment with panobinostat, and selectively sensitizes CD4 T cells with viral reactivation to NK cell-mediated killing by increasing the expression ligands to activating NK receptors. Therefore, IFN-α2a may be able to induce innate and cell-autonomous immune activity against CD4 T cells in which HIV-1 is effectively reactivated with panobinostat, and in this way act synergistically with panobinostat in eliminating the reservoir of HIV-1 infected cells.

The following hypotheses will be tested in this clinical trial:

**Hypothesis 1:** Combined treatment with panobinostat and PEG-IFN-α2a is safe and well-tolerated in participants with HIV-1 infection who have virological suppression (HIV RNA <50 copies/mL) and CD4 T cell counts >400 cell/mm$^3$ while receiving combination ART.

**Hypothesis 2:** Combined treatment with panobinostat and PEG-IFN-α2a in ART-treated HIV-1 patients will be significantly more effective in reducing the reservoir of HIV-1-infected cells than treatment with panobinostat alone, or IFN-α2a alone. During the combined treatment, panobinostat will reactivate active viral gene expression in latently infected CD4 T cells, while PEG-IFN-α2a will activate innate effector cells and increase cell-autonomous immune activity against CD4 T cells in which viral reactivation occurs.

## 6.0 STUDY DESIGN

This study will be a prospective, randomized, open-label, dose-escalation exploratory clinical trial with the primary objective to evaluate the safety of combined treatment with the HDACi panobinostat and pegylated Interferon-α2a, and to assess the efficacy of the combined treatment regimen to reduce the reservoir of HIV-1 infected cells in comparison to treatment with panobinostat as a single agent. Sequential cohorts with increasing doses of panobinostat will be enrolled. The first two dosing cohorts (stages 1 and 2) will serve primarily to assess the safety of panobinostat administration together with pegylated IFN-α2a; the third dose cohort (stage 3) has a larger sample size to allow for comparison of the effects of panobinostat plus pegylated IFN-α2a versus panobinostat or pegylated IFN-α2a alone on the HIV reservoir. The clinical trial will involve a collaboration of three institutions: the Division of Infectious Diseases at Massachusetts General Hospital in Boston, MA, the Division of Infectious Diseases at the Brigham and Women's Hospital in Boston, and the Novartis Institute of Biomedical Research in Cambridge. The clinical trial will be conducted in the Infectious Diseases Clinical Trials Unit (CTU) at the Massachusetts General Hospital.

Participants must have HIV-1 RNA levels <50 copies/mL for at least two years, must have been on suppressive antiretroviral therapy for at least 2 years, must have a CD4 T cell count >400 cells/mm$^3$ at study screening, and must have been on a stable and acceptable ART regimen for at least 12 weeks prior to screening. An acceptable regimen includes 2 NRTIs with either one NNRTI (efavirenz or rilpivirine) or a non-boosted integrase inhibitor (raltegravir or dolutegravir). Patients who started treatment during early disease (within <12 months after transmission) and patients who started treatment in chronic infection ($\geqslant$ 12 months after HIV-1 transmission) are eligible to participate.

After obtaining informed consent, all study participants will have a history and physical exam performed and have laboratory tests to confirm they meet all inclusion and exclusion entry criteria. Women of childbearing potential will have a urine pregnancy test before treatment and after treatment during study participation. All participants will receive treatment comprising one week of panobinostat (dosed every second day on e.g. Monday, Wednesday, Friday), followed by three weeks off-treatment for observation. In stage 1, participants will receive panobinostat at a dose of 5 mg TIW; this dose will be escalated to 10 mg TIW (stage 2) and 15 mg TIW (stage 3), if the safety review of each preceding step is acceptable. Participants will be randomized to receive panobinostat alone (Arm A, n=2 participants in stages 1 and 2; n=4 participants in stage 3), or in combination with pegylated IFN-α2a (Arm B, n=6 participants in stages

1 and 2, n=10 participants in stage 3); in stage 3, patients will also be randomized to a control arm of n=4 study subjects receiving Interferon-α2a only (Arm C). Subcutaneous injections with pegylated Interferon-α2a will be administered at the start of the week-long treatment course. ART will be continued during the entire study period in all study participants. Participants will undergo close monitoring for side effects during the entire time of study participation. The total study duration will be 2 months. Blood samples will be obtained for immunological and virological assays at study baseline and at selected time points during the treatment and observation periods as described below. The study design is summarized in Figure 1.

## 7.0 SELECTION, ENROLLMENT AND RANDOMIZATION OF PARTICIPANTS

7.1 Inclusion Criteria

The study will include participants who meet all of the following criteria:

7.1.1 Between 18 to 65 years of age at the time of study screening.

7.1.2 Written informed consent signed prior to all study procedures.

7.1.3 HIV-1 infection as documented by any licensed ELISA test kit and confirmed by Western blot, HIV-1 culture, HIV-1 antigen, plasma HIV-1 RNA, immunofluorescent antibody test (IFA), or a second antibody test by a method other than ELISA. Tests from any time prior to entry are acceptable.

7.1.4 Receiving suppressive antiretroviral therapy for a minimum of 24 consecutive months prior to screening with no interruption of therapy. Participants must have been on the same ART regimen for at least 12 weeks prior to screening. Participants must not have a history of antiretroviral treatment failure.

7.1.5 Participants must take an acceptable ART regimen at the time of study screening. Acceptable regimens include 2 NRTIs in combination with either an NNRTI (efavirenz or rilpivirine) or a non-boosted integrase inhibitor (raltegravir or dolutegravir or bictegravir). FDA-approved dual drug regimens such as the rilpivirine/dolutegravir combination (Juluca) are also acceptable. Triple NRTI regimens, protease inhibitor- or cobicistat-containing regimens are not permitted.

7.1.6 Patients who started antiretroviral treatment in early HIV-1 infection (within <12 months of HIV-1 transmission), and patients who started antiretroviral treatment in chronic infection ($\geqslant$12 months after HIV-1 transmission) are eligible for this study.

7.1.7 Investigator anticipates that a fully active, alternative antiretroviral regimen can be constructed in the event of virological failure of the current ART regimen.

7.1.8 Documented suppressed HIV-1 RNA. Participants must have plasma HIV-1 RNA values <50 copies/ml on at least three consecutive measurements during the 24 months prior to the study entry, except for a single blip of <400 copies/mL (that is, if a study candidate has a single HIV-1 RNA that is >50 copies/mL but <400 copies/mL with subsequent HIV-1 RNA values <50 copies/mL, then he or she will not be excluded). Three consecutive HIV-1 plasma RNA levels below the detection threshold of commercial PCR assays with other threshold levels (e.g.<75 copies/mL) are also acceptable.

7.1.9 CD4 T cell count $\geq$400 cells/mm$^3$ at screening visit.

7.1.10 Laboratory values at screening visit that meet the following criteria:

a. Hemoglobin $\geq$ 12.0 g/dL for men and $\geq$ 11.0 g/dL for women

b. Absolute neutrophil count $\geq$ 1500 cells/mm$^3$

c. Platelet count $\geq$ 150,000/mm$^3$

d. Prothrombin time (PT) < 1.1 x upper limit of normal (ULN) and partial thromboplastin time (PTT) < 1.1 x ULN

e. Creatinine level < 1.1 x ULN

f. Total serum bilirubin < 1.1 x ULN

g. AST (SGOT) and ALT (SGPT) < 1.1 x ULN

7.1.11 Normal TSH. If K and Mg levels are below the limits of normal, participants will be provided with supplements and their levels will be rechecked. Supplementations will continue until electrolyte levels are normalized.

7.1.12 Negative serologic test for HBsAg.

7.1.13 Negative serologic test for antibodies to HCV or negative HCV PCR if anti-HCV antibodies are positive.

7.1.14 QTc interval in an ECG performed at the screening visit must be <450msec for men and <470msec for women.

7.1.15 A negative T spot TB test or a negative PPD skin test within the last 24 months. Participants with positive assays may participate if they have completed a recommended treatment course for latent TB in the past.

7.1.16 Participants should have received vaccination for pneumococcal disease within the last 5 years. Participants may still be enrolled in case there is a medical or personal contraindication against pneumococcal vaccination.

7.1.17 No evidence of clinical coronary heart disease, as determined by a stress echocardiogram, conducted within 2 years prior to study initiation. Data from a non-imaging exercise stress test or a nuclear imaging stress test conducted within two years prior to study initiation are also acceptable. However, when stress tests without imaging were done, a resting echocardiogram should be performed prior to enrollment to assess the cardiac ejection fraction. Patients who are unable, or predicted to be unable, to achieve >85% of their maximal predicted heart rate will undergo a dobutamine stress echocardiography instead of an exercise stress echocardiography since an exercise stress test would be insufficiently sensitive in this case. The stress test will be conducted at the Massachusetts General Hospital Cardiology division. Dr. Rajeev Malhotra, the protocol cardiologist, will facilitate short-term scheduling of patients.

Patients with no history of coronary artery disease (CAD) or clinical symptoms suggestive of CAD, who have excellent exercise capacity and achieve >70% but less than 85% of the maximum age-predicted heart rate during stress echocardiography and under these conditions have no clinical, EKG, or echocardiographic evidence of cardiac ischemia, can be considered for participation in this study. The eligibility of these subjects should be assessed on a case-by-case basis with consultation from experts.

No evidence for coronary artery disease can also be documented by a negative coronary angiography or by a negative stress magnetic resonance imaging study. The procedural report of these tests should also include documentation of cardiac function (e.g. left-ventricular ejection

fraction). If this information is not included in the procedural report, a resting echocardiography should also be performed.

7.1.18 No clinically significant eye disease, as determined by a baseline fundoscopic eye exam. The eye exam will be performed with an opthalmoscope (Welch Allyn, PanOptic Ophthalmoscope), and electronic retinal photographs will be taken of each eye.

7.1.19 For females of reproductive potential, urine pregnancy test (latter with a sensitivity of 15-25 mIU/mL) at the screening visit within 30 days prior to treatment by any US laboratory that has a CLIA certification or its equivalent.

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 or
- Women who have not undergone surgical sterilization (e.g. hysterectomy, or bilateral oophorectomy, or bilateral salpingectomy).

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 of the male partner), FSH measurement elevated into the menopausal range (as established by the reporting laboratory).

If the female participant cannot provide written proof of a male partner's vasectomy status, the verbal report of her partner's status should be written into the source documents.

7.1.20 Female participants of reproductive potential must refrain from participating in active attempts to become pregnant, and, if participating in sexual activity that could lead to pregnancy, the participant must agree to use at least two reliable forms of contraception that are non-estrogen based. All participants of reproductive potential must continue to use contraceptives for 90 days after completing panobinostat/IFN-α2a treatment.

Acceptable forms of contraception include:

- Condoms (male or female) with or without spermicidal agent
- Diaphragm or cervical cap with spermicide
- Non-hormonal intrauterine device (IUD)
- 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

Providers and 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. Study 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. Study participants should discuss contraceptive choices and HIV risk reduction methods with their healthcare provider.

7.1.21 Female participants who are not of reproductive potential are not required to practice contraception.

7.1.22 Male study participants must use a condom during intercourse while taking panobinostat and for five half-lives (5x16h, total of 80 hours) after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. The partners of patients should also use contraception to avoid pregnancy.

7.2 Exclusion Criteria

7.2.1 Confirmed HIV-1 RNA >50 copies/mL within 24 months of screening, except for a single blip of <400 copies/mL during the 24 months prior to screening.

7.2.2 Participants with moderate or severe, uncontrolled psychiatric disease, a history of a previous suicide attempt or a history of prior hospitalization for mental illness will not be enrolled.

7.2.3 Any past evidence of medical conditions associated with chronic liver disease (e.g. genetic hemochromatosis, autoimmune hepatitis, alcoholic liver disease).

7.2.4 Any evidence of active, immunologically mediated disease (e.g. inflammatory bowel disease, systemic lupus erythematosus, autoimmune hemolytic anemia, scleroderma, severe psoriasis, rheumatoid arthritis).

7.2.5 Severe retinopathy due to diabetes, hypertension, cytomegalovirus or macular degeneration.

7.2.6 Evidence of cardiac disease such as: congestive heart failure, clinically significant coronary artery disease, ECG changes consistent with myocardial ischemia or bifascicular hemiblock (right bundle branch block and left anterior hemiblock), ventricular tachyarrhythmia, moderate or severe hypertension, ventricular fibrillation or Torsade de Pointes, bradycardia defined as HR < 50 bpm. Patients with pacemakers are eligible if HR ≥ 50 bpm.

7.2.7 Known history of active thyroid disease requiring medication that is not under control. Patients are permitted to receive thyroid hormone supplements to treat underlying hypothyroidism.

7.2.8 Breastfeeding.

7.2.9 Presence of an active bacterial, fungal, viral or protozoal infection requiring systemic anti-infective therapy (other than HIV infection or chronic herpes simplex virus infection requiring suppressive therapy).

7.2.10 Uncontrolled seizure disorder.

7.2.11 History or other evidence of severe illness or other conditions that would make the participant, in the opinion of the investigator, unsuitable for the study (e.g. conditions that could potentially be exacerbated by the study drugs).

7.2.12 History of malignancy of any organ system (other than localized basal cell or squamous cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.

7.2.13 Female participants who are pregnant or nursing a child. Pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

7.2.14 History of solid organ transplantation with an existing functional graft.

7.2.15 Use of any immunomodulatory agents within 30 days prior to study enrollment or planned use during the trial. Influenza vaccination or other routine vaccines will be permitted 30 days or more prior to administration of study medication

7.2.16 Active drug or alcohol use or dependence that, in the opinion of the sponsor, would interfere with adherence to study requirements.

7.2.17 Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the participant in the study. The Investigator should make this determination in consideration of the participant's medical history and/or clinical or laboratory evidence of any of the following:

- Inflammatory bowel disease
- Major gastrointestinal tract surgery such as gastrectomy or gastroenterostomy
- Pancreatic insufficiency

7.2.18 Use of HIV protease inhibitor or other strong or moderately strong CYP3A4 inhibitors:

Strong inhibitors of CYP3A4 include: boceprevir clarithromycin, cobicistat, conivaptan, indinavir, itraconazole, ketoconazole, fluconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, aprepitant, grapefruit juice.

Moderate inhibitors of CYP3A4 include: amprenavir, aprepitant, atazanavir, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil.

Co-medication with weak inhibitors of CYP3A4 will be permitted. Weak inhibitors of CYP3A4 include: alprazolam, amlodipine, atorvastatin and other statins, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, zileuton.

Note: Use of azithromycin, regular orange juice and dihydropyridine calcium channel blockers (e.g. amlodipine, felodipine, nicardipine, nifedipine) are allowed.

7.2.19 Since panobinostat is a weak inhibitor of CYP2D6, participants using pharmaceuticals that are CYP2D6 substrates with a narrow therapeutic window are not permitted. Such agents are: thioridazine, tamoxifen, and the antiarrhythmics mexiletin, propafenone and flecainide. Drugs that are CYP2D6 substrates with a large therapeutic index such as certain anti-emetics, anti-hypertensives, and anti-depressants are generally safe to be co-administered with panobinostat.

7.2.20 Participant has a history of anaphylaxis, allergy or serious adverse reactions to Interferon-$\alpha$2a/Interferon-$\alpha$2b or panobinostat.

7.2.21 Participant taking any of the following medications at the time of study entry: systemic steroids (inhaled or nasal steroid therapy or low dose oral steroid treatment up to no more than 7.5mg of Prednisone per day or the equivalent dose of alternative corticosteroids are permitted), interleukins, systemic interferons or systemic chemotherapy.

7.2.22 Regular use of concomitant medication with a known potential to lead to QTc prolongation or Torsades de pointes. These drugs include: quinidine, procainamide, disopyramide or any other class IA antiarrhythmic drug, sotalol, cisapride, amiodarone, bretylium, disopryramide, dofetilide, ibutilide or any other class III antiarrhythmic drug, macrolide antibiotics (clarithromycin, erythromycin. telithromycin), thioridazine, mesoridazine, chlorpromazine, pimozide, halofantrine, chloroquine, pentamidine, astemizole, arsenic trioxide, bepridil, domperidone, methadone, droperidol, levomethady. This list of medications was developed in collaboration with an external cardiology consultant, and represents those medications which are deemed to have an unacceptable risk of co-administration with panobinostat.

Note: azithromycin, ciprofloxacin, levofloxacin and moxifloxacin are allowed.

### 7.3 Participant Recruitment, Information and Consent

Written information and advertisements approved by the IRB may be used for recruitment purposes. Individuals treated at MGH, BWH, other Harvard University CFAR-associated institutions, and other hospitals in the Boston area, such as Fenway Health, Tufts Medical Center, and the Boston Medical Center, are permitted to participate; all possible candidates will be referred to MGH for evaluation and possible study participation. Eligible study participants may receive an invitation to participate in the study if the participant has previously agreed to be contacted in such matters. Invitation may also be provided as part of routine medical visits to the Department of Infectious Diseases at MGH, the MGH Clinical Trials Unit or BWH, or to other hospitals. Interested participants can contact the primary Investigator or study nurse to receive written information and schedule an appointment for further information, possibly attended with a companion. If the participant then wishes more time to consider participation in the study, presence of a companion, or repetition of information, a new appointment will be scheduled for this.

Individuals from investigators' own clinics are also potentially eligible for this study. Patients of the investigators will be informed of the study by participant summary sheets or one of the co-investigators (who do not serve as the patient's primary physician). A study co-investigator distinct from the patient's primary physician will conduct the informed consent process with interested patients from the investigators' clinics.

Individuals who participated in stage 1 or 2 are permitted to take part in stage 3 if they have not experienced a (clinical or laboratory) grade 3 or 4 adverse events during stage 1 or 2.

### 7.4 Study participant replacement

In stage 1 and 2, up to two participants dropping out of the study prior to study completion will be replaced by a new study subject. If, however, the subjects discontinue the study due to safety or tolerability concerns, the subjects will not be replaced. In stage 1, 2 and 3, all participants dropping out of the study prior to initiation of the first dose of the study medication will be replaced.

### 7.5 Randomization

Participants will be randomized to treatment Arm A or treatment Arm B or treatment Arm C (in stage 3 only). Participants in treatment Arm A (n=2 participants in stage 1 and 2; n=4 participants in stage 3) will receive treatment with panobinostat only, and participants in treatment Arm B (n=6 participants in stage 1 and 2; n=10 participants in stage 3) will receive combined treatment with panobinostat and pegylated IFN-α2a. Participants in Arm C (n=4 in stage 3) will receive treatment with pegylated IFN-α2a only.

Randomization will occur on day 0 of the study, prior to administration of the first dose of the study medication. Participants will be informed about the randomization decision, and open-label study medication will be administered.

## 8.0 STUDY TREATMENT

### 8.1 Panobinostat

#### 8.1.1 Formulation

Panobinostat is a highly potent class I/II HDAC inhibitor belonging to the hydroxamic acid class of compounds. The drug product provided is an immediate-release solid oral dosage form tablet containing 5 mg panobinostat for stage 1, 10 mg panobinostat for stage 2, and 15 mg panobinostat for stage 3. For further details on physical, chemical and pharmaceutical properties refer to the Investigator's Brochure. The drug will be packed and labeled as investigational product in accordance with current guidelines and applicable regulatory requirements.

The Massachusetts General Hospital Pharmacy will be responsible for the import, labeling and storage of the investigational drug. The study Investigators or the study nurse will request the appropriate quantity of the investigational drug from the MGH Pharmacy prior to dispensing to study participants. The investigational drug will then be delivered with the required labeling containing batch number, manufacturing date and time, project name, contact person and drug ID number.

**Note**: Refer to the Investigator's Brochure for further information about panobinostat and its components.

8.1.2 Administration

Panobinostat will be orally administered as a 5 mg tablet (stage 1), a 10 mg tablet (stage 2, two 5 mg tablets can also be used) and a 15 mg tablet (stage 3, three 5 mg tablets can also be used) every second day during the treatment week (total of three oral doses). The first dose of panobinostat will be administered concomitantly to the corresponding subcutaneous injection of PEG-IFN-α2a in Arm B.

The MGH Pharmacy will be responsible for secure and correct storage of the investigational drug until reception at the MGH Clinical Trials Unit, after which the Investigators will be responsible. The investigational drug will be clearly marked and stored in a locked medicine storage room at the MGH Pharmacy. Lists of received, used and remaining quantities of the investigational drug will be kept. Any discrepancies must be resolved.

8.1.3 Storage

Panobinostat will be clearly marked and stored in a locked medicine storage room at room temperature.

8.2 Peginterferon alfa-2a, (Pegylated interferon α-2a, Pegasys™)

8.2.1 Formulation

PEG-IFN-α2a will be used in single-use vials for this study. Other excipients include benzyl alcohol, sodium chloride, sodium acetate trihydrate, acetic acid, polysorbate 80, and water. For further information about this product, refer to the FDA-approved package insert. PEG-IFN-α2a will be obtained from Roche Laboratories by the MGH pharmacy in syringes containing 180mcg of the drug in 1ml. PEG-IFN-α2a supplied by Roche in a single-use syringes containing 180mcg of the drug in 0.5ml is also acceptable. Commercially available PEG-IFN-α2a, manufactured by Roche and provided as syringes containing 180mc of the drug, can also be used.

8.2.2 Administration

180mcg of PEG-IFN-α2a will be administered by subcutaneous injection once at the beginning of the treatment week in Arm B. One dose of IFN-α2a will be given. Injection of IFN-α2a will be given simultaneously with the first dose of panobinostat.

8.2.3 Storage

PEG-IFN-α2a will be stored and refrigerated at 2° to 8° C (36° to 46° F) prior to dispensing.

8.3 Accountability of study medication

The study participants in Arm B will receive PEG-IFN-α2a injections by study staff during their study visits. Panobinostat doses will be taken by participants in the clinic on day 0. The remaining tablets will be dispensed to participants and self-administered by participants at the scheduled time points.

8.4 Dosing schedule for investigational drugs:

The investigational drugs will be administered as summarized in Figure 1 and Table 1.

## 8.5 Monitoring for adherence to investigational drugs

The first dose of the panobinostat (in study arm A and B) and pegylated IFN-α2a (in study arm B or C only) will be administered during admission to the hospital under direct observation by study nurses or physicians. Subsequent doses of panobinostat can be self-administered by patients at home, at pre-defined time points. Internet-based scheduling tools will be used to remind patients of taking panobinostat as scheduled, if patients agree to this procedure.

For each participant, received and remaining tablets of the investigational drugs will be accounted for during follow-up visits; results will be noted in the CRF. If non-adherence is suspected based on these evaluations, study staff will inform the protocol chairs and review the importance of adherence to all study medications with the participant and ongoing adherence support will be provided. The study chair may exclude a participant from continuing the study if there is evidence for a level of non-compliance with study medication that, in the investigators' judgments, may compromise study results.

## 8.6 Concomitant Medication

### 8.6.1 Prohibited Medications

Participants will be excluded from the study if they are taking any of these medications during the course of this clinical trial:

- Systemic steroids up to 7.5 mg of Prednisone per day (or equivalent dose of alternative steroids); inhaled or nasal steroid therapy is also permitted
- Interleukins
- Systemic interferons other than the study medications
- Systemic chemotherapy
- Ritonavir, cobicistat or other similarly potent inhibitor of CYP3A4
- Grapefruit juice is a moderate to strong CYP3A inhibitor and may increase absorption and exposure to panobinostat. Therefore, participants will be instructed not to consume grapefruit juice during the study
- Pharmaceuticals that are strong or moderately strong CYP3A4 inhibitors, or CYP2D6 substrates with a narrow therapeutic window (see section 7.2.18 and 7.2.19)
- Drugs with a known potential to lead to QTc prolongation (see section 7.2.22)

### 8.6.2 Required Medication

Participants are required to maintain a fully suppressive ART regimen (defined above) throughout entire study period. These medications will not be provided by the study. ART that includes a protease inhibitor or cobicistat is not permitted.

### 8.6.3 Changes in cART Therapy

Changes in ART will be allowed for toxicity so long as a protease inhibitor or cobicistat is not included in the new regimen. These changes should be discussed with the study co-chairs. See Section 11.8 for procedures to be followed in case of virological failure.

### 8.6.4 Other concomitant medication

Any other current medical therapy either recorded at study entry or initiated during the study will be recorded in the CRF. Initiation of medical therapy that requires use of a drug specified in the exclusion criteria will result in withdrawal from the investigational drug. Medication entries should be specific to

trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date, and the reason for therapy.

## 9.0 CLINICAL AND LABORATORY EVALUATIONS

### 9.1 Study Conduct

#### 9.1.1 Ethics and Regulatory Considerations

The study will be conducted according to Good Clinical Practice (GCP) as specified in the ICH guidelines. The Sponsor will ensure that this study is conducted in agreement with all applicable laws, regulations and relevant ethics of Massachusetts General Hospital, Harvard Medical School, the City of Boston, the Commonwealth of Massachusetts and the United States.

#### 9.1.2 Informed Consent

Informed consent will be obtained prior to the performance of any study procedures (including blood tests). The responsible investigator physician will review the consent with the patient. Consent will be documented by dated signatures of the patient, and the person obtaining consent. The informed consent will include all standard elements including, at a minimum, description of the study goals, entry criteria, details of the study, known risks of the therapy, participant's rights and criteria for record review by outside agencies (FDA for example). No elements of the informed consent will be waived. Only a fully IRB-approved consent will be used.

### 9.2 Definition of clinical evaluations

#### 9.2.1 Medical history

A medical history will be taken at the screening visit and should summarize all previous diagnoses, any allergies and a detailed medication history, including the start and stop dates of any antiretroviral medication (estimated if the exact dates cannot be obtained), and any immune-based therapies. A complete list of all prescription, non-prescription and alternative medications taken within 30 days prior to study entry with start and stop dates will also be recorded.

#### 9.2.2 Clinical assessment and complete physical exam

Complete physical exam is required at baseline and includes examination of the eye (with retinal photographs), skin, head, mouth, neck; auscultation of the chest, cardiac exam; abdominal exam and exam of extremities. The clinical assessment will also include signs and symptoms, diagnoses, height, weight and vital signs (temperature, blood pressure, pulse).

#### 9.2.3 Targeted Physical exam

A targeted physical examination will be driven by any signs and symptoms previously identified or new that the participant has experienced since the last visit. If indicated based on the participant's symptoms and history, evaluation for suicidal ideation will be performed using the Columbia Suicide Severity Rating Scale (available at http://www.cssrs.columbia.edu/).

#### 9.2.4 Pre-treatment assessments

Pre-treatment assessments will be performed on the first day of the treatment week, prior to administration of the investigational drugs. Pre-treatment assessments on these days will include:

- ECG: QTc time must be <450msec for men and <470mesc for women.
- Vital signs: Systolic blood pressure must be between 90-150 mm Hg, diastolic blood pressure must be between 65-100 mm Hg, heart rate must be between 50-100 bpm. Oral temperature measured according to standard procedures must be lower than 100.5F.

- Pregnancy test (urine HCG test, only in women of childbearing potential): Results must be negative.
- Lab tests: Most recent safety lab tests must be within the following limits:

  a. Hemoglobin $\geq$ 12.0 g/dL for men and $\geq$ 11.0 g/dL for women

  b. Absolute neutrophil count $\geq$ 1500 cells/$mm^3$

  c. Platelet count $\geq$ 150,000/$mm^3$

  d. Creatinine level < 1.1 x ULN

  e. Total serum bilirubin < 1.1 x ULN

  f. AST (SGOT) and ALT (SGPT) < 1.1 x ULN

  g. Mg, K > LLN. If the value is < LLN, then the patient's potassium or magnesium should be supplemented following the availability of that laboratory result. Patients must then undergo a repeat biochemistry test to demonstrate values ≥ LLN. These values must be ≥ LLN before the patient is dosed with oral panobinostat.
- Targeted physical exam: Targeted physical must not reveal new signs of organ dysfunction or acute illness.
- Eye exams will be performed using an ophthalmoscope (Welch Allyn, PanOptic Opthalmoscope) and retinal photographs will be taken from each eye and electronically documented. These fundoscopic exams will be non-mydriatic.

If any of these criteria are not met, study medication must not be given. Delay of the study drug administration for up to two weeks until all criteria are met is possible if permitted by the study chairs.

## 9.3 Schedule of Events

### 9.3.1 Overview

The study will comprise three phases:

1. A pre-treatment screening/observation phase

2. A treatment phase of 1 week with panobinostat only (Arm A), pegylated IFN-α2a only (Arm C) or the combination of panobinostat and pegylated IFN-α2a (Arm B).

3. A post-treatment observation period of three weeks.

A graphical overview of the study is given in Figure 1. A summary of all study procedures at each visit is provided in Table 1. Time windows and blood draws for each study visit are also listed in Table 1.

### 9.3.2 Screening/pre-entry phase

Once a candidate for study entry has been identified, the patient will be scheduled to meet with a study representative to discuss the study. If the patient decides to participate, s/he will sign the IRB-approved consent form. Subsequently, the participant will have a screening visit; this visit can occur immediately after signing the consent form.

During this screening visit (V1), the patient will be questioned regarding their medical history and will have laboratory testing performed to determine eligibility for the study. The following procedures will be performed:

- Obtain a medical history, including all information relevant to inclusion and exclusion criteria
- Review concomitant medications
- Perform a complete physical exam, including a non-mydriatic fundoscopic eye exam
- Perform a 12-lead ECG to calculate QTc intervals
- Schedule patient for a cardiac stress echocardiogram test (unless data already available)
- Obtain samples for screening laboratory tests:
    - Plasma HIV-1 RNA testing by Roche Taqman Version 2.0 assay.
    - CD4 T cell counts.
    - HIV antibody (if not previously documented).
    - TSH levels.
    - Urine HCG pregnancy test for female participants of childbearing potential.
    - PPD skin test or T spot TB test (unless data already available).
    - Hematology parameters and chemistry parameters as per Table 1.

If the candidate is eligible for the trial, he or she will return for one pre-entry visit. At this visit (V2), the following procedures will be performed:

- Pregnancy test (women of childbearing age).
- Other lab tests as indicated in Table 1.
- Collection of blood/serum for virological and immunological and gene expression assays.
- Immunogenetic studies for HLA class I and IL-28B genotyping.
- Record baseline level of diarrhea, nausea and vomiting that patients experience with their regular antiretroviral regimen.

| | Screening/Pre-Entry | | Treatment Phase | | | | Post-Treatment Observation | |
|---|---|---|---|---|---|---|---|---|
| **Time** | **≤-30d‡** | **≤-10d‡** | **D0 (0h)** | **D0 (6h)** | **D2** | ***D4 (6h)** | **D10** | **D28** |
| **Windows** | | | | | | **+1** | **+/- 2** | **+/- 2** |
| **Amount Collected from Blood Draws (cc)** | **49** | **91** | **60** | **57** | | **87** | **99** | **87** |
| **IFN-α2a injection (Arm B and C only)** | | | X | | | | | |
| **Panobinostat (Arm A and B only)** | | | X | | X | X | | |
| **Visit numbers** | **V1** | **V2** | **V3** | | | **V4** | **V5** | **V6** |
| **Phone call for evaluation of AEs** | | | | | X | | | |
| **CBC[1]** | X | X | X | | | X | X | X |
| **HLA, KIR, IL-28b GT** | | X | | | | | | |
| **Liver function tests[2]** | X | | | | | X | | X |
| **Chemistry[3]** | X | X | | | | X | X | X |
| **TSH** | X | | | | | | | |
| **Pregnancy testing[4]** | X | X | X | | | | | X |
| **Hep B/C serologies, PPD/TB Spot PT, PTT** | X | | | | | | | |
| **Eye exam** | X | | X | | | | | |
| **Stress echocardiogram/dobutamine stress test** | X | | | | | | | |
| **HIV antibody** | X | | | | | | | |
| **Differential blood count and CD4/CD8 T cell counts** | X | X | X | | | X | X | X |
| **Plasma HIV-1 RNA** | X | | X | X | | X | X | X |
| **Complete/targeted physical exam** | X | X | X | | | X | X | X |
| **Panobinostat PK** | | | X | X | | X | X | |
| **ECG** | X | | X | X | | X | | |
| **Histone acetylation levels** | | X | X | X | | X | X | X |
| **HIV-1 DNA** | | X | X | | | X | X | X |
| **Viral outgrowth assays** | | X | | | | | X | |
| **CD4 T cell -associated HIV-1 RNA** | | X | X | X | | X | X | X |
| **HIV-1 DNA in CD4 T cell subsets** | | X | | | | | X | |
| **Immune phenotyping** | | X | X | X | | X | X | X |
| **Functional immune assays** | | X | | X | | X | X | |
| **Gene expression profiling** | | X | | | | | X | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Immune activation markers** | | X | | X | | X | X | |

**Table 1:** Schedule of events during the study. (*blood draws on this day will occur 6h after administration of study drug). [1]CBC includes WBC, RBC, PLT, Hgb, Hct, MCV, MCH, RDW, MCHC, MPV. [2]Liver function tests include AST/ALT, TBili, DBili, Albumin. [3]Chemistry levels include Na, K, Cl, $HCO_3$, BUN, Crea, Glucose, Mg. [4]Women of childbearing potential only. ǂ**Number reflects time interval during which study visit should occur from Study Entry.**

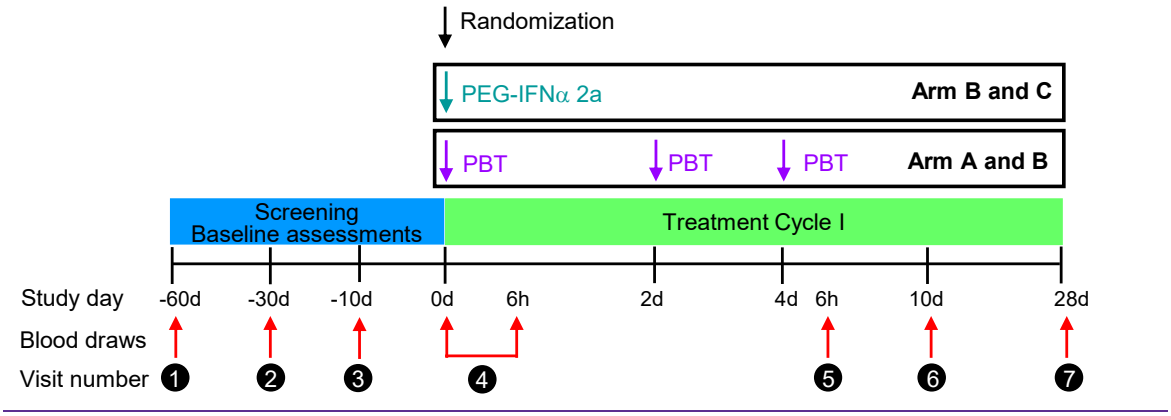


**Figure 1:** Study overview. PBT refers to panobinostat.

9.3.3 Treatment phase

Study entry will be defined as the day on which the first dose of study drug is administered (day=0, visit V3).

On this day, participants will have the following procedures performed:

- Perform a pregnancy test, ECG and vital signs/physical exam (including eye exam), as described in pre-treatment assessment (9.2.4).
- Review concomitant medications.
- Collect blood for baseline immunologic and virologic assays.
- Perform randomization to treatment Arm A or B or C.
- After the above procedures are completed, administer one s.c. dose of PEG-IFN-α2a in patients randomized to treatment Arm B and C.
- Immediately after the first administration of PEG-IFN-α2a, participants will be asked to take the first pill of panobinostat p.o., at the stage-specific dose if randomized to arm A or B.
- At 6h after administration of panobinostat, blood samples will be collected for virological, immunological and pharmacokinetic assays.
- 4-6 hours after administration of panobinostat, at the time of Cmax for panobinostat, a 12-lead ECG will be performed.
- On discharge, participants randomized to stage A or B will receive two more stage-specific panobinostat doses and will be instructed to take them in the mornings of study day 2 and day 4.

On Day 2, participants will be called by phone by one of the study investigators to discuss possible side effects. Participants will return on Day 4, six hours after administration of the third dose of panobinostat (visit V4), for collection of blood samples for virological, immunological and gene expression studies, as described in Table 1, and for an ECG. The full volume of blood to be collected on day 4 will only be collected if the most recently available hemoglobin level is $\geqslant$ 12.0 g/dL for men and hemoglobin $\geqslant$ 11.0 g/dL for women.

9.3.4 Post-treatment observation period

Participants will return for additional collection of blood samples for virological and immunological analyses on day 10 (visit V5) and 28 (visit V6) (see Table 1). Preceding each blood collection, the hemoglobin levels determined from the visit before (visit V4 and V5, respectively) will be used to assess the participant's ability to give blood. A minimum requirement of hemoglobin ⩾ 12.0 g/dL for men and hemoglobin ⩾ 11.0 g/dL for women will be used.

9.4 Long-term follow-up

All participants will be encouraged to follow-up with their primary HIV care providers after completion of this study, and to actively participate in age-appropriate screening exams recommended by the US Preventative Services Task Force (USPSTF, http://www.uspreventiveservicestaskforce.org). All participants will be entered into a study registry where they will be contacted once a year (by phone or in person) for 10 years after completion of their study participation to determine if any diseases that may be attributable to the study medication have occurred.

9.5 Early termination visit

Any participant who discontinues study treatment prematurely should be encouraged to continue to participate in all scheduled visits.

A participant may voluntarily discontinue participation in this study at any time. The investigator may also, at his or her discretion, discontinue the participant from participating in this study at any time. If a participant is prematurely discontinued from participation in the study for any reason, the investigator must make every effort to perform the following evaluations:

- Perform clinical evaluation.
- Review adverse events and concomitant medications.
- Obtain samples for laboratory tests:
    - Hematology (CBC/differential), Chemistry testing.
    - HIV RNA testing by Roche Taqman Version 2.0 assay.
    - CD4 T cell counts.
    - Collection of blood samples for virological and immunological assays.

9.6 Pregnancy

Women of childbearing potential will be required to have a negative urine pregnancy test prior to first study drug administration. Any woman who becomes pregnant during the study period will not receive any further study medication and will be followed for safety until the end of the study or until the outcome of the pregnancy, whichever is longer. The participant will be advised to have her infant undergo regular doctor's visits for 6 months following birth in order to assess and record any abnormal health outcomes.

In addition, if the participant continues her pregnancy, the patient is encouraged to prospectively register her pregnancy in the "Antiretroviral Pregnancy Registry" (In US and Canada: 1-800-258-4263, international: 910-256-0238).

## 10.0 STUDY MONITORING

10.1 Internal Safety Review Committee (ISRC)

This committee will consist of the following four individuals: Dr. Mathias Lichterfeld, Dr. Daniel Kuritzkes (study co-chairs), Dr. Rajesh Gandhi (protocol clinician) and Dr. Lu Zheng (protocol statistician).

The committee will meet by conference call every month during the trial or at an appropriate interval based on the pace of enrollment. A **quorum** of **three** Committee members is required for each scheduled meeting, teleconference or unscheduled meeting. A project manager will be responsible for tabulating all adverse events, distributing these tables to the members of the Internal Safety Review Committee and organizing the meetings.

The committee will review all adverse events that occur during the trial. The Internal Safety Review Committee will be responsible for forwarding the following reports to the Safety Monitoring Committee for immediate review:

a. Serious adverse events.

b. Grade 3 and 4 adverse events that are related to the study medication.

c. CD4 T cell count decline to <50% of relative CD4 cell count compared to baseline (average of the screening and pre-entry visits) that is not attributable to non-adherence with antiretroviral medication.

10.2 Safety Monitoring Committee (SMC)

This committee will consist of the following three individuals: Dr. Martin Hirsch (chair), Dr. Joseph Eron (member) and Dr. Rebecca Gelman (statistician).

A **quorum** of **all three** Committee members is required at scheduled meetings, teleconferences or unscheduled meetings. All members will have signed a Confidentiality Agreement. In addition, members will treat the reports, meeting discussions, minutes and recommendations of the SMC as confidential.

The committee will meet to review safety information at scheduled meetings two times per year during the study. Unscheduled meetings will be convened in case of serious adverse events or grade 4 toxicity events that are attributable to the study medication.

10.3 Definitions of Adverse Reactions

10.3.1 Adverse event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation participant that occurs after providing written informed consent for participation in a study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product or other protocol-imposed intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product or other protocol-imposed intervention, regardless of attribution.

An AE **does** include:

- Exacerbation of a pre-existing illness.
- An increase in frequency or intensity of a pre-existing episodic event or condition.
- A condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Continuous, persistent disease or symptoms present at baseline that worsen following the start of the study.
- Overdose of either study drug or concurrent medication, even when not associated with any signs or symptoms.
- Complications that occur as a result of protocol-mandated interventions (e.g. invasive procedures such as cardiac catheterizations).

An AE **does not** include:

- Pregnancy
- A medical or surgical procedure (e.g. surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure may be an AE.
- A pre-existing disease or condition present or detected at the start of the study that does not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalizations for cosmetic elective surgery, social and/or convenience admissions).
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (e.g. invasive procedures, modification of participant's previous therapeutic regimen). Intercurrent illnesses that occur after screening but before starting treatment, and that are not the result of protocol-mandated procedures, do not need to be captured as AEs.

10.3.2 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e. it does not include a reaction that, had it occurred in a more serious form, might have caused death).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly/birth defect.
- Is an event that required intervention to prevent permanent impairment or damage.
- Important medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered serious adverse events when, if based upon appropriate medical judgment, might jeopardize the participant and might require medical or surgical intervention to prevent one of the outcomes listed above.

10.4 Monitoring for Adverse Events

10.4.1 Recording of Adverse Events

The occurrence of adverse events should be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination, laboratory test, or other assessments.

Each reported AE or SAE will be described by its duration (i.e. start and end dates), suspected relationship to the study drugs, and grade of seriousness.

At each visit, the participant will have an opportunity to spontaneously mention any new medical problems. The investigator should inquire about adverse events by asking one of the following standard questions:

"Have you had any (other) medical problems since the last visit?"

"How have you felt since your last clinical visit?"

The investigators are responsible for the detection and documentation of events meeting the definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

10.4.2 Attribution of Adverse Events

Investigators must determine if there is a reasonable possibility that the study drugs caused or contributed to an AE or SAE. The relationship assessment should consider the following aspects:

- A temporal relationship between the event and the administration of the study drug
- A plausible biological mechanism for the event to cause the AE
- Another possible etiology for the AE
- Previous reports of similar AE associated with the study drug or other agents in the same drug class
- Recurrence of the AE after re-challenge or resolution after de-challenge, if applicable

The terms used to assess the relationship between an event and the study agents are:

- Related:

  There is a plausible temporal relationship between the onset of the AE and administration of the study drug(s) and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug(s); and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.

- Not Related:

  Evidence exists that the AE has an etiology other than the study drug (e.g. preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to study drug administration (e.g. cancer diagnosed 2 days after first dose of study drug).

When an AE is assessed as "not related" to the study agents, an alternative etiology, diagnosis or explanation should be provided. When new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required.

Expected adverse events are those adverse events that are listed or characterized in the Package Inserts or current Investigators' Brochures of the study drugs.

Unexpected adverse events are those not listed in the Package Insert or current Investigator's Brochure or are not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the Package Inserts or Investigators' Brochures.

10.4.3 Grading of Adverse Events

The intensity of adverse events will be graded according to the NIH Division of AIDS "System for Grading the Severity of Adult Adverse Events" in its most updated version (Version 2.0, November 2014). (http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf).

10.5 Reporting of Adverse Events

10.5.1 General Reporting Procedures

Any adverse event occurring during the study must be documented in the participant's study records, and on the AE or SAE pages of the case report form (CRF). The investigators will record all adverse events. A

causal relationship to study drug is not necessarily implied. The investigators are responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the medical officer of DAIDS, Dr. Larry Fox (LFOX@niaid.nih.gov), the FDA, appropriate IRB(s), and the companies providing the study drugs (Novartis and Genentech Inc.).

All SAEs will be reported to these institutions within 24h after the investigators are made aware of the event.

10.5.2 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and study treatment is initiated and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed prior to study treatment.

10.5.3 Reporting of Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is alright to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

10.5.4 Reporting of Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g. “more frequent headaches”).

10.5.5 Reporting of Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions or
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

10.5.6 Reporting of SAEs

All SAEs occurring between study entry and the end of study in each participant must be reported promptly once the investigator determines that the event meets the protocol definition of an SAE.

The initial notification should include, as a minimum, sufficient information to permit identification of:

- The reporter
- The participant
- Adverse event(s)
- Date of onset

The investigators will inform the local IRB, regulatory authorities (FDA), the Medical and Program officers assigned to the protocol at the Division of AIDS (DAIDS) at NIH, the Safety Monitoring Committee (SMC) and the medication suppliers (Novartis and Genentech Inc.) of any SAE within a maximum of 24 hours

after the investigators are made aware of the event using a dedicated SAE form. Facsimile transmission is the preferred method to transmit this information. In the event of a death or a serious adverse event determined by the investigator to be related to the study medication, receipt of the fax must be confirmed by a telephone call.

A separate set of SAE CRF pages should be used for each SAE. However, if at the time of initial reporting multiple SAEs are present that are temporally and/or clinically related, they may be reported on the same SAE CRF page.

The investigators should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms. New or updated information should be recorded on the originally completed SAE CRF pages with all changes signed and dated by the investigators.

**Primary Study Contact for Reporting of Serious Adverse Events:**
Massachusetts General Hospital, Infectious Disease Unit
Dr. Rajesh Gandhi, MGH pager # 36298
Dr. Mathias Lichterfeld, MGH pager #12897
Phone: 617-726-3819 (24h/24h)

10.5.7 Reporting of Deaths

All deaths that occur during the study period, regardless of attribution, will be reported to the appropriate parties as an SAE. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, "Unexplained Death" will be reported. A copy of any post-mortem findings, including histopathology, should be provided on an updated SAE CRF page.

10.5.8 Reporting of Pregnancy

If a participant becomes pregnant during the study, treatment will be discontinued (i.e. no additional dose of study medication will be given) and the Early Termination Visit procedures will be performed. The outcome of any pregnancy occurring during the study period (at a minimum, up to and including one month [minimum 30 days] after receiving the last treatment dose) in a participant treated with study medication must be reported. Although not considered an SAE, pregnancy should be reported similarly. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drugs should be reported as an SAE.

Any reports of pregnancy following the start of administration with the study drugs will be transmitted to the pharmaceutical companies supplying the study drugs within thirty (30) calendar days of the Awareness Date.

10.5.9 Reporting of Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior study drug exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

10.5.10 Contact information for Reporting of adverse events

For reporting of serious adverse events to the NIH DAIDS, the DAIDS Expedited Adverse Event Reporting Form (EAE form) should be used. This form can be found at the website of the DAIDS safety office (http://rsc.tech-res.com/safetyandpharmacovigilance) and is included in the appendix. This form will be emailed to Dr. Larry Fox, the assigned medical officer at DAIDS (LFOX@niaid.nih.gov).

For adverse event reporting to Genentech Inc., reports should be faxed to Genentech Drug Safety at the following numbers: (650) 225-4682 or (650) 225-5288. A cover sheet for fax transmission is included in the appendix of this protocol. Occasionally, Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request. For questions regarding SAE reporting to Genentech, the Genentech Drug Safety Office should be contacted at (888) 835-2555.

For adverse event reporting to Novartis, reports should be faxed to the Local Novartis Drug Safety and Epidemiology Safety Desk using the fax number (877) 778-9739. A cover sheet for fax transmission is included in the appendix of this protocol.

10.5.11 Reconciliation

In all safety reporting, the Sponsor agrees to conduct reconciliation for the product. Genentech, Novartis and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

10.6 Reporting to FDA

Since this is an Investigator-Sponsored IND Study, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80. Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines:

- *7 Calendar Day Telephone or Fax Report:*

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of panobinostat or pegylated IFN-α2a. An unexpected adverse event is one that is not already described in the Investigators' Brochures for the study drugs. Such reports are to be telephoned or faxed to the FDA and the collaborating pharmaceutical companies within 7 calendar days of first learning of the event.

- *15 Calendar Day Written Report*

The Investigators are also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of the study drugs. An unexpected adverse event is one that is not already described in the Investigators' Brochures for the study drugs.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, the collaborating pharmaceutical companies, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a Medwatch 3500 form, but alternative formats are acceptable (e.g. summary letter). The FDA fax number for IND Safety Reports is: 1 (800) FDA-0178.

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety (Fax: (650) 225-4682 or (650) 225-5288), to Novartis Drug Safety ((877) 778-9739) and to the IRB (phone: 617-424-4148).

- *IND Annual Reports*

IND annual reports will be submitted to the FDA by the Sponsor-Investigator. Copies of such reports should be faxed to Genentech Drug Safety (Fax: (650) 225-4682 or (650) 225-5288) and to Novartis Drug Safety ((877) 778-9739).

Any other study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech and Novartis. This includes the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech and Novartis. Copies of such reports should be mailed to the assigned Genentech Clinical Operations contact for the study: pegasys-gsur@gene.com.

10.7 Follow-up of Adverse Events

All AEs and SAEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the participant is lost to follow-up. The investigators are responsible to ensure that follow-up includes any supplemental investigations that may be indicated to elucidate as completely as practical the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

10.8 Contraindications to further administration of study drugs

Clinical events listed below constitute absolute **contraindications to further administration** of the study medication; if any of these events occur during the study, the participant must not receive additional doses of the investigational product but may continue other study procedures at the discretion of the investigators. The participant must be followed until resolution of the event, as with any adverse event.

- Early or delayed hypersensitivity reactions
- Pregnancy

The following adverse events constitute **contraindications to administration** of the study medication **at that point in time**; if any one of these adverse events occurs at the time scheduled for administration of the study drugs, administration of study drugs will be delayed for a maximum of one week or withdrawn from study participation at the discretion of the investigators. The participant must be followed until resolution of the event, as with any adverse event (see Section 10.7).

- Acute disease, defined as the presence of a moderate or severe illness with or without fever. However, study medication can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e. oral temperature < 100.5F.
- Oral temperature of ≥ 100.5F

10.9 Criteria for Study Continuation to stage 2 and 3

After completion of stage 1, all safety data will be reviewed by the internal safety review committee (ISRC), the external safety monitoring committee, the IRB and the FDA. The study can only proceed to stage 2 if all of these committees agree that the safety profile in stage 1 is acceptable. A similar interim review will occur after completion of stage 2 to determine study progression to stage 3.

Dose escalation criteria are defined as:

a) No more than one subject has experienced a ≥ Grade 3 toxicity event that is related to study treatment (as judged by the investigators) prior to or on Day 28 after the treatment administration; however, if

grade 3 toxicity events are limited to clinically insignificant laboratory abnormalities, the independent SMC may, after a detailed review of all safety events, allow progression of the study to the next stage.

b) None of the subjects have experienced a serious or worse AE or toxicity that is Grade ⩾ 4 and related to study treatment (as judged by the investigators) prior to or on Day 28 after the treatment administration.

c) No patient has experienced a cardiac ischemic event or shown ECG evidence of myocardial ischemia during the study treatment.

## 11.0 TOXICITY MANAGEMENT

It is possible that some participants will experience transient or prolonged adverse effects during the trial. The following guidelines should be followed for managing toxicity of the study medication.

### 11.1 Early or delayed hypersensitivity reactions

Early or delayed hypersensitivity reactions constitute absolute **contraindications to further administration** of the study medication. If any of these adverse events occur during the study, the participant must not receive additional doses of the investigational products but may continue other study procedures at the discretion of the investigators. The participant must be followed until resolution of the event, as with any adverse event.

### 11.2 Grade 2 adverse events

Participants experiencing grade 2 AE(s), which the patient believes is/are tolerable and in the Investigators' judgment is/are acceptable, may continue treatment at the current dose and schedule. More frequent patient monitoring may be required, and participants must be informed to contact the Investigators immediately if there is any worsening of symptoms. If a patient experiences new (or treatment emergent) grade 2 AE(s) considered at least possibly related to the study medication, and which the patient finds intolerable or in the Investigators' judgment is/are not acceptable, treatment must be held until the AE(s) resolves to grade ≤ 1. Study treatment may then be restarted at the same dose and schedule. If the same intolerable grade 2 AE(s) occurs again, the study treatment must again be temporarily discontinued until the toxicity resolves to grade ≤ 1. At the discretion of the Investigators, participants with repeated grade 2 AEs of major organs (e.g. heart, lungs, CNS) may be discontinued from further study treatments.

### 11.3 Grade 3 and Grade 4 adverse events

If a study participant develops a grade 3 or 4 adverse event that is assessed as being related to the study medication, the person must not receive additional doses of the study medication but may continue other study procedures at the discretion of the investigators. The participant must be followed until the resolution of the event.

| TOXICITY | | ACTION |
|---|---|---|
| Diarrhea | Grade 2: Persistent episodes of unformed to watery stools OR increase of 4-6 stools over baseline per 24h period. | Use anti-diarrheal medication. Correct electrolytes. Dosing of study medication may continue at current level. |
| | Grade 3: Bloody diarrhea OR increase of >7 stools per 24h period OR fluid replacement indicated | Discontinue dosing permanently, unless diarrhea is attributed to alternative disease such as C. diff infection or Norovirus infection. |
| | Grade 4: Life threatening consequences (e. g. hypotensive shock) | |
| Nausea/Vomiting | Grade 2: Persistent nausea resulting in decreased oral intake for 24-48h | Discontinue dosing. |
| | Grade 3-4: per DAIDS/NIH criteria | |
| Total bilirubin | Grade 2: 1.6x to < 2.6x ULN | Discontinue dosing. |
| | Grade 3: 2.6x to < 5x ULN | |
| | Grade 4: > 5x ULN | |
| AST/ALT Elevations | Grade 2: up to 5x ULN | Discontinue dosing. |
| | Grade 3: up to 10x ULN | |
| | Grade 4: > 10x ULN | |
| **Table 2:** Management of GI Toxicity | | |

Participants who experience a grade 3 or grade 4 adverse event not attributable to the investigational products or are confined to asymptomatic laboratory abnormalities may be allowed to continue treatment at the investigators' discretion, unless regulated otherwise in Tables 2-4.

11.4 Specific management of panobinostat and PEG-IFN-α2a toxicity

11.4.1 Diarrhea

Diarrhea is a recognized side effect of panobinostat, although the frequency of diarrhea with low-dose panobinostat is expected to be low. Each patient should be instructed to have loperamide readily available and to begin treatment for diarrhea at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient.

| TOXICITY | | ACTION |
|---|---|---|
| Thrombocytopenia | Grade 2 (PLT 50,000-99,999/ul) | Discontinue dosing. |
| | Grade 3 (PLT<50,000/ul)<br>Grade 4 (PLT <25,000/ul) or | |
| Neutropenia | Grade 1 (ANC 800-1000/ul) | none |
| | Grade 2 (ANC 600-799/ul) | If ANC >750/ul, patient may continue study drugs<br>If ANC <750/ul, discontinue dosing permanently |
| | Grade 3 (ANC 400-599/ul) | Discontinue dosing permanently. |
| | Grade 4 (ANC <400) | |

| | | |
|---|---|---|
| Anemia | Grade 2 (Hgb 9 < 10g/dL) | If clinically asymptomatic, no change in dosing. Phlebotomy-related blood loss should be considered when deciding to continue dosing. |
| | Grade 3 (Hgb 7 < 9g/dL) | Discontinue dosing. |
| | Grade 4 (Hgb <7g/dL) | |
| **Table 3:** Management of hematologic toxicity | | |

Loperamide 4 mg should be taken at the first loose stool or more frequent than usual bowel movements, followed by 2 mg as needed, no more frequently than every 4 hours, not to exceed a total of 16 mg in 24 hours. Participants with diarrhea grade ≥ 2 despite this loperamide regimen should be managed as described in Table 2. Additional treatment should be provided in accordance with institutional standard of care and/or local guidelines. Premedication with loperamide is not recommended. The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Participants should be advised to contact their physician to discuss any laxative use.

11.4.2 Nausea, Vomiting, liver toxicity

Nausea, vomiting and liver toxicity should be managed according to Table 2.

11.4.3 Hematologic toxicity

Both PEG-IFNa2a and panobinostat can cause hematologic toxicity. Hematologic toxicity during the study should be managed per Table 3.

11.4.4 QTc prolongation

Panobinostat can cause prolongation of the QTc interval in ECGs, although clinically significant QTc prolongation is unlikely with low dose panobinostat.

ECGs will be performed during the screening/pre-entry visits as well as during the treatment week. Guidelines for the management of QTc prolongation in the context of this study are provided in Table 4. All cardiac events should be treated as per the local standard of care and referred to a cardiologist if clinically indicated. Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to QTc prolongation should be discussed with the study chairs.

| QTc ABNORMALITY | ACTION |
|---|---|
| QTc ≥450 msec (men) or ≥470msec (women) OR >60 msec increase from baseline average | Check and correct serum potassium and magnesium if indicated.<br>Discontinue dosing. |
| Average QTc ≥500 msec | |
| **Table 4:** Management of QTc interval prolongation during treatment | |

11.5 Abnormal CD4 T cell counts

For any CD4 T cell decline of 50% or greater, or if the CD4 T cell count is <200/mm$^3$, the participant will be contacted and asked to return for a repeat test as soon as the participant is available. If repeated

measurements of CD4 T cell counts confirm an absolute CD4 T cell decline of 50% or more relative to baseline (average of screening and pre-entry values) or an absolute CD4 T cell decline below 200/$mm^3$ cells, the results should be discussed with the study chairs. The chairs will discuss these results with the patient's primary HIV clinician and may decide to continue the study medication with close monitoring of CD4 T cells if the relative CD4 T cell count is ≤5 percentage points lower from the baseline relative CD4 T cell count.

11.6 Adverse reactions due to ART

Any participant experiencing an AE that is attributable to background ART may have the event treated according to recommendations in the package insert(s) of the product(s) or current treatment guidelines. Irrespective of possible causality, all non-serious AEs and SAEs must be recorded in the CRF. All changes to a participant's ART regimen should be discussed with the study co-chairs and must be accurately recorded on the CRF.

11.7 Other abnormal laboratory or clinical findings

Abnormal laboratory tests and abnormal clinical findings will be categorized using a standard grading scale described before.

Abnormal laboratory findings (e.g. clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g. ECGs, X-rays, vital signs) that are judged by the investigators as **clinically significant** will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 10.3.1 ("Definition of an AE"), or SAE, as defined in Section 10.3.2 ("Definition of a SAE"). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigators as more severe than expected for the participant's condition, or that are present or detected at the start of the study and do not worsen, will **not** be reported as AEs or SAEs.

Participants with grade 3 and 4 asymptomatic and clinically insignificant laboratory abnormalities may continue to receive cART and remain on the treatment schedule at the investigators' discretion, unless regulated otherwise in Tables 2 to 4.

Any abnormal clinical finding will be reported as an SAE if it meets the criteria defined above.

11.8 Antiretroviral treatment failure

HIV treatment failure is defined as a confirmed HIV-1 RNA increase to >400 copies/mL for more than 4 weeks. This level is higher than typical in clinical trials, due to the fact that panobinostat can increase plasma HIV- RNA as a result of increased transcription (not replication).

An increase in viral load to >1000 copies/mL among study participants should be confirmed with repeat testing on samples obtained at least 7 days apart. If there is a confirmed increase to >1000 copies/mL in plasma HIV-1 RNA viral loads in participants on ART, a plasma specimen should be obtained and sent for evaluation of antiretroviral drug resistance. Confirmed HIV-1 relapse specimens must have repeated detection of >1000 copies/mL for successful HIV-1 drug resistance testing.

Clinical management of HIV-1 virologic breakthrough and treatment failure will be handled by the investigators according to current HIV treatment guidelines.

# 12.0 TERMINATION RULES

## 12.1 Termination rules for individual participants

### 12.1.1 Participant Withdrawal from Study

Participant withdrawal from study is defined as any participant who does not complete the final follow-up visit or an early termination visit defined in this protocol. Reasons why a study participant does not complete final visits can include:

- Participant request (withdrawal of consent)
- Protocol violation
- Adverse events or reactions
- Any condition, interaction, or contraindication where continued participation in the study will result in an unacceptable risk for the participant, as assessed by the Investigators or advisers
- Discontinuation of the study by the Sponsor
- Lost to follow-up
- Investigator determination in consultation with study co-chairs, e.g. for repeated non-adherence to study protocols

Investigators will contact participants who fail to return for planned visits and if possible schedule a new visit. Information related to study withdrawal is documented in the CRF including the reason for withdrawal, date of withdrawal, and whether the participant or Investigators made this decision. Participants withdrawn from the study will contribute with data for the statistical analyses until the date of withdrawal. Participants withdrawn from the study will resume routine treatment following standard treatment guidelines.

### 12.1.2 Withdrawal from the investigational drug

Withdrawal from the investigational drug is defined as a participant who discontinues study treatment but agrees to continue follow-up until completion of the study. Any participant who withdraws from the investigational drug after having received at least one dose of study medications will be asked to return for all subsequent study visits. If withdrawal from the investigational drug is due to adverse events, this will be followed up as detailed under 10.7.

Study participant will be withdrawn from the investigational drug in case of the following events:

- Participant request (withdrawal of consent)
- Pregnancy
- Development of a grade 3 or 4 adverse event that is related to the investigational products. Participants with grade 3 or 4 adverse events limited to laboratory abnormalities without clinical signs and symptoms or are clearly attributable to other diseases may be allowed to continue
- Early or delayed hypersensitivity reaction
- Investigator determination in consultation with study co-chairs, e.g. for repeated non-adherence to study protocols
- Termination of the study by the Protocol Safety Monitoring Committee, NIAID, FDA or the pharmaceutical companies providing the investigational agents
- Any condition, interaction, or contraindication where continued participation in the study will result in an unacceptable risk for the participant, as assessed by the Investigators or advisers

Information related to withdrawal from the investigational drug is documented in the CRF including the reason for withdrawal, date of withdrawal, and whether the participant or Investigators made this decision. Participants withdrawn from the investigational drug will contribute with data for the statistical analyses until the date of withdrawal. Participants withdrawn from the investigational drug will resume routine treatment and control at the Department of Infectious Diseases following standard treatment guidelines.

12.2 Temporary suspension of all study drug administration in all study participants

The following events will trigger a temporary suspension of all study drug administration:

- Development of a grade 4 adverse event that is related to the study medication
- At least two participants experience sustained antiretroviral treatment failure that is not attributable to non-adherence with antiretroviral medications. Sustained HIV rebound is defined as HIV RNA levels >400 copies/mL for longer than a 4-week period.
- At least two participants experience a significant and sustained CD4 T cell count decline that is not attributable to non-adherence with antiretroviral medications. A significant and sustained CD4 T cell count decline is defined as two measurements taken at least two weeks apart of either a) CD4 T cell counts that are <50% of the baseline relative CD4 T cell count (average of screening and pre-entry values) or b) CD4 T cell counts <200/$mm^3$.

The SMC will review these events to determine if any study procedures should be changed. After this review, the SMC may allow the study to continue. A quorum of three Committee members is required for the review of the event(s) and for providing recommendation. The FDA will be informed in the event that temporary suspension of study medication occurs.

12.3 Permanent suspension of all study medication in all study participants

After review and confirmation by the SMC, permanent suspension of all study medications will be considered if:

- Two or more participants who received study medication develop any grade 4 adverse event that is related to the study medication.
- Two or more participants experience sustained antiretroviral treatment failure not attributable to non-adherence with antiretroviral medication.
- Two or more participants experience a significant and sustained CD4 T cell count decline that is not attributable to non-adherence with antiretroviral medications.
- At the request of the pharmaceutical companies providing the investigational agents (Novartis AG and Roche AG).

The SMC will review the event to determine if any study procedures should be changed. After this review, the SMC may allow the study to continue. A quorum of three Committee members is required for evaluation of the event(s) and for providing recommendation. The final decision for study suspension remains with the Sponsor. The FDA will also be informed in the event that permanent suspension of study medication occurs.

## 13.0 SAMPLE HANDLING AND ANALYSIS

13.1 Treatment and Storage of biological samples

Whole blood and serum will be collected in standard collection tubes containing EDTA or Heparin as anticoagulant. PBMC for virological and immunological assays will be extracted by Ficoll density centrifugation and cryopreserved according to standard procedures.

13.2 Standard laboratory assays

The following measurements will be performed when indicated in Table 1.

13.2.1 Virology

Screening HIV-1 RNA tests must be performed using the Roche Taqman version 2.0 assay by a laboratory that possesses CLIA certification or its equivalent. Eligibility will be determined based on the screening value.

13.2.2 Chemistry

Sodium, potassium, chloride, BUN, $HCO_3^-$, creatinine, ALT (SGPT), AST (SGOT), and total bilirubin will be measured in the clinical laboratory of the Massachusetts General Hospital according to standard procedures.

13.2.3 Hematology

Hemoglobin, mean corpuscular volume (MCV), white blood cell count (WBC), differential WBC, platelet count, partial thromboplastin time, prothrombin time will be measured in the clinical laboratory of the Massachusetts General Hospital according to standard procedures.

13.2.4 Other laboratory studies

TSH, HBsAg, HBV DNA PCR, HCV Ab and HCV RNA PCR will be done at the local clinical laboratories of MGH.

13.3 Virologic assays for HIV-1 reservoir quantification

The following virological assays will be performed for measuring effects of the study medication on size of the viral reservoir.

13.3.1 CD4 T cell-associated HIV-1 RNA

Unspliced HIV-1 RNA in isolated CD4 T cells will be measured using established protocols to determine the influence of the study medication on HIV-1 RNA transcription.

13.3.2 Proviral HIV-DNA in CD4 T cells

Proviral HIV-1 DNA will be analyzed in isolated total CD4 T cells, using optimized protocols for quantitative analysis of HIV-1 DNA. Analysis of proviral HIV-1 DNA in sorted naive, central-memory, effector-memory, terminally-differentiated CD4 T cells and CD4 T memory stem cells will be performed if sufficient PBMC are available.

13.3.3 Analysis of integrated HIV-1 DNA and HIV-1 2-LTR circles.

If sufficient PBMC are available, chromosomally integrated HIV-1 DNA and viral 2-LTR circles will be analyzed using DNA extracted from CD4 T cells, according to established experimental protocols.

13.3.4 HIV Reactivation Assay

This assay is performed to assess changes in the functional HIV-1 reservoir after study treatment. The majority of the proviral HIV DNA sequences is defective virus not capable of completing replication cycles and therefore not able to drive viral rebound in the absence of cART. The HIV reactivation assay measures changes in the frequency of cells latently infected with replication competent virus, i.e. integrated HIV DNA capable of resuming viral replication once reactivated. As an alternative to HIV reactivation assays, the TILDA assay or full-genome HIV-1 sequencing assays will be considered.

13.3.5 Residual HIV-1 plasma RNA

Residual plasma viremia will be determined by single-copy assay (SCA). This assay is a real-time PCR-based method that can accurately quantify far lower levels of viremia than currently available commercial assays[53].

13.3.6 Phylogenetic studies

Cell-associated and plasma HIV-1 RNA and cell-associated HIV-1 DNA will be subjected to viral sequencing studies to investigate phylogenetic associations between reactivated virus in CD4 T cells, plasma viral sequences and proviral HIV-1 DNA in total CD4 T cells and specific CD4 T cell subsets.

13.4 Immunologic Assays

13.4.1 Immune phenotyping

Phenotypic characteristics of different leukocellular subsets during treatment with study medication will be analyzed using standardized flow cytometry or cytometry-by-time-of-flight assays (CyTOF). Activation, maturation and differentiation markers of CD4 and CD8 T cells, B cells, NK cells, regulatory T cells, myeloid and plasmacytoid dendritic cells will be analyzed.

13.4.2 Functional immunologic assays

The functional assays described below will be considered:

13.4.2.1 Cytokine secretion assays

Cytokine in CD4, CD8 T cells and NK cells will be measured using intracellular cytokine staining protocols, followed by flow cytometric/CyTOF analysis.

13.4.2.2 Cytotoxicity assays

Cytotoxic activities of NK cells and cytotoxic T cells will be analyzed by flow cytometry- or CyTOF-based intracellular quantification of cytotoxic granules, and/or by cellular degranulation assays.

13.4.2.3 Proliferation assays

Proliferative activities of HIV-1-specific CD8 T cells will be analyzed after CFSE staining, using in vitro tissue culture assays.

13.4.2.4 Elispot assays

The magnitude and breadth of HIV-1-specific CD8 T cells will be analyzed by interferon-γ elispots, using established protocols.

13.4.3 Analysis of immune activation

Immune activation will be determined by proportions of CD38/HLA-DR positive CD4 and CD8 T cells. The following soluble markers of immune activation will be considered: 2D-Dimer, IL-6, hs-CRP, IP-10.

13.5 Gene Expression Profiling

Gene expression intensities of interferon-stimulated genes will be analyzed using PCR or microarray-based assays.

13.6 Immunogenetic Studies

HLA class I alleles and SNPs in the region of the IL-28B gene locus (rs12979860, rs8099917, rs12980275) will be typed in all study participants using standard protocols.

13.7 Exploratory Analyses

Other exploratory virological and immunological parameters may be analyzed, as new assays may become available. The PBMCs and serum collected for storage will be used for these exploratory assays.

## 14.0 DATA EVALUATION AND STATISTICAL ANALYSIS

14.1 Co-primary Endpoints

- The cumulative frequency and severity of grade ≥ 1 adverse events, grade ≥ 1 laboratory abnormality, and other serious adverse events (SAEs) during the one week treatment period.
- Changes from baseline in the reservoir of HIV-1 infected CD4 T cells, measured on a log scale using assays to evaluate CD4 T cell-associated proviral HIV-1 DNA, after completion of the combined treatment (on day 10 after study initiation) in treatment arm A vs. treatment arm B vs. treatment arm C.

14.2 Secondary Endpoints

- Change from baseline in the levels of infectious viral units per million CD4 T cells (IUPM) as determined by viral outgrowth assays and TILDA assays after study completion.
- Change from baseline in histone H3 acetylation in CD4 T cells during treatment with the study medication, as determined by changes in the acetylated H3 mean fluorescence intensity determined by flow cytometry.
- Change from baseline in levels of CD4 T cell-associated HIV-1 RNA during treatment with study medication, determined by qRT-PCR.
- Change from baseline in levels of plasma HIV-1 RNA during treatment with study medication, determined by single-copy assay or standard HIV-1 plasma assays.
- Change from baseline in levels of CD4 T cell-associated HIV-1 2-LTR circles and chromosomally integrated proviral HIV-1 DNA during treatment with study medication.
- Change from baseline in levels of HIV-1 DNA in different CD4 T cell subsets (naïve, T memory stem cells, central-memory, effector-memory, terminally-differentiated) during treatment with study medication.
- Change from baseline in frequency and function of innate and adaptive immune effector cell responses during treatment with study medication, as determined using phenotypic and functional immunologic assays.
- Change from baseline in levels of cellular and soluble immune activation markers during treatment with study medication, as determined by ELISA assays, luminex assays and flow cytometry.
- Change from baseline in expression patterns of interferon-stimulated genes (ISG) during treatment with study medication.
- Comparison of all immunological and virological parameters in study participants treated with IFN-α and panobinostat stratified according to HLA class I and IL-28B genotypes.

14.3 Sample Size Considerations

The primary efficacy analysis will compare changes from baseline to post-treatment HIV-1 DNA changes between the randomized treatment arms in stage 3. Allowing for one unevaluable participant in each arm due to lost to follow-up, ART discontinuation and/or other reasons, and under the assumption that a common standard deviation of change (measured as difference of log10 transformed HIV-1 DNA copies/million CD4 T cells) in all treatment arms is 0.436 (derived from baseline to end-of-study change in

the CLEAR study), the study with N=18 participants (9 evaluable participants treated with panobinostat and PEG-IFN-α2a and 3 each treated with panobinostat or PEG-IFN-α2a alone) will have 80% power to detect an effect size of 0.82 $\log_{10}$ (6.6-fold) in change of proviral CD4 T cell-associated HIV DNA level from baseline to day 10 in participants treated with panobinostat and PEG-IFN-α2a compared to participants treated with panobinostat or PEG-IFN-α2a only using a one-sided Wilcoxon rank sum test on a level of alpha=0.05, assuming a normal distribution. The above power estimation does not take into account of multiple comparisons for this pilot study.

| | N =8 | N =8 |
|---|---|---|
| True Probability | Probability of at least 1 event | Probability of at least 2 events |
| 0.01 | 0.08 | 0.00 |
| 0.05 | 0.34 | 0.06 |
| 0.10 | 0.57 | 0.19 |
| 0.12 | 0.64 | 0.25 |
| 0.15 | 0.73 | 0.34 |
| 0.20 | 0.83 | 0.50 |
| **Table 7:** Probability of safety endpoints in stage 1 and 2. | | |

Regarding the assessment of safety, Table 7 and Table 8 display the probability of observing at least one or two participants with primary safety event with n=8 and 18 receiving study treatment. If the true probability is 10%, the study will have >57% probability of observing at least one participant with primary safety event in Stage 1 and 2 with 8 participants. The probability will be 85% for Stage 3 with N=18 participants.

| | N =18 | N =18 |
|---|---|---|
| True Probability | Probability of at least 1 event | Probability of at least 2 events |
| 0.01 | 0.17 | 0.01 |
| 0.05 | 0.60 | 0.23 |
| 0.10 | 0.85 | 0.55 |
| 0.12 | 0.90 | 0.65 |
| 0.15 | 0.95 | 0.78 |
| 0.20 | 0.98 | 0.90 |
| **Table 8:** Probability of safety endpoints in stage 3. | | |

## 14.4 Final Analyses

### 14.4.1 Analysis of demographics

Demographic characteristics (age, gender and race) and health status characteristics (baseline CD4 counts, nadir CD4 T cell counts, pre-ART HIV-1 RNA levels, cART duration) will be tabulated by randomized treatment.

### 14.4.2 Analysis of safety

For the safety analysis, AEs and SAEs will be recorded as described in this protocol and will be summarized in terms of frequency, severity and level of attribution to the study medication. Data will be reported as the

absolute and relative number of participants experiencing at least 1 event, the total number of events, the type of events, and the causality assessment. Due to the low expected safety event rates (based on the prior clinical study with panobinostat in HIV-1 participants), the study is not powered to do a formal statistical comparison between the randomized arms. AE rates will be presented for descriptive purposes.

14.4.3 Statistical analysis of virological and immunological data

The primary efficacy endpoint is the change from baseline to day 10 in the number of HIV-1 infected CD4 T cells, as assessed by proviral CD4 T cell-associated HIV-1 DNA levels determined on a log-scale. The null hypothesis of no difference in the primary efficacy endpoint between the randomized treatments will be tested using a one-sided Wilcoxon rank sum test. The null hypothesis will be rejected with a $p<0.05$.

Changes in the frequency of HIV-1-infected CD4 T cells (determined by levels of CD4 T cell-associated proviral HIV-1 DNA) from baseline to completion of the treatment phase will also be summarized as secondary efficacy endpoints and compared between the two randomized treatments. Mean and quartile plots will be used to summarize these efficacy endpoints at each visit. If feasible with the modest sample size, longitudinal data methods will also be used to evaluate and estimate treatment effects.

Analysis for the primary efficacy endpoint will use a modified intent-to-treat analysis, limiting to participants who have received at least one dose of randomized treatment and have data at baseline and day 10. Participants who go off ART, experience virologic failure or discontinue study participation for other reasons will be excluded from the efficacy analysis. For this analysis, mixed models with repeated measures will be considered (MMRM). Missing data will be managed using guidelines defined by the National Research Council[54].

Primary safety endpoints will be tabulated by Cohorts and randomized treatments.

Analyses of secondary virologic and immunologic outcomes will parallel the primary analyses outline above.

Baseline immunologic and virologic parameters will be assessed at multiple pre-entry timepoints (see Table 1). For analysis of primary and secondary endpoints, the mean of multiple baseline assessments will be used.

Secondary analyses of all immunologic and virologic parameters stratified by genetic polymorphisms (in HLA and IL-28B genes) will also be carried out.

Associations between changes in the various virologic and immunologic measurements will be evaluated using scatterplots and correlation coefficients.

## 15.0 DATA MANAGEMENT

15.1 Data Management

All study patient visits will be documented by the study nurses and physicians on case report forms provided by the sponsor. A study data manager will be responsible for storing these patient-related data in paper or electronic form at a central repository in the hospital.

15.2 Confidentiality

Data on participants enrolled will be coded with a non-identifiable number. Access to confidential data such as participant identifiers and specific demographic data will be restricted to only those research team members for whom access is necessary, as defined by the study sponsor.

## 16.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by requirements for authorship promulgated by the International Committee of Medical Journal Editors (ICMJE), which have been adopted by many biomedical journals and are posted on its website at http://www.icmje.org. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical companies and DAIDS providing the investigational drugs at least thirty (30) days [or, for abstracts, at least five (5) working days] prior to submission.

## 17.0 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 NIH.

All infectious specimens will be transported using packaging mandated in the Code of Federal Regulations, CDC 42 CFR Part 72. Please also refer to individual carrier guidelines, e.g. FedEx, Airborne, for specific instructions.

## 18.0 PROTOCOL REGISTRATION

### 18.1 Introduction

Prior to implementation of this protocol, and any subsequent full version amendments, the study site must have the protocol and the protocol informed consent form approved, as appropriate, by the local institutional review board (IRB)/ethics committee (EC) 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.

### 18.2 Initial Registration

Site-specific informed consent forms (ICFs) *WILL NOT* be reviewed or approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

### 18.3 Amendment Registration

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, the study site should implement the amendment immediately. The study site is 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 ICF(s) *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 Amendment Registration Notification 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.

## 19.0 REFERENCES


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## 20.0 APPENDIX:

20.1 Genentech Safety Reporting Fax Cover Sheet

**SAFETY REPORTING FAX COVER SHEET**

**GENENTECH SUPPORTED RESEARCH**

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

| | |
|---|---|
| Genentech Study Number | |
| Principal Investigator | |
| Site Name | |
| Reporter name | |
| Reporter Telephone # | |
| Reporter Fax # | |

| | |
|---|---|
| Initial Report Date | [DD] / [MON] / [YY] |
| Follow-up Report Date | [DD] / [MON] / [YY] |

| | |
|---|---|
| Subject Initials<br>(Enter a dash if patient has no middle name) | [ ] - [ ] - [ ] |

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

20.2 Novartis Safety Reporting Fax Cover Sheet

NOVARTIS

**Interventional Clinical Trial SAE Fax Cover Sheet**

To: Local Novartis Drug Safety and Epidemiology Safety Desk

Fax Number: 877-778-9739

Investigator contact details:

Fax number : _____

Phone number : _____

| | |
|---|---|
| Study Name | |
| Centre Number | |
| Patient Number | |

Relationship between study treatment and event(s) is:

# Suspected/Unknown

*This document contains important safety information.*

*If fax is received in error, please forward to +44 1403 323500*

Version 1.0, 01_Jul_2010

NOVARTIS

**Interventional Clinical Trial SAE Fax Cover Sheet**

To: Local Novartis Drug Safety and Epidemiology Safety Desk

Fax Number: 877-778-9739

Investigator contact details:

Fax number : _____

Phone number : _____

| | |
|---|---|
| Study Name | |
| Centre Number | |
| Patient Number | |

Relationship between study treatment and event(s) is:

# Not Suspected

*This document contains important safety information.*

*If fax is received in error, please forward to +44 1403 323500*

20.3 DAIDS Expedited Adverse Event Reporting Form (EAE form)

## Division of AIDS Safety Office
## EXPEDITED ADVERSE EVENT (EAE) Reporting Form

*Please type or print in English*

**Why are you not using DAERS?**

**Reason for submitting report beyond the 3 reporting days** (if applicable)**:**

| SENDER INFORMATION | | |
|---|---|---|
| **To:** DAIDS SAFETY OFFICE | **Sender Name:** | |
| **Fax:** 1-800-275-7619 (USA) or + 1-301-897-1710 (International) | **Phone:** | **Fax:** |
| **Phone:** 1-800-537-9979 (USA) or + 1-301-897-1709 (International) | **E-mail:** | |
| **E-mail:** RCCSafetyOffice@Tech-Res.com | **Date Sent:** (DD/MON/YYYY) | **No. of Pages:** (including this cover sheet) |

| REPORTER AND SITE INFORMATION | | |
|---|---|---|
| **Site Name:** | **Site ID:** | |
| **Site Awareness Date:** DD/MON/YYYY | **Site Report Date:** DD/MON/YYYY | |
| **Reporter Same as Sender? YES ☐ NO ☐** If YES, do not repeat contact information provided above. | **Reporter Name:** | |
| | **Phone:** | **Fax:** |
| | **E-mail:** | |

| KEY EAE REPORT INFORMATION | |
|---|---|
| **Participant ID:** | **Protocol No(s)/Version No(s):** |
| **New Report:** ☐ (Send all pages of the completed form.) **Update Report:** ☐ (Provide date of original report.) | **Date of Initial Report:** DD/MON/YYYY |
| **Pages:** ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ ALL ☐ OTHER (For Update Reports, submit only updated pages. Check all that apply.) | |

| - - - - SAFETY OFFICE USE ONLY - - - - | |
|---|---|
| **Received Date Stamp:** | |
| **AE NUMBER:** ☐☐☐☐☐☐☐☐☐☐ | **PROTOCOL NUMBER(S):** |
| **Report Received By:** ☐ Fax ☐ E-mail ☐ Express Mail | |

EAE Reporting Form v2.0 27/APR/2010

Participant ID: _____ Site Report Date: _____ DD/MON/YYYY

| 1. | PARTICIPANT INFORMATION For each question below, please check the appropriate box. | |
|---|---|---|
| **Date of Birth:** _____ DD/MON/YYYY *OR* **Age at time of event:** ___ ☐ Days * ☐ Months* ☐ Years * *Pediatric Studies Only* | | |
| **Sex at Birth:** ☐ Male ☐ Female ☐ Unknown | **Height:** _____ ☐ cm ☐ in | |
| **If Female, Pregnant?:** ☐ Yes ☐ No ☐ Unknown (**If Yes**) **Duration**: ___ week(s) | **Weight:** _____ ☐ kg ☐ lb | |
| **Ethnicity:** ☐ Hispanic or Latino ☐ Non-Hispanic or Latino ☐ Unknown ☐ Not Reported ☐ Other _____ | **Race:** ☐ American Indian or Alaska Native ☐ Black or African American ☐ White ☐ Native Hawaiian or Other Pacific Islander ☐ Asian ☐ Not Reported ☐ Unknown ☐ Other _____ | |

Participant ID: _____ Site Report Date: _____ DD/MON/YYYY

| 2. | PRIMARY ADVERSE EVENT | | | | |
|---|---|---|---|---|---|
| **Primary AE** List only one Primary AE | **Severity Grade of Primary AE*** | **Onset Date** DD/MON/YYYY | **Status Code**** | **Status Date** DD/MON/YYYY |
| | | | | |

***Severity Grade of Primary AE:***

**1** – Mild
**2** – Moderate
**3** – Severe
**4** – Life Threatening
**5** – Death

****Status Code at Most Recent Observation:***

**1** – Recovered/Resolved
**2** – Recovering/Resolving
**3** – Not Recovered/Not Resolved
**4** – Recovered/Recovered with Sequelae
**5** – Death
**6** – Unknown

**Country of AE Origin:**

**Is this a Serious Adverse Event (SAE) as defined by ICH* E2A?**
*(*International Conference on Harmonization)*

☐ **YES**
☐ **NO**

**If Yes, check all that apply:**

- ☐ Results in death
- ☐ Is life-threatening
- ☐ Requires inpatient hospitalization or prolongation of existing hospitalization
- ☐ Results in persistent or significant disability/incapacity
- ☐ Is a congenital anomaly/birth defect
- ☐ Is an important medical event that 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 other outcomes listed in the definition above

**If No, check applicable box:**

- ☐ None of the above – This is not an SAE, but is a protocol-specific reporting requirement
- ☐ None of the above – This is not an SAE, but is of sufficient concern to report to DAIDS.

Comment(s): _____

Participant ID: _____ Site Report Date: _____
DD/MON/YYYY

| 3. | NARRATIVE CASE SUMMARY | Include clinical course, therapeutic measures, outcome, relevant past medical history, any other contributing factors, alternative etiologies, and other relevant information. Use additional page(s) as needed. |
|---|---|---|
| | | |

Participant ID: _____ Site Report Date: _____ DD/MON/YYYY

| 4a. | FOR STUDY AGENTS OTHER THAN VACCINES OR THERAPEUTIC VACCINES<br>For therapeutics administered on a cyclic schedule, also complete the Supplemental DAIDS EAE Report Form and check here ☐ if attached. | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Protocol Number:** (include information on co-enrolled protocols here) | | | | | | |
| | **Study Agent:** | *Example* | **Agent 1** | **Agent 2** | **Agent 3** | **Agent 4** | **Agent 5** |
| | **Generic/INN Name: OR the Study Agent Name/Abbreviation as listed in the Protocol** If combination agent, list as separate components separated by a slash. | *Abacavir Sulfate/ Lamivudine/ Zidovudine* | | | | | |
| | **Relationship to Primary AE*:** | *Related* | | | | | |
| | Provide relationship of each component when using a combination study agent. Refer to example and form completion instructions for details. | *Abacavir = Related*<br>*Lamivudine = Related*<br>*Zidovudine = Not Related* | | | | | |

** Related — There is a reasonable possibility that the AE may be related to the study agent(s).*
*Not Related — There is not a reasonable possibility that the AE may be related to the study agent(s).*

| | Study Agent: | | Agent 1 | Agent 2 | Agent 3 | Agent 4 | Agent 5 |
|---|---|---|---|---|---|---|---|
| A | **Dose/Unit/ Schedule:** | | | | | | |
| B | **Route:** | | | | | | |
| C | **Date of First Dose:** DD/MON/YYYY | | | | | | |
| D | **Date of Last Dose:** DD/MON/YYYY | | | | | | |
| E | **Action Taken with Study Agent**:** | | | | | | |
| F | **Date of Action Taken With Study Agent:** DD/MON/YYYY | | | | | | |
| G | **Distributed by DAIDS:** | | Yes ☐ No ☐ | Yes ☐ No ☐ | Yes ☐ No ☐ | Yes ☐ No ☐ | Yes ☐ No ☐ |
| | **If No, specify manufacturer. If unknown, specify distributor.** | | | | | | |
| H | **Lot No:** | | | | | | |

** C Continued without change O Course completed or Subject Off Study Agent at AE Onset D Permanently Discontinued R Dose or Schedule Reduced T Temporarily Held U Unknown

Participant ID: _____ Site Report Date: _____ DD/MON/YYYY

**4b. FOR VACCINES ONLY (INCLUDING THERAPEUTIC VACCINES)**
For therapeutics administered on a cyclic schedule, also complete the Supplemental DAIDS EAE Report Form and check here ☐ if attached.

| | | | | | |
|---|---|---|---|---|---|
| **Protocol Number:** (include information on co-enrolled protocols here) | | | | | |
| **Study Arm:** | | | | | |
| **Study Agent:** | **Agent 1** | **Agent 2** | **Agent 3** | **Agent 4** | **Agent 5** |
| **Generic/INN Name: OR the Study Agent Name/Abbreviation as listed in the Protocol** | | | | | |
| **Relationship to Primary AE*:** | | | | | |
| ** Related — There is a reasonable possibility that the AE may be related to the study agent(s). Not Related — There is not a reasonable possibility that the AE may be related to the study agent(s).* | | | | | |
| **Dose/Unit:** | | | | | |
| **Route:** | | | | | |
| **Device Lot Number:** (if known/if applicable) | | | | | |

**List all dates (DD/MON/YYYY) of vaccine administration/agent(s) administered/site of administration** ☐ **N/A**

| A. DD/MON/YYYY | B. DD/MON/YYYY | C. DD/MON/YYYY | D. DD/MON/YYYY | E. DD/MON/YYYY |
|---|---|---|---|---|
| **Agent (s) Administered:** | **Agent(s) Administered:** | **Agent(s) Administered:** | **Agent(s) Administered:** | **Agent(s) Administered:** |
| **Site of Administration** (if known/if applicable): ☐Left Arm ☐Right Arm ☐Left Leg ☐Right Leg ☐Other _____ | **Site of Administration** (if known/if applicable): ☐Left Arm ☐Right Arm ☐Left Leg ☐Right Leg ☐Other _____ | **Site of Administration** (if known/if applicable): ☐Left Arm ☐Right Arm ☐Left Leg ☐Right Leg ☐Other _____ | **Site of Administration** (if known/if applicable): ☐Left Arm ☐Right Arm ☐Left Leg ☐Right Leg ☐Other _____ | **Site of Administration** (if known/if applicable): ☐Left Arm ☐Right Arm ☐Left Leg ☐Right Leg ☐Other _____ |

**Action Taken with Study Agent** (enter code for the vaccine treatment regimen from codes listed below):**

**Date of Action Taken With Study Agent:** DD/MON/YYYY

** C Continued without change; O Course completed or Subject Off Study Agent at AE Onset; D Permanently Discontinued; R Dose or Schedule Reduced; T Temporarily Held; U Unknown

Participant ID: _____ Site Report Date: _____ DD/MON/YYYY

## 5. CONCOMITANT MEDICATIONS

If there were any concomitant medications that may have contributed to the primary adverse event, the details should be entered below. Any additional concomitant medications being taken at the onset of the primary adverse event should be faxed, emailed, or attached to this report.

NONE ☐

| Medication | Contributory to AE | Approximate Duration of Use | Date of Last Dose | Indication | Route of Administration | Schedule of Administration | Comments |
|---|---|---|---|---|---|---|---|
| 1. | | | | | | | |
| 2. | | | | | | | |
| 3. | | | | | | | |
| 4. | | | | | | | |
| 5. | | | | | | | |
| 6. | | | | | | | |
| 7. | | | | | | | |

## 6. OTHER CLINICALLY SIGNIFICANT EVENTS ASSOCIATED WITH PRIMARY AE

NONE ☐

| Other Clinically Significant Events Associated with Primary AE | Severity Grade | Onset Date DD/MON/YYYY | Comments |
|---|---|---|---|
| 1. | | | |
| 2. | | | |
| 3. | | | |
| 4. | | | |
| 5. | | | |

## 7. RELEVANT LABORATORY TESTS

If there were any laboratory tests relevant to the primary adverse event, the details of the laboratory tests should be entered below. Any additional laboratory tests should be faxed, emailed, or attached to this report.

NONE ☐

| Test | Collection Date DD/MON/YYYY | Result | Units | Lab Normal Range | Infectious Agent (for microbiological tests only) | Body Site (for microbiological tests only) |
|---|---|---|---|---|---|---|
| 1. | | | | | | |
| 2. | | | | | | |
| 3. | | | | | | |
| 4. | | | | | | |

Participant ID: _____ Site Report Date: _____ DD/MON/YYYY

| 8. | RELEVANT DIAGNOSTIC TESTS (NON-LAB)<br>If there were any diagnostic tests relevant to the primary adverse event, the details of the diagnostic tests should be entered below. Any additional diagnostic tests should be faxed, emailed, or attached to this report. | NONE ☐ |
|---|---|---|

| Test | Body Area | Test Date DD/MON/YYYY | Results/Comments |
|---|---|---|---|
| 1. | | | |
| 2. | | | |
| 3. | | | |
| 4. | | | |

| 9. | ADDITIONAL INFORMATION<br>Check the box for each type of document attached. Check all that apply. | NONE ☐ |
|---|---|---|

☐ Autopsy Report ☐ Concomitant Medication(s) ☐ Progress Note(s)

☐ Pathology Report(s) ☐ Laboratory Test(s) ☐ Discharge Summary

☐ Radiology Report(s) ☐ Diagnostic Test(s) ☐ Other, specify: _____

## CERTIFICATION INFORMATION

I CERTIFY THAT THE DATA PROVIDED ON THIS FORM ARE ACCURATE AND COMPLETE.

Site Investigator/Study Physician Signature: _____ Date: _____ DD/MON/YYYY

Site Investigator/Study Physician Name Printed: _____

Participant ID: _____ Site Report Date: _____ DD/MON/YYYY

## SUPPLEMENTAL DAIDS EXPEDITED ADVERSE EVENT (EAE) FORM

**Use for therapeutic study agents administered on a cyclic schedule.**
**For multiple study agents on a cyclic schedule, create one page for each study agent.**

**Study Agent Name:** _____

| | |
|---|---|
| **1. If event occurred during a dosing cycle:** ☐ N/A<br>a. Highest dose in this cycle: _____<br>b. Date this cycle started: DD/MON/YYYY _____<br>c. Date previous cycle started: DD/MON/YYYY _____<br>d. Number of previous cycles: _____ | **2. If an event did not occur during a dosing cycle:** ☐ N/A<br>a. Highest dose in previous cycle: _____<br>b. Date previous cycle started: DD/MON/YYYY _____<br>c. Number of previous cycles: _____ |