A phase 2a, randomized study of romidepsin with or without 3BNC117 to evaluate the effects on the HIV-1 reservoir (ROADMAP)

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Statement of Compliance

The clinical trial will be conducted in compliance with the protocol, with the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and with 45 CFR 46 and 21 CFR 50, 56 and 312. All protocol investigators have completed Protection of Human Subjects Training.

Signature Page 1

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal and E.U. regulations and ICH guidelines.

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Principal Investigator: _____
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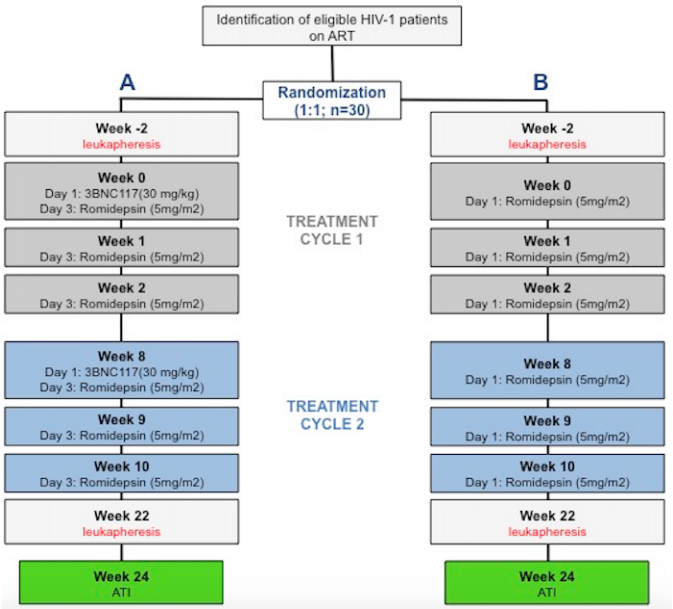
List of Abbreviations

AU	Aarhus University
AUH	Aarhus University Hospital
3BNC117	Anti-HIV-1 bNAb targeting the CD4 binding site of gp120
Ab	Antibody
AE	Adverse Event/Adverse Experience
ART	Antiretroviral Therapy
ATI	Analytic Treatment Interruption
bNAbs	Broadly Neutralizing Antibodies
CD4	T-cell Surface Glycoprotein CD4
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRSO	Clinical Research Support Office
CTSA	Clinical and Translational Science Award
CCTS	Center for Clinical and Translational Science
CU	Cologne University
CUH	Cologne University Hospital
DC	Dendritic Cell
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
gp120	HIV-1 Envelope Glycoprotein 120
HDAC	Histone deacetylase
HIPAA	Health Insurance Portability and Accountability Act
HIV-1	Human immunodeficiency virus
hu-mice	Humanized Mice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
I.M.	Intramuscularly
IND	Investigational New Drug
IRB	Institutional Review Board
I.V.	Intravenously
N	Number (typically refers to participants)
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
PBMC	Peripheral Blood Mononuclear Cell
PI	Principal Investigator
RU	The Rockefeller University
RUH	The Rockefeller University Hospital
QA	Quality Assurance
QC	Quality Control
RNA	Ribonucleic Acid
SAE	Serious Adverse Event/Serious Adverse Experience
S.C.	Subcutaneously
SHIV	Chimeric Simian/Human Immunodeficiency Virus
SOP	Standard Operating Procedure
T cell	T lymphocyte
V3 loop	Third Variable Loop of the HIV-1 Virion Envelope Glycoprotein 120

Study Schema

Title	A phase 2a, randomized study of romidepsin with or without 3BNC117 to evaluate the effects on the HIV-1 reservoir (ROADMAP)
Short Title	Romidepsin plus 3BNC117 phase 2a study
Protocol Number	MCA-896
Phase	Phase 2a
IND Sponsor	The Rockefeller University
Study Center(s)	The Rockefeller University (RUH; Coordinating Site), New York, NY, U.S.A. University Hospital of Cologne, Cologne, Germany Aarhus University Hospital, Aarhus, Denmark
Principal Investigators	Marina Caskey, MD, Ole Sogaard, MD PhD, Gerd Faetkenheuer, MD
Study Design	This is a randomized interventional phase 2a trial of 3BNC117 and romidepsin in HIV-1-infected patients on ART, conducted as a multi-center study at the Department of Infectious Diseases, Aarhus University Hospital, Denmark, the Rockefeller University Hospital, USA, and the University Hospital of Cologne, Germany. Participants will be randomized 1:1 in a non-blinded fashion to receive one of two regimens: A) Two treatment cycles each consisting of one 3BNC117 infusion (30mg/kg) + three romidepsin infusions (5mg/m^2); or B) Two treatment cycles each consisting of three romidepsin infusions (5mg/m^2). ART will be discontinued 16 weeks after the start of the second treatment cycle (analytical treatment interruption, ATI) and subjects will be monitored weekly for safety and viral rebound. The study outline is shown in **Figure 1**. The targeted enrolment is 30 subjects (15 per arm). Leukapheresis will be performed before and after the two treatment cycles to guarantee sufficient material to investigate changes in the reservoir after the interventions.

	Figure 1. Study Design:  The following criteria will require resumption of ART: • CD4+ T cell-count <350 cells/mm³ (confirmed by repeat measurement) • 2 consecutive plasma HIV-1 RNA measurements ≥ 200 copies/mL or above their setpoint viremia (if documented) • Subject request • Continued ART interruption will, in the opinion of the investigator or study advisers, pose an unacceptable risk to the subject. If HIV-1 RNA remains undetectable at week 36, subjects will be offered to continue off ART with close monitoring, in conjunction with the subject's primary medical provider, as long as HIV-1 viral rebound does not occur. ART resumption will follow same criteria as detailed above. All subjects will be followed for a total of 48 weeks from enrollment.
Study Duration	50 weeks per participant; total planned study duration 24 months
Objectives	Primary Objective: - Evaluate the effects of romidepsin plus 3BNC117 or romidepsin alone on delaying or preventing viral rebound in HIV-1-infected individuals during an analytical interruption of ART. Secondary Objectives: - Evaluate the safety of romidepsin plus 3BNC117 or romidepsin alone in ART-treated HIV-1 infected individuals; - Evaluate the effects of romidepsin plus 3BNC117 or romidepsin alone on the size of the replication competent HIV-1 reservoir in ART-treated HIV-1-infected individuals; - Evaluate the immunomodulatory effects of romidepsin plus 3BNC117 or romidepsin alone in ART-treated HIV-1-infected individuals.
Number of Subjects	30 (15:15)

Study Population	HIV-infected males and females, between the ages of 18-65, on ART for at least 24 months, with HIV-1 RNA plasma level of < 50 copies/ml by standard assays for at least 18 months, and with current CD4+ T cell counts > 500 cells/μl.
Inclusion / Exclusion Criteria	Inclusion Criteria: *1.* Adults age 18-65 years with documented HIV-1 infection *2.* CD4+ T-cell count >500 cells/mm3 at screening *3.* On ART for a minimum of 18 months and HIV-1 RNA plasma level of < 50 copies/ml by standard assays for at least 12 months (a single viral load measurement > 50 but < 500 copies/ml during this time period is allowable). *4.* Individuals on protease inhibitor or NNRTI-based regimens, or regimens containing cobicistat must be willing to switch to an integrase-inhibitor-based regimen (raltegravir or dolutegravir) prior to enrollment. Exclusion Criteria: 1. Use of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the investigators within the last 6 months 2. Pregnancy as determined by a positive urine or serum beta-hCG. 3. Participant unwilling to use two reliable contraception methods (i.e. condom with spermicide, diaphragm with spermicide, progestin-only containing intrauterine device (IUD) (eg, Mirena, Implanon), non-estrogen containing formulations of hormonal birth control drugs with condom) for the study duration. Romidepsin may interact with estrogen-based contraceptives and such agents may be unreliable in participants receiving romidepsin. 4. Currently breast-feeding. 5. History of resistance to 2 or more classes of antiretroviral medications 6. Any medical, psychiatric, social, or occupational condition that, as judged by the investigators, would interfere with the evaluation of study objectives (such as severe alcohol or drug abuse, dementia). 7. Acute or chronic hepatitis B or C infection as indicated by the presence of Hepatitis B surface antigen (HBsAg) or hepatitis C virus RNA (HCV-RNA) in blood. 8. A history of AIDS-defining illness within 3 years prior to enrollment. 9. History of B-cell lymphoma, including CNS lymphoma 10. CD4 nadir < 200 cells/mm^3 within the last 5 years. 11. History of significant coronary artery disease, myocardial infarction, percutaneous coronary intervention with placement of cardiac stents, or family history of sudden death at age < 50 years. 12. ECG at screening that shows QTc >450 msec when calculated using the Fridericia formula from either lead V3 or V4, pathological Q-waves (Q-wave > 40 msec or depth > 0.4-0.5 mV), evidence of a ventricular pre-excitation syndromes, complete or incomplete LBBB or RBBB, second or third degree heart block, QRS duration > 120 msec, or bradycardia defined by sinus rate < 50 bps 13. Use of QT-prolonging medication, renal or hepatic disease, structural heart disease or left ventricular dysfunction 14. Any symptomatic or asymptomatic arrhythmia excluding sinus arrhythmia and bradycardia ≥ 50 bps. 15. Use of Coumadin or Coumadin derivatives 16. Laboratory abnormalities in the parameters listed below:

	a. Absolute neutrophil count ≤ 1,000 cells/µl b. Hemoglobin < 11 gm/dL c. Platelet count < 125,000 cells/µl
Inclusion / Exclusion Criteria	d. ALT ≥ 1.25 x ULN e. AST ≥ 1.25 x ULN f. Total bilirubin > 1.0 ULN g. eGFR < 60 mL/min/1.73m^2 17. Any vaccination within 14 days prior to 3BNC117 administration 18. Receipt of any therapeutic HIV vaccine in the past 19. Receipt of any anti-HIV monoclonal antibody in the past, or HDAC inhibitor of any kind in the past 2 years. 20. Participation in another clinical study of an investigational product currently or within past 12 weeks, or expected participation during this study.
Study Product, Dose, Route, Regimen	- 3BNC117 (RUhumab-001) is a recombinant, fully human monoclonal antibody (mAb) of the IgG1κ isotype that specifically binds to the CD4 binding site (CD4bs) within HIV-1 envelope gp-120. - Romidepsin is an HDAC inhibitor that has emerged as one of the potent inducers of HIV-1 transcription. Romidepsin displays isoform specificity towards class I HDACis, which are particularly important to maintaining HIV-1 latency. Romidepsin will be provided by Celgene for use in this study. In Group A, one intravenous infusion of 3BNC117 mAb (30 mg/kg) will be administered at week 0 and a second infusion at week 8 via a peripheral vein over 60 minutes. In Groups A and B, one intravenous infusion of romidepsin (5 mg/m^2) will be administered at weeks 0, 1, and 2 (treatment cycle 1), and weeks 8, 9, and 10 (treatment cycle 2), via a peripheral vein over 120 minutes (**Figure 1**). In Group A, the start of each romidepsin cycle will begin 2 days after the 3BNC117 infusion.

Statistical Methodology	The sample size calculation is based on the primary endpoint: time to viral rebound during ATI or time to reinitiation of ART in participants who restart ART before viral rebound. Viral rebound is defined as HIV-1 RNA ≥ 200 copies/mL on 2 consecutive measurements during ATI. If viral rebound occurs, the date of the first measurement of HIV-1 RNA ≥ 200 copies/mL will be defined as "date of viral rebound." We will compare days from date of ART interruption until viral rebound or restarting of ART in arm A to arm B (1:1 randomization). Given a standard deviation (SD) of 10 (days), enrolling 12 patients in each of the two arms, will have 80% power to detect ≥ 13 days (approximately 2 weeks) difference in time to viral rebound at a 5% significance level (Davey et al., 1999; Hamlyn et al., 2012; Hill et al., 2014). To accommodate for dropouts, 30 study subjects may be enrolled in the study (15 in each arm). A dropout rate of 5-15% is anticipated. The number and percentage of subjects experiencing one or more AEs will be summarized by relationship to study drug and severity. AEs will also be summarized by severity grade and by relationship to study drug according to the CTCAE v4.03 (infusion-related AEs) and DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0 (non-infusion-related AEs) grading scales. Changes will be calculated relative to the values collected at baseline. The Wilcoxon-Mann-Whitney test will be used as primary analysis for the primary outcome. The Kaplan-Meier estimator will be used as secondary analysis to assess the magnitude of the difference between the survival curves for the two study groups. We will use the log-rank test to compare time to viral rebound during ATI in the two arms.
Statistical Methodology	The Wilcoxon-Mann-Whitney will be used to determine changes from baseline to the pre-ATI time-point in reservoir size for each group. Fishers exact or chi-square test will be used to compare the proportion of subjects in both groups with detectable viremia during each romidepsin treatment. Functional properties of cytotoxic T cells and NK cells will be correlated to changes in total HIV-1 DNA and IUPM. Flow cytometry data will be evaluated by Boolean partitioning of NK and T cell responses into distinct responding populations (Lamoreaux et al., 2006). Finally, correlation analysis will be performed to identify the markers most likely associated with time to viral rebound. As exploratory analysis, a linear regression model will be used to determine predictors of log-transformed time to viral rebound in both arms. P values <0.05 will be considered statistically significant.

1 Key Roles

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2 Lay Summary

Despite effective combination antiretroviral therapy (ART), HIV-1 persists as latent infection. Upon treatment interruption, the virus quickly replicates and viremia rebounds to pre-treatment levels. The primary barrier preventing HIV-1 eradication by ART is a pool of long-lived latently infected memory CD4+ T-cells. These cells harbor silent integrated proviral DNA capable of resuming HIV-1 expression upon activation. In the inactive, resting state these cells cannot be recognized or eliminated by the immune system or antiretroviral drugs. Importantly, latently HIV-1 infected cells can be induced to resume HIV-1 expression by latency reversing agents (LRAs). This in turn could expose infected cells to immune-mediated recognition and killing. 3BNC117 is the first broadly neutralizing antibody (bNAb) against HIV-1 having demonstrated potent activity against HIV-1 in humans. Unlike ART, bNAbs can engage the host immune system by virtue of their Fc effector domains and thereby accelerate clearance of cell-free virus, induce antibody dependent cytotoxicity to kill infected cells, and produce immune complexes that activate dendritic cells to become potent antigen presenting cells.

The aim of this protocol is to evaluate the effect of a combination of a potent LRA (i.e. romidepsin) with bNAb-mediated clearance of viral-antigen producing cells as a novel approach to reduce the HIV-1 reservoir in chronically infected patients on suppressive ART.

3 Objectives and Rationale

3.1 Introduction

3.1.1 Background

Despite the major success of combination antiretroviral therapy (ART) in suppressing viral replication and preventing disease progression, HIV-1 infection persists and is not eliminated by available antiretroviral drugs. When ART is discontinued, viral rebound occurs within 2-3 weeks in most subjects (Davey et al., 1999) (Strategies for Management of Antiretroviral Therapy Study et al., 2006). Even in the context of suppressive ART, HIV infection is characterized by persistent low level HIV-1 viremia and immune activation and cell-associated HIV-1 remain relatively stable (Deeks et al., 2013). Studies have shown that intensified antiretroviral regimens do not affect low level viremia and do not result in lower levels of HIV-1 persistence (Markowitz et al., 2014; McMahon et al., 2010).

The primary barrier preventing HIV-1 eradication by ART is a pool of long-lived latently infected memory CD4+ T-cells (Chomont et al., 2009; Finzi et al., 1997). These cells harbor silent integrated proviral DNA capable of resuming HIV-1 expression upon activation (Archin et al., 2009; Bosque and Planelles, 2009; Finzi et al., 1999). In the inactive, resting state these cells cannot be recognized or eliminated by the immune system or antiretroviral drugs. Importantly, latently HIV-1 infected cells can be induced

to resume HIV-1 expression by latency reversing agents (LRAs) (Ylisastigui et al., 2004). This in turn could expose infected cells to immune-mediated recognition and killing.

Recent clinical trials have demonstrated proof-of-concept that the state of HIV-1 latency can be disrupted safely in patients on ART by a group of LRAs called histone deacetylase inhibitors (HDACi)(Archin et al., 2012; Elliott et al., 2014). However, the outcome of these trials plus an accumulating body of ex vivo research also suggest that, in the majority of patients, reactivation alone does not reduce the HIV-1 reservoir - possibly because of insufficient immune mediated killing of reactivated cells (Ho et al., 2013; Shan et al., 2012). This calls for combining LRAs with immune targeted interventions such as HIV-1-specific monoclonal antibodies.

A fraction of HIV-infected individuals (10 – 30%) mount a serologic response that can neutralize a broad spectrum of HIV-1 isolates (Simek et al., 2009). Although broadly neutralizing antibodies that arise during HIV infection fail to resolve established infection, the selection of resistant strains indicates that bNAbs exert selective pressure on the virus. Importantly, several different groups of investigators have shown that macaque chimeric simian/human immunodeficiency virus (SHIV) infection can be prevented by passive transfer of broadly neutralizing anti-HIV-1 monoclonal antibodies, (Shingai et al., 2013). Broadly neutralizing antibodies might also play a role in the treatment of HIV infection.

Broadly neutralizing antibodies (bNAbs) differ from other therapeutic modalities for HIV in several respects. First, they can neutralize the pathogen directly; second, they have the potential to clear the virus and infected cells through engagement of innate effector responses; and third, immune complexes produced by the passively transferred antibodies may enhance the immune response to HIV. In fact, a subset of bNAbs may inhibit cell-to-cell transmission of HIV at very low concentrations (Malbec et al., 2013). Experiments in humanized mice and non-human primates indicate that combinations of bNAbs can lead to rapid virologic suppression that is sustained for as long as mAb levels are maintained above a certain threshold (Barouch et al., 2013).

In SHIV-infected nonhuman primates, 3BNC117 induces rapid viral suppression as monotherapy (Shingai et al., 2013). Also, 3BNC117 monotherapy is able to prevent infection in macaques challenged with $SHIV_{AD8EO}$ or $SHIV_{DH12\text{-}V3AD8}$ more effectively than the previously described antibody VRC01(Shingai et al., 2014). While antibody monotherapy did not control HIV-1 infection in viremic, untreated hu-mice, a single neutralizing antibody, *i.e.* 3BNC117, was able to sustain undetectable viral loads after initial suppression by antiretroviral therapy. Whereas hu-mice that received ART normally rebounded immediately after the drugs were terminated, continuing a single antibody was sufficient to maintain control after ART interruption in 50-86% of the hu-mice, for as long as antibody concentrations remained therapeutic (Horwitz et al., 2013a). Mice that escaped 3BNC117 carried resistance mutations in the CD4bs at positions $YU2^{(279\text{-}281)}$ or $YU2^{(458/459)}$. In contrast, viruses that emerged after immunotherapy was terminated did not contain antibody resistance mutations and remained sensitive to

neutralization by the antibody. Early phase 1 results show that 3BNC117 is active in reducing viremia in HIV-1-infected humans (Caskey et al., 2015a).

Passive administration of less potent, first generation anti-HIV-1 bNAbs has been evaluated in ART-interruption settings in humans. In these studies, 13-16 antibody infusions were administered intravenously at doses ranging from 0.5 to 2 g and were generally found to be safe and well tolerated. Furthermore, one of the antibodies (2G12) seemed to delay viral rebound in several participants. This effect was rather limited, as 2G12 did not neutralize the donor's virus isolates with sufficient potency (Trkola et al., 2005a) (Mehandru et al., 2007a).

The SMART randomized trial demonstrated that episodic ART, guided by drop in CD4+ count (ART reinitiated if CD4+ T cell count < 250 cells/µl), leads to increased risk of opportunistic infections or death from any cause, as compared with continuous ART, during a median follow-up time of 16 months (Strategies for Management of Antiretroviral Therapy Study et al., 2006). While structured treatment interruptions (STIs) have traditionally been avoided given safety concerns, it should be noted that, in the first 16 weeks following randomization into the SMART study, there were no deaths in either treatment group – those that received continuous ART or those that received episodic ART guided by CD4 count. In addition, the differences in risk of opportunistic diseases and major cardiovascular, renal, and hepatic diseases between the two groups occurred predominantly after 16 weeks, increased over time and were strongly associated with low CD4 counts as well as increased viral loads. Recent evidence suggests that short analytical treatment interruption, in individuals with preserved CD4 count and virologic suppression, is safe and is an accepted tool to evaluate new therapeutic modalities (Kutzler and Jacobson, 2008; Rothenberger et al., 2015). Thus, brief ART interruption can be used to study the role that recently isolated anti-HIV-1 bNAbs might have in controlling or preventing HIV-1 replication.

In support of the idea that bNAbs and inducers can alter the reservoir, combinations of these agents were shown to interfere with the establishment of and disrupt the reservoir in humanized mice by a mechanism that requires engagement of antibody Fc effector functions (Bournazos et al., 2014; Halper-Stromberg et al., 2014). We propose to conduct a proof-of-concept study that will combine bNAb-mediated clearance of viral-antigen producing cells (i.e. 3BNC117) with a potent LRA (i.e. romidepsin) as a novel approach to reduce the HIV-1 reservoir in chronically infected individuals on suppressive ART.

This study will address several gaps in current knowledge: 1) The effect of combining ART+LRA+bNAb vs. ART+LRA alone on the size of the HIV-1 reservoir and time to viral rebound following ART interruption; 2) The impact of repeated exposure to a potent LRA with an interval of 2 months; 3) Correlates for time to viral rebound in patients receiving LRAs and combined LRA+bNAb; 4) The immunomodulatory effects of LRA and bNAb treatment by characterizing phenotypic as well as functional changes in antigen-presenting (DCs, macrophages/monocytes) and effector cells (NK, NKT, CD8+ cells).

3.1.2 3BNC117

3BNC117 is a broadly neutralizing and highly potent anti-HIV-1 antibody. 3BNC117 was initially cloned from one B cell isolated from a volunteer infected with HIV-1 clade B, who controls his HIV-1 infection without antiretroviral therapy. 3BNC117 targets the CD4 binding site (CD4bs) within HIV-1 envelope gp-120. It showed an average IC_{80} on a combined group of 95 tier 2 viruses of 1.4 µg/ml when evaluated by *in vitro* neutralization assays (Scheid et al., 2011). 3BNC117 also showed *in vivo* activity in experiments in both humanized mice and non-human primates. In chronically infected animals, passive administration of 3BNC117 alone or in combination with other potent neutralizing antibodies suppressed plasma viremia to levels below detection (Horwitz et al., 2013b; Klein et al., 2012; Shingai et al., 2013). Moreover, 3BNC117 administration protected both humanized mice (Gruell et al., 2013) and rhesus macaques (Shingai et al., 2014; Shingai et al., 2013) from challenge with HIV-1 and tier 2 SHIVs, respectively.

3BNC117 has been manufactured for clinical use under cGMP by Celldex Therapeutics. The manufacture of the recombinant human monoclonal 3BNC117 was carried out by *in vitro* serum-free CHO cell culture. 3BNC117 was manufactured as a sterile solution intended for parenteral use, in compliance with Good Manufacturing Practices (GMP). No animal-derived raw materials were used during the cell culture, purification, and formulation of the drug substance. The drug substance was manufactured in a dedicated suite utilizing single-use equipment (e.g., WAVE bioreactor) to minimize potential for product cross contamination. A low pH step and a nanofiltration step were used for virus inactivation and reduction. Viral clearance studies used the model viruses PPV and A-MuLV. Testing for adventitious agents was performed in accordance to FDA Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997). An ongoing drug product stability testing program monitors the quality of 3BNC117 over the duration of the clinical dosing period. Stability is evaluated in real time at the recommended storage conditions of 5 ± 3°C as well as at accelerated temperature conditions of 25 ± 2°C / 60 ± 5% RH.

3.1.2.1 Clinical Safety of other anti-HIV Monoclonal Antibodies.

Monoclonal antibodies are a growing part of the therapeutic arsenal. While each mAb product has unique safety issues related to its mechanism of action, the major safety concern related to mAbs in general is infusion/hypersensitivity reactions, which are more common for mAbs that contain murine elements. 3BNC117 is a fully human recombinant form of a naturally existing human mAb. Passive administration of antibodies is successfully used to prevent or treat several viral diseases and several monoclonal antibodies are being developed for use in either prevention or treatment of infectious diseases.

Passive administration of anti-HIV-1 antibodies has also been evaluated in humans. HIV Immune Globulin (HIVIG) was in clinical use in the 1990s before the advent of highly effective ART. HIVIG was also evaluated in HIV-infected pregnant females and their newborns in a phase III trial to assess whether HIVIG plus single dose nevirapine given to mothers and infants would provide additional benefit over single dose nevirapine alone

for prevention of peripartum HIV transmission. While there was no demonstrable difference in treatment efficacy, the study showed that that there were no significant differences in mortality or serious AEs between the two arms of the trial (Onyango-Makumbi et al., 2011).

Several monoclonal antibodies that target HIV-1 have been evaluated in clinical studies. For example, 2F5 and 4E10 are IgG1 (kappa) monoclonal antibodies that target the membrane-proximal ectodomain of gp41, while 2G12 binds to a carbohydrate moiety on the silent face of gp120. These neutralizing antibodies were evaluated in combination in HIV-infected individuals (Armbruster et al., 2004). The antibodies were administered intravenously at 0.5 to 1 g doses; 4 to 8 weekly infusions were given. The antibodies were safe and well tolerated and no clinical or laboratory abnormalities were observed throughout the studies. A low-level antibody response against 2G12 was found in two subjects.

Two other studies included HIV-infected subjects on combination ART and plasma viral levels < 50 copies/ml (Trkola et al., 2005a), n = 14; (Mehandru et al., 2007a); n =10. The antibodies were administered intravenously at doses ranging from 1 to 2 g for each antibody; 13-16 weekly antibody infusions were given. ART was interrupted following 1 or 4 antibody infusions. Antibody infusions were well tolerated in most subjects; mild and transient side effects were reported only occasionally. No serious adverse events (SAEs) were recorded. In both studies, the use of mAbs was safe and generally delayed, but did not prevent viral rebound. The emergence of resistance to 2G12, however, demonstrated that the antibody exerted selective pressure on the circulating viral strains. It is important to note that the antibodies used in these studies have far lower potency and breadth than the more recently isolated neutralizing antibodies, such as 3BNC117. Moreover, in contrast to 3BNC117, these antibodies had very limited effect in the treatment of HIV in humanized mice (Poignard et al., 1999).

3.1.2.2 Preclinical Toxicity Studies with 3BNC117

A tissue cross-reactivity study, performed on a full panel of tissues from humans and rats, showed good concordance of binding between the two species. While 3BNC117 showed widespread cytoplasmic binding, it is generally understood that cytoplasmic binding is considered of little to no toxicologic significance. Membrane binding of 3BNC117 was restricted to two limited/rare cell types in conjunctival recesses and in the urinary bladder (neither of which correlated with findings in the repeat dose toxicology study).

The antibody 3BNC117 was evaluated for safety in a multidose study in rats. Despite some animals producing anti-drug antibodies, the rats appeared to have maintained adequate drug exposure in the study, with twice per week dosing for four weeks. Aside from injection site findings, there were no 3BNC117 related effects, in the Main and Recovery group animals, on clinical observations, body weight, food consumption, body temperature, clinical pathology parameters, organ weights or macroscopic and microscopic observations, and the NOEL (no observable effect level) was determined to be the high dose of 60 mg/kg twice a week for four weeks.

3.1.2.3 Clinical Experience with 3BNC117

3BNC117 is currently being evaluated in a phase 1 study in both HIV-uninfected and HIV-infected subjects (protocol MCA-835) and in an exploratory phase 2 study in HIV-infected subjects (protocol MCA-867).

In protocol MCA-835, study subjects are administered one or two intravenous infusions of 3BNC117 at increasing dose levels (1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg), and are followed for 24 weeks after last infusion. As of 7 November 2015, 55 subjects (22 HIV-uninfected, 19 viremic HIV-infected and 14 ART-treated HIV-infected individuals) have enrolled in the study. Five HIV-uninfected individuals have received two infusions of 3BNC117 at 30 mg/kg, 12 weeks apart. Twenty-two subjects (3 HIV-uninfected and 19 HIV-infected) have been administered one dose of 30 mg/kg.

Overall, 3BNC117 has been generally safe and well-tolerated, mild transient myalgia, fatigue and headache have occurred. Some participants reported ophthalmic complaints, but a causal relationship with 3BNC117 was not established. No SAEs or grade 3/4 AEs deemed related to 3BNC117 have occurred. A safety data summary is included in the Investigator's Brochure (IB).

Preliminary PK data show that 3BNC117's half-life is 17.6 days in HIV-uninfected and 9.6 days in viremic HIV-infected individuals. 3BNC117 decay rates following first and second 10 mg/kg infusions are similar. Available PK data in ART-treated HIV-infected individuals with HIV-1 viral loads (VL) < 20 copies/ml show that 3BNC117 levels decline at slower rate than in viremic individuals.

A transient decline in HIV-1 viremia, of approximately 0.5 log, occurred following the administration of 3 mg/kg of 3BNC117 to three HIV-infected subjects with detectable viremia. Of the 3 individuals receiving the 10 mg/kg dose of antibody, only 2 responded with a decrease in viremia of 0.69 and 1.36 $\log_{10}$. The individual that did not respond was infected with 3BNC117-resistant virus (2C4; IC_{50} > 20µg/ml at baseline). All nine viremic individuals that received the 30 mg/kg dose of 3BNC117 showed rapid decreases in their viral loads that varied between individuals from 0.8 to 2.5 $\log_{10}$. The median time to reach the nadir in viremia was 7 days, and the mean drop in VL was 1.48 $\log_{10}$ at nadir. but could be as long as 21 days. Emergence of resistant viral strains was variable, with some individuals remaining sensitive to 3BNC117 for a period of 28 days after infusion (Caskey et al., 2015b). Virologic data will continue to be analyzed under protocol MCA-835, as additional HIV-infected subjects are enrolled.

In protocol MCA-867, HIV-infected individuals on suppressive ART are administered two 30 mg/kg intravenous infusions of 3BNC117 at week 0 and week 3. ART is discontinued 2 days after the first 3BNC117 infusion. Subjects are followed weekly and ART is resumed if viral rebound occurs or CD4+ T cell counts decline to < 350 cells/mm^3. As of 7 November 2015, 8 individuals have been enrolled. 3BNC117 infusions have been well tolerated, with few mild and moderate AEs reported to date.

3.1.3 Romidepsin

Romidepsin is an HDAC Inhibitor that has emerged as one of the potent inducers of HIV-1 transcription and it is ~1000 fold more potent than SAHA (vorinostat) in inducing latent HIV-1 expression (Wei et al., 2014). Romidepsin displays isoform specificity towards class I HDACIs, which are particularly important to maintaining HIV-1 latency. Romidepsin is FDA-approved for use in the US in patients with cutaneous and peripheral T-cell lymphoma, and is used at a dose of 14 mg/m^2. *In vitro* studies have demonstrated that Romidpesin is capable of activating HIV RNA expression at doses as low as 15-40 percent of the clinical dose of 14 mg/m^2 (Wei et al., 2014). Additionally, in a proof-of-concept trial, romidepsin was capable of activating HIV RNA expression at a dose of 5mg/m^2 (Sogaard et al., 2015). Romidepsin will be provided by Celgene for use in this study.

3.1.3.1 Preclinical Toxicity Studies with Romidepsin

No specific fertility studies have been conducted with romidepsin in humans. Based on non-clinical findings in repeat-dose toxicity studies, romidepsin has the potential to affect male and female fertility. In a 26 week study in rats, testicular atrophy or degeneration at repeated dosing at ≥ 0.33 mg/kg/week corresponding to 1.98 mg/m^2 or a steady state mean AUC0-∞ 10.3 ng.hr/mL. In dogs, romidepsin caused hypospermia in the testes at doses ≥ 1.0 mg/kg corresponding to 20mg/m^2. In rats, at doses ≥0.1 mg/kg/week corresponding to 0.6 mg/m^2 or a mean steady state AUC0-∞ 4.9 nghr/mL, females exhibited atrophy in the ovary, uterus, vagina and mammary glands. Further, maturation arrest of ovarian follicles was observed in female rats at ≥ 0.3 mg/kg/week corresponding to 1.8 mg/m^2. Romidepsin has shown developmental toxicity in non-clinical studies. In this study, the use of two contraceptive methods for both female and male study subjects is required for the duration of the study; this is specified in the exclusion criteria.

3.1.3.2 Clinical Experience with Romidepsin

In clinical trials, the most common adverse events (AE) associated with romidepsin included gastrointestinal (nausea, vomiting, diarrhea/constipation), hematologic (thrombocytopenia, leucopenia (neutro- and lymphopenia) and anemia), asthenic (asthenia, fatigue, malaise and lethargy) and electrolyte abnormalities (hypomagnesemia, hypokalemia and hypocalcemia), hyperglycaemia and pyrexia. Overall, the most common grade 3/4 events reported were anaemia, thrombocytopenia, neutropenia, leukopenia and fatigue. These AE should be interpreted in the context of patients with severe haematological cancers. The detailed results of the pooled safety analysis are presented in the IB.

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. A possible association between romidepsin and reactivation of DNA viruses has been described in 3 case reports (Ritchie et al., 2009). In this small case series, there was

a temporal association with reactivation and administration of the HDACi, but it is important to keep in mind that these patients were all patients with advanced cancer and immunosuppression. In the CLEAR study, including aviremic adults with HIV-1 infection, the participants received oral panobinostat (20 mg) three times per week every other week for 8 weeks while maintaining ART. Concentrations of cytomegalovirus DNA (in urine) and Epstein-Barr virus DNA (in blood) were repeatedly quantified during panobinostat treatment, but no evidence of unintended DNA virus reactivation was recorded (Rasmussen et al., 2014).

During a pilot study of 6 HIV-1 patients on long-term ART who received 3 infusions of 5 mg/m^2 of romidepsin over the course of 3 weeks, no serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSAR) were observed (Sogaard et al., 2015). Forty-one AE were registered during follow-up of which 35 AEs were considered related to romidepsin. All drug-related AEs were mild (grade 1, n=35) and resolved spontaneously within a few days. The most common romidepsin-related AEs were abdominal symptoms (e.g. nausea [n=11], borborygmia [n=4], abdominal pain [n=2]) and fatigue (n=5). Modest changes in white blood cell counts (WBC) and T cell counts were observed during the study with the lowest levels generally observed after the second romidepsin infusion, but no further decline following the third infusion. Reassuringly, neutrophil counts below 1,000 cells/mm^3, CD4+ cell counts below 350 cells/mm^3, or platelet counts below 100,000 cells/mm^3 were not observed.

A phase 1b/2a study (REDUC trial) was conducted to evaluate the effects of immunizations with a protein vaccine (Vacc-4x/rhuGM-CSF) followed by romidepsin on the HIV-1 reservoir of HIV-1-infected individuals on antiretroviral therapy. Study participants were administered a series of six intradermal immunizations over 12 weeks. The immunization phase was followed by 5 mg/m^2 romidepsin infusions once weekly for 3 weeks while maintaining ART. Romidepsin was administered intravenously over 4 hours. 96% the 141 reported adverse events were of grade 1 severity. 57 grade 1 AEs were considered related to romidepsin, with fatigue (14 individuals) and nausea (15 individuals) being the most frequently reported. The observed adverse events did not lead to dose de-escalation or other modifications of the study regimen. In addition, there were no clinically significant adverse effects of the investigational therapies on blood biochemistry parameters (Leth et al., *in press*).

Romidepsin is also being evaluated in ART-treated HIV-infected individuals in a phase 1/2 multi-site trial conducted in the US. This study aims to evaluate romidepsin's safety and its ability to induce HIV-1 expression in HIV-infected individuals who are on suppressive ART regimens (NCT01933594).

3.2 Hypothesis

The combined administration of two infusions of 3BNC117 (30 mg/kg) together with six infusions of romidepsin (5 mg/m^2) will prevent or delay the return of HIV-1 viremia during an analytical treatment interruption compared with administration of romidepsin alone.

3.3 Aims

Primary Objective:

- Evaluate the effects of romidepsin plus 3BNC117 or romidepsin alone on delaying or preventing viral rebound in ART-treated HIV-1-infected individuals during an analytical interruption of ART.

Secondary Objectives:

- Evaluate the safety of romidepsin plus 3BNC117 or romidepsin alone in ART-treated HIV-1 infected individuals;
- Evaluate the effects of romidepsin plus 3BNC117 or romidepsin alone on the size of the HIV-1 reservoir in ART-treated HIV-1-infected individuals;

Exploratory Objectives:

- Evaluate the effects of romidepsin plus 3BNC117 or romidepsin alone on HIV-1 transcriptional activity and plasma HIV-1 RNA in ART-treated HIV-1-infected individuals
- Evaluate the immunomodulatory effects of romidepsin plus 3BNC117 or romidepsin alone in ART-treated HIV-1-infected individuals.
- Evaluate the pharmacokinetics of romidepsin in HIV-1-infected individuals

3.4 Primary Endpoint

- Days to viral rebound during ATI or days to reinitiation of ART in participants who restart ART before viral rebound. Viral rebound is defined as HIV-1 RNA $\geq$ 200 copies/mL on 2 consecutive measurements during ATI. If viral rebound occurs, the date of the first measurement of HIV-1 RNA $\geq$ 200 copies/mL will be defined as "date of viral rebound."

3.5 Secondary Endpoints

- Safety evaluation, as measured by rate and severity of adverse events (AE), serious adverse events (SAE), and serious unexpected serious adverse reactions (SUSAR).

- Size of the functional, latent HIV-1 reservoir as determined by the number of infectious units per 10^6 resting memory $CD4^+$ T cells (IUPM) using a viral outgrowth assay before and after therapy. Post therapy measurements will occur after the second cycle, just before ATI. These measurements will be performed in Dr. Siliciano's laboratory.

- Size of the proviral HIV-1 reservoir as determined by total HIV-1 DNA and episomal HIV-1 DNA (2-LTR) in circulating total $CD4^+$ T cells at baseline, after each romidepsin cycle, prior to the ATI period (week 24), and at the end of the study (week 48).

- Plasma HIV-1 RNA, as measured by a routine clinical assay (Cobas Taqman; detection limit 20 copies/mL), a transcription mediated amplification (TMA)-based assay (detection limit 12 copies/ml) and/or a single copy assay (detection limit 1-2 copies/mL).

3.6 Exploratory Endpoints

- HIV-1 transcriptional activity as determined by unspliced HIV-1 RNA in circulating total $CD4^+$ T cells.

- Phylogenetically compare viruses grown from PBMCs collected from participants while on ART to rebound viruses collected after ART interruption.

- Plasma cytokine and immune activation biomarker levels.

- Change from baseline in the capacity of NK and CD8+ T cells to mediate inhibition of viral replication ex vivo.

- Absolute cell counts and phenotypic characteristics for T and NK cells using standard cell marker panels by flow cytometry (e.g. CD3, CD4, CD8, CD45RA, CCR7 for T cells and CD16/CD56 for NK cells). Functional properties of cytotoxic T cells and NK cells will be investigated by analyzing cytokine secretion properties (e.g. IL-2, IFN-γ, TNF-α) and surface expression of CD107a/b as a surrogate marker of cytotoxic activities. CD69, CD161, NKp46, NKG2, and CD85J expression will be analysed on NK cells.

- Absolute counts, phenotypic characteristics, and functional properties of monocytes and dendritic cells using standard cell marker panels by flow cytometry.

- Romidepsin levels at the end of infusion and at 1 day after each infusion in treatment cycle 1.

4 Study Design

The design is a randomized interventional phase 2a trial of romidepsin with or without 3BNC117 in HIV-1-infected patients on ART, conducted as a multi-center study at the Department of Infectious Diseases, Aarhus University Hospital, Denmark, the Rockefeller University Hospital, USA, and the University Hospital of Cologne, Germany. Enrollment will be competitive; it is anticipated that each site will enroll approximately 10 participants.

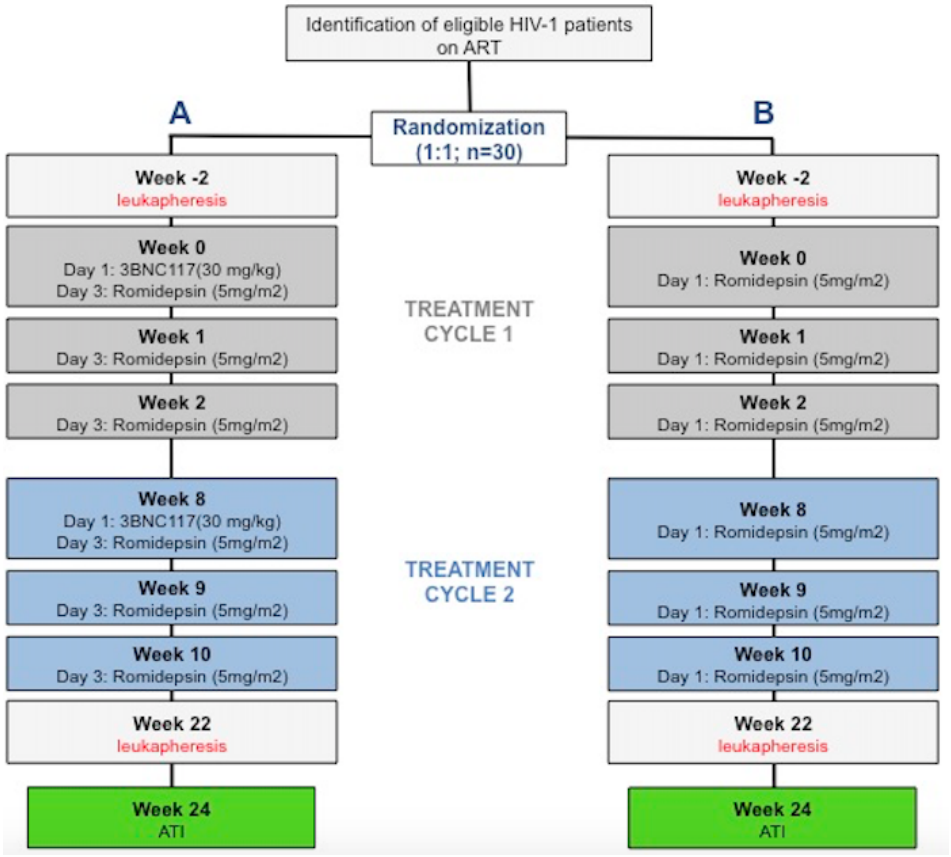
Participants will be randomized 1:1 in a non-blinded fashion to receive one of two regimens:

A) Two treatment cycles each consisting of 3BNC117 infusions (30mg/kg) + three romidepsin infusions (5mg/m^2); or
B) Two treatment cycles each consisting of three romidepsin infusions (5mg/m^2).

ART will be discontinued 16 weeks after the start of the second treatment cycle (analytical treatment interruption, ATI) and subjects will be monitored closely for viral rebound. The study outline is shown in **Figure 1**. The targeted enrolment is 30 subjects (15 per arm).

Leukapheresis will be performed before and after the two treatment cycles to guarantee sufficient material to investigate changes in the reservoir after the interventions.

Figure 1. Study Design



5 Study Population

HIV-infected males and females, between the ages of 18-65, on ART for at least 24 months, with HIV-1 RNA plasma level of < 50 copies/ml by standard assays for at least 18 months, and with current CD4+ T cell counts > 500 cells/µl.

5.1 Inclusion Criteria

1. Adults age 18-65 years with documented HIV-1 infection
2. CD4+ T-cell count > 500 cells/mm^3 at screening
3. On ART for a minimum of 18 months and HIV-1 RNA plasma level of < 50 copies/ml by standard assays for at least 12 months (a single viral load measurement > 50 but < 500 copies/ml during this 12 month time period is allowable).

4. Individuals on protease inhibitor, NNRTI-based regimens, or regimens containing cobicistat must be willing to switch to an integrase-inhibitor-based regimen (raltegravir or dolutegravir) prior to enrollment.

5.2 Exclusion Criteria

1. Use of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the investigators within the last 6 months.
2. Pregnancy as determined by a positive urine or serum beta-hCG.
3. Participant unwilling to use two reliable contraception methods (i.e. condom with spermicide, diaphragm with spermicide, progestin-only containing intrauterine device (IUD) (eg, Mirena, Implanon), non-estrogen containing formulations of hormonal birth control drugs with condom) for the study duration. Romidepsin may interact with estrogen-based contraceptives and such agents may be unreliable in participants receiving romidepsin.
4. Currently breast-feeding.
5. History of resistance to 2 or more classes of antiretroviral medication.
6. Any medical, psychiatric, social, or occupational condition that, as judged by the investigators, would interfere with the evaluation of study objectives (such as severe alcohol or drug abuse, dementia, autoimmune diseases).
7. Acute or chronic hepatitis B or C infection as indicated by the presence of Hepatitis B surface antigen (HBsAg) or hepatitis C virus RNA (HCV-RNA) in blood.
8. A history of AIDS-defining illness within 3 years prior to enrollment.
9. History of B-cell lymphoma, including CNS lymphoma
10. CD4 nadir < 200 cells/mm^3 within the last 5 years.
11. History of significant coronary artery disease, myocardial infarction, percutaneous coronary intervention with placement of cardiac stents, or family history of sudden death at age < 50 years.
12. ECG at screening that shows QTc >450 msec when calculated using the Fridericia formula from either lead V3 or V4, pathological Q-waves (Q-wave > 40 msec or depth > 0.4-0.5 mV), evidence of a ventricular pre-excitation syndromes, complete or incomplete LBBB or RBBB, second or third degree heart block, QRS duration > 120 msec, or bradycardia defined by sinus rate < 50 bps.
13. Use of QT-prolonging medication, renal or hepatic disease, structural heart disease or left ventricular dysfunction
14. Any symptomatic or asymptomatic arrhythmia excluding sinus arrhythmia or bradycardia ≥ 50 bps.
15. Use of Coumadin or Coumadin derivatives
16. Laboratory abnormalities in the parameters listed below:
    a. Absolute neutrophil count ≤ 1,000 cells/µl
    b. Hemoglobin < 11 gm/dL
    c. Platelet count < 125,000 cells/µl
    d. ALT ≥ 1.25 x ULN
    e. AST ≥ 1.25 x ULN

f. Total bilirubin > 1.0 ULN
g. eGFR < 60 mL/min/1.73m^2

17. Any vaccination within 14 days prior to 3BNC117 administration;
18. Receipt of any therapeutic HIV vaccine in the past;
19. Receipt of any anti-HIV monoclonal antibody in the past, or HDAC inhibitor of any kind in the past 2 years;
20. Participation in another clinical study of an investigational product currently or within past 12 weeks, or expected participation during this study.

6 Methods and Procedures

6.1 Screening Procedure and Study Visits

The Time of Events Schedule summarizes the frequency and timing of various study assessments. See Appendix A. Recruitment, screening and all visits during the study period are performed either at The Rockefeller University Hospital (RUH) outpatient clinic, at the Aarhus University Hospital (AUH) outpatient clinic or at the infectious diseases outpatient clinic of the University Hospital of Cologne (UCH).

6.1.1 Pre-Screening Questionnaire

Subjects eligible for enrollment might be recruited at the RUH, AUH or UCH outpatient clinics. Potential participants will first undergo pre-screening by telephone to assess medical history, preliminary HIV risk assessment, and qualification for the study. Potential volunteers will have the opportunity to discuss the study and ask questions of the study recruiter at this time. Those who are eligible and interested in participating will attend a screening visit at the RUH, the AUH or the UCH Outpatient Clinics.

6.1.2 Screening Visits

Screening Visit (day -56 to 0):

Study personnel will answer any questions about the study. Written informed consent will be obtained prior to conducting any study procedures. To ensure informed consent, the principal investigator or designee will discuss the following processes individually with each volunteer:

1. Pregnancy avoidance counseling. Sexually active males and females, participating in sexual activity that could lead to pregnancy, should use two reliable forms of contraception for the duration of the trial.
2. Risk reduction counseling. Sexually active males and females will be asked to use condoms during the short analytical treatment interruption due to the risk of intermittent viremia.
3. One must assume that no improvement in control of HIV infection will occur given the exploratory nature of this study.
4. Subjects agree to stopping their antiretroviral medications as planned in the protocol and agree to return for scheduled follow up visits for monitoring of plasma virus levels.

If the volunteer consents to participate, site personnel will:

- Obtain a complete medical history (including concomitant medications and cardiovascular history);
- Assure that all inclusion criteria are met and there are no exclusion criteria;
- Review subject's previous HIV-1 viral load and CD4 measurements (records should be available for at least 1.5 years prior to screening);
- Perform an ECG;
- Perform a general physical examination including height, weight, vital signs (pulse, respiratory rate, blood pressure and temperature), examination of skin, respiratory, cardiovascular and abdominal systems, and an assessment of cervical and axillary lymph nodes;
- Collect blood and urine specimens for all tests as indicated in the Time of Events Schedule, including plasma HIV-1 RNA levels and CD4 counts;
- Perform a pregnancy test for all female volunteers;

6.1.3 Change in ART regimen

Upon meeting eligibility criteria, individuals on protease inhibitor or NNRTI-based regimens, or regimens containing cobicistat will be switched to an integrase-inhibitor-based regimen (raltegravir or dolutegravir) that does not contain cobicistat. The change in ART regimen will occur at least 2 weeks prior to baseline leukapheresis (Visit 2, week -2).

Study investigators will discuss changes in ART regimen with the participant's primary care physician.

6.1.4 Leukapheresis / Blood Draw visits

Leukapheresis will be performed on day -14 and day 154 (12 weeks after completion of treatment cycle 2).

On leukapheresis visits, site personnel will:

- Answer any questions about the study;
- Perform leukapheresis;
- Obtain changes in concomitant medications;
- Assess weight, height and vital signs (pulse, respiratory rate, blood pressure and temperature);
- Perform a directed physical examination;
- Perform a pregnancy test for all female volunteers;
- Perform pregnancy avoidance counseling;
- Collect blood and urine specimens for all tests as indicated in the Time of Events Schedule (Appendix A);
- Assess the occurrence of any adverse events;

Leukapheresis samples will be used for viral outgrowth assay and other research assays.

6.1.5 Treatment Cycles 1 and 2

3BNC117 infusion visits (days 0 and 56 for Group A only)

Prior to drug infusion, site personnel will:

- Answer any questions about the study;
- Review interim medical history (including concomitant medications);
- Review safety laboratory data;
- Perform a physical examination including weight, vital signs (pulse, respiratory rate, blood pressure and temperature) and any further examination indicated by history or observation;
- Collect blood and urine specimens for all tests as indicated in the Time of Events Schedule (Appendix A);
- Perform pregnancy and safe sex counseling;
- Perform a pregnancy test for all pre-menopausal female volunteers and obtain results prior to drug infusion;
- Perform baseline assessment and record any systemic symptoms;
- 3BNC117 will be prepared for administration according to the Site Pharmacy Standard Operating Procedures;
- 3BNC117 mAb will be administered via a peripheral vein by slow intravenous infusion.
- The infusion will take approximately 60 minutes.
- Subjects will be observed for adverse reactions at the study site for 1 hour after end of infusion. Presence or absence of adverse events will be recorded at 1 hour post infusion.
- Vital signs (pulse, respiratory rate, blood pressure and temperature) will be monitored at the end of infusion, 30 (+/- 5 min) minutes, and 1 hr (+/- 5 min) post infusion.
- If volunteers develop acute infusion reaction during 3BNC117 administration, the infusion will be held. Rescue medications, including acetaminophen, diphenhydramine and glucocorticoids will be available in the RUH, AUH or UCH infusion unit for use if clinically indicated. Infusion may be reinitiated after symptoms improve, and the remaining dose will be administered over 3 hours.

<u>Romidepsin infusion visits (days 2, 9, 16, 58, 65, and 72 for Group A; days 0, 7, 14, 56, 63, and 70 for Group B)</u>

Prior to drug infusion, site personnel will:

- Answer any questions about the study;
- Review interim medical history (including concomitant medications);
- Review safety laboratory data, including electrolytes;
- Perform a physical examination including weight, vital signs (pulse, respiratory rate, blood pressure and temperature), and any further examination indicated by history or observation;
- Collect blood and urine specimens for all tests as indicated in the Time of Events Schedule (Appendix A);
- Perform pregnancy and safe sex counseling;

- Perform a pregnancy test for all pre-menopausal female volunteers (blood will be sent STAT) and obtain results prior to drug infusion;
- Perform baseline assessment and record any systemic symptoms;
- Participants will be administered prophylactic ondansetron 8 mg, orally (PO), approximately 30 minutes prior to starting the infusion.
- Additional details regarding romidepsin administration are described below in Section 6.2.4
- If volunteers develop acute infusion reaction during romidepsin administration, the infusion will be held. Rescue medications, including acetaminophen, diphenhydramine and glucocorticoids will be available at the site infusion unit for use if clinically indicated. Infusion may be reinitiated after symptoms improve as per Appendix D.

Post-infusion follow up visits (days 3, 10, 12, 17, 23, 30, 59, 66, 68, 73, 75, 82 for Group A; days 1, 8, 10, 15, 21, 28, 57, 64, 66, 71, 73, 80 for Group B).

After romidepsin infusions, follow up visits will be performed two to three times a week (see the Time of Events Schedule, Appendix A).

On these visits, site personnel will:

- Answer any questions about the study;
- Review interim medical history (including concomitant medications);
- Review safety laboratory data;
- Perform a directed physical examination including vital signs (pulse, respiratory rate, blood pressure and temperature), and any further examination indicated by history or observation;
- On the visits that occur the day following romidepsin infusion, an ECG will be performed;
- Collect blood and urine specimens for all tests as indicated in the Time of Events Schedule (Appendix A);
- Assess the occurrence of any adverse events;

Specific procedures to be performed at each clinic visit are illustrated in the Time of Events Schedule (Appendix A).

Contact only visit (day 119 for Group A, day 119 for Group B)
Six weeks after the conclusion of the second treatment cycle, participants will be contacted by phone or email to assess for any changes to their medication or adverse events.

6.1.6 Analytical treatment interruption

During ART interruption follow up visits will be performed on a weekly basis (Appendix A, Time of Events Schedule).

- Answer any questions about the study;

- Review of interim medical history and use of concomitant medications;
- Assessment of adverse events;
- Pregnancy counseling (monthly) and pregnancy testing (every 2 weeks);
- Review of safety laboratory data (monthly);
- Directed physical examination including weight, vital signs (pulse, respiratory rate, blood pressure and temperature), and any further examination indicated by history or observation;
- Collection of blood and urine specimens for all tests as indicated in the Time of Events Schedule (Appendix A);
- In case of adverse event(s), the volunteer will be assessed and followed up by the clinical team. Supplemental visit(s) for further investigation can be planned at the discretion of the principal investigator or designee. Supplemental visit(s) may be recommended if clinically indicated or to clarify observations. Any abnormalities (adverse events) attributed to study drug, including laboratory abnormalities, should be subsequently followed until the event or its sequelae resolve or stabilize.

6.1.7 ART interruption and re-initiation of combination ART

ART regimen will be discontinued at week 24, 16 weeks after the second 3BNC117 infusion. ART will be discontinued for 12 weeks and if viral rebound does not occur, subjects can remain off ART with continued follow up.

At week 36, if a subject's HIV-1 VL remains undetectable, the subject will have the option to restart ART at that time or to continue weekly follow up through the end of the study (week 48). During the ATI, ART will be resumed if plasma HIV-1 RNA level ≥ 200 copies/ml in 2 consecutive measurements or if CD4+ count drops < 350 cells/µl and the result is confirmed upon repeat measurement. In this case repeat measurements are performed at the next scheduled visit. If the HIV-1 RNA level is found to be ≥ 1000 copies/ml the subject will be contacted to return to clinic as soon as the result becomes available. Upon viral rebound, viral genotyping will be performed to determine if any resistance mutations are present. ART will also be reinitiated if the participant becomes pregnant, or if otherwise clinically indicated.

Subjects who experience viral rebound during the ATI will be followed on a modified schedule (Appendix B). These subjects will have study visits every 2 weeks until their HIV-1 VL is undetectable on 2 consecutive measurements. At that point, they will be followed every 8 weeks until the final visit at week 48.

Subjects' primary care physicians will be contacted when virologic rebound occurs and periodically throughout the study.

During ATI phase of the study subjects may be at increased risk of transmitting HIV to their partners and of HIV-1 superinfection from an HIV-infected partner. Therefore, subjects will be asked to use male or female condoms for the duration of ART interruption. In the event of a high-risk exposure to an HIV-infected partner, a subject may re-initiate ART as clinically indicated by his/her HIV primary care physician.

6.1.8 Final Visit/Early Termination Visit

Assessments will be undertaken according to the Time of Events Schedule (Appendix A).

6.1.9 Long term safety follow up (Years 2 and 3)

Volunteers will be contacted by telephone or email 2 and 3 years after last romidepsin infusion to collect information regarding new health concerns, diagnoses, hospitalizations, or congenital abnormalities.

6.1.10 Discontinuation of 3BNC117 infusion and/or volunteer withdrawal from study

6.1.10.1 Discontinuation of 3BNC117 infusion

The 3BNC117 infusion will be discontinued for any of the following reasons:

1. Any immediate hypersensitivity reaction (such as urticarial rash; bronchospasm; laryngeal edema; anaphylaxis; syncope).
2. Life threatening medical event during 3BNC117 infusion.

6.1.10.2 Discontinuation from subsequent 3BNC117 infusion

Volunteers will be discontinued from second 3BNC117 infusion for any of the following reasons:

1. A disease or condition or an adverse event that may develop, regardless of relationship to 3BNC117, if the principal investigator or designee is of the opinion that another 3BNC117 infusion will jeopardize the safety of the volunteer.
2. Any immediate hypersensitivity reaction (such as urticarial rash; bronchospasm; laryngeal edema; anaphylaxis; syncope).
3. Life threatening medical event following 3BNC117 unless not related to the investigational product.
4. Intercurrent use of immunosuppressive medication considered significant by the trial physician (e.g., systemic corticosteroids).
5. Pregnancy.
6. Subject's request to discontinue further 3BNC117 infusions.
7. ALT or AST increases of or exceeding 3 x the upper limit of normal with concurrent increase in total bilirubin of or exceeding 2 x the upper limit of normal.

6.1.10.3 Discontinuation of Romidepsin infusion

The romidepsin infusion will be discontinued for any of the following reasons:

1. Any immediate hypersensitivity reaction (such as urticarial rash; bronchospasm; laryngeal edema; anaphylaxis; syncope).
2. Life threatening medical event during romidepsin infusion.

6.1.10.4 Discontinuation from subsequent Romidepsin infusions and Romidepsin dosing modification

Participants should continue to receive therapy until they complete the planned infusions or study treatment is not tolerated. If study drug-related toxicities are observed, treatment can be resumed only if these toxicities have returned to baseline level or their severity decreased to ≤ grade 1 according to the Common Terminology Criteria for Adverse Events v.4.03 (CTCAE) for infusion-related toxicity and the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0 for non-infusion-related toxicity. Discontinuation from subsequent romidepsin infusions will occur for the following reasons:

1. Grade 3 or 4 adverse events deemed related to romidepsin. Review by the protocol safety review team (PSRT) and the safety monitoring committee (SMC) will occur to determine if romidepsin may be restarted at a reduced dose. Guidelines for romidepsin dose reduction are provided in Appendix D.
2. A second occurrence of a grade 3 abnormality of ALT, AST, total bilirubin, ANC, platelet count, or hemoglobin.
3. Grade 4 abnormalities of ANC, platelet count, or hemoglobin. A review by the PSRT and SMC will occur to determine if a study pause is required.
4. ALT or AST increases of or exceeding 3 x the upper limit of normal with concurrent increase in total bilirubin of or exceeding 2 x the upper limit of normal. In this instance, discontinuation of 3BNC117 will occur as well. A review by the PSRT and SMC will occur to determine if a study pause is required.

The dose of romidepsin may be modified for a participant (Appendix D). 3BNC117 dose modification is not allowed.

6.1.10.5 Withdrawal from the study (Early Termination)

Volunteers may be withdrawn from the study permanently for the following reasons:

1. Volunteers may withdraw from the study at any time if they wish to do so, for any reason.
2. Following an adverse event at the discretion of the investigator (or designee).
3. Request of the primary care provider if s/he thinks the study is no longer in the best interest of the subject.
4. Subject judged by the investigator to be at significant risk of failing to comply with the protocol in a manner that might lead to harm to self or seriously interfere with the validity of the study results.
5. At the discretion of the FDA, Danish Health Authority, the PEI, the BfArm or investigator.

6.1.10.6 Follow up after withdrawal from the study (Early Termination)

Any adverse event resulting in withdrawal of a volunteer will be followed up until resolution or until the adverse event is judged by the principal investigator or designee to have stabilized where possible.

At the time of withdrawal, provided the volunteer is willing, all visit procedures from the final study visit will be performed as per the Time of Events Schedule (Appendix A).

The date and reason for withdrawal from the study (early termination) should be collected and reported to the Sponsor at the RU, the SMC and the local IRBs. Volunteers who are withdrawn from the study (early termination) after receiving at least one dose of 3BNC117 or romidepsin will not be replaced, but, wherever possible, will be followed until the time of their final planned visit.

A pregnant volunteer will not receive a 3BNC117 and/or romidepsin infusion. If pregnancy occurs after any 3BNC117 and/or romidepsin infusion, the participant will be asked to return for follow up every 4-6 weeks until delivery. Approximately 2-4 weeks after delivery, the baby will be examined by a pediatrician of the participant's choosing to assess the health status of the baby. Financial assistance will be provided to pay for the visit if necessary. The health status of the baby will be reported to the Sponsor at the RU, the SMC and the local IRBs.

6.2 Study Procedures

6.2.1 Consent Procedure

Prior to the initiation of any study related procedures, the potential subjects will be given a copy of the most recent IRB approved informed consent to read. Additionally, the PI or study staff member who has been designated to consent will discuss the specifics of the study including but not limited to the purpose of the research, procedures, time commitment, required tasks, test article or device, alternative treatments, benefits, risks, confidentiality etc. in a comprehensible (non-scientific) manner, using language readily understandable by the subject. Subjects will be told that participation is voluntary and that, if they do not consent, they will not be penalized. The person consenting will assure the voluntariness of the subject.

A private, confidential setting will be provided for the potential subject to read and discuss the informed consent free from coercion, undue influence or constraints of time. All subjects will be given a chance to ask questions and express concerns. They will be given the option to take the consent home and discuss it with family, friends, and /or health care providers. After a subject and the person conducting the consenting signs and dates the consent, the subject will be given a copy of the signed informed consent form.

An enrollment note will be written in the source document as to who obtained consent, how, when were questions asked and answered, and that a copy of the informed consent was given to the subject.

The "Teach Back" method will be used in the clinical research setting to ask research participants to repeat or "teach back" the information, concepts and directions that the staff member has attempted to convey to the subject. This method is used to assess

comprehension and retention of protocol requirements, adverse event information, risks and benefits, and the subject's rights described in the Informed Consent process.

Subjects for whom English, German or Danish is not a primary language will not be included in this study.

6.2.2 Study Assignment

This is a randomized, open-label study. The study drugs are dispensed as specified by the randomization scheme generated by the Institute of Medical Statistics, Informatics and Epidemiology (IMSIE), University of Cologne. Participants are centrally assigned to a single treatment according to randomly permuted blocks of varying length. Randomization is stratified by study site and implemented as a 24-7 Internet service.

6.2.3 3BNC117 Administration Procedure

3BNC117 will be provided in single-use vials containing 5 ml of the product at a concentration of 20 mg/ml. The site research pharmacist will calculate the volume of 3BNC117 to be administered. 3BNC117 will be administered as a slow intravenous infusion over 60 minutes in the site infusion unit. The calculated dose of 3BNC117 will be diluted in 0.9% Sodium Chloride, USP to a volume of 250 ml. 3BNC117 should be administered within 3 hours of preparation.

3BNC117 will be administered intravenously, via a peripheral vein in one of the upper extremities. The administration site should be free of potentially complicating dermatologic conditions. At the end of infusion, the IV line will be flushed with 20 ml of Normal Saline to ensure all the medication has been delivered.

Volunteers will remain in the infusion unit for 1 hour after drug infusion. If volunteers develop acute infusion reaction during 3BNC117 administration, the infusion will be held. Rescue medications, including acetaminophen, diphenhydramine and glucocorticoids will be available for use if clinically indicated. Infusion may be reinitiated after symptoms improve, and the remaining dose will be administered over 3 hours.

6.2.4 Romidepsin Administration Procedure

Romidepsin is supplied as a kit containing 1 vial of romidepsin, 10 mg, and 1 vial of diluent for romidepsin, 2 mL, per carton. The volume of romidepsin to be administered will be calculated by the site research pharmacist, and diluted in 500 mL 0.9% Sodium Chloride, USP. Romidepsin is chemically stable for up to 8 hours at room temperature, upon reconstitution. When diluted in 500 mL 0.9% Sodium Chloride, USP, solution is stable for 24 hours. Romidepsin infusions will be administered over 120 minutes. Only staff trained to administer chemotherapeutic agents will administer romidepsin.

Romidepsin infusions will be administered by a trained research nurse with extensive experience with IV medication and the treatment of acute infusion-related reactions.

- Check electrolytes prior to infusion. Infusion will be administered if potassium, magnesium and calcium levels are within normal range. If potassium, magnesium and/or calcium level(s) are outside of the normal range, a repeat measurement will be obtained. If the electrolyte abnormality is confirmed, the infusion will be postponed. The participant will be supplemented as medically indicated and retested prior to infusion.
- Premedicate with ondansetron 8mg orally at least 30 min prior to infusion, to prevent nausea or vomiting
- Perform ECG 30 min after ondansetron, before infusion starts. The pre-infusion ECG will be read by a cardiologist. Infusion will be administered if QTc < 450 msec. (QTc measured from lead V3 or V4, using the Fridericia formula).
- Participants will be kept on continuous cardiac monitoring during infusion and a repeat ECG will be performed at 1 hour, during the infusion. If at 1 hour of infusion the QTc is > 450 msec or if it increases > 10 msec, hold infusion and consult with a cardiologist to determine appropriate monitoring and/or management, as clinically indicated;
- ECG will be repeated at the end of the infusion. If the QTc is > 450 msec or if it increases > 10 msec from the post-antiemetic ECG, repeat ECGs will be performed and vital signs measured at 2 and 4 hours post infusion and a cardiologist will be consulted to determine appropriate monitoring and/or management, as clinically indicated.
- Allergic reactions to romidepsin are uncommon but during the first 10 minutes of infusion all subjects will be under direct observation for acute allergic reactions.
- Vital signs (pulse, respiratory rate, blood pressure and temperature) will be monitored at the end of infusion, 30 (+/- 5) minutes, and 1 hour (+/- 5 min) post infusion.
- Subjects will be observed for adverse reactions at the study site for 1 hour after end of infusion.
- The study sites will have full and immediate access to handle and treat all acute medical emergencies including severe drug reactions.
- A medical doctor dedicated to the study will be present at all times at the study site during the infusions.
- A prescription for ondansetron will be given to participants to ameliorate any symptoms that may develop in the 48 hours following romidepsin infusion.

6.2.5 Medical History and Physical Examination

At the time of screening, a past medical history will be collected that will include details of any previous reaction to vaccination, and contraceptive practices. Interim medical histories will be collected at time-points according to the Time of Events Schedule (Appendix A).

A general physical examination will be conducted including weight, height, vital signs, and examination of skin, respiratory, cardiovascular, central nervous and abdominal systems. At the time of 3BNC117 and romidepsin infusions and at selected time-points thereafter, general and/or directed physical examinations will be performed according to

the Time of Events Schedule (Appendix A). A directed physical examination will include vital signs and any further examination indicated by history or observation.

6.2.6 Blood Collection and Shipment

Venous blood will be collected at every study visit, usually from the antecubital fossa, according to the Time of Events Schedule (Appendix A). Total volume collected during the study will not exceed 550 ml in any 8-week period.

All specimens will be handled according to Processing Laboratory SOPs. Frozen PBMCs, plasma and serum will be processed and stored at the study sites.

6.2.7 Monitoring for cytokine release associated adverse events and treatment of cytokine release syndrome

Based on previous clinical experience with similar monoclonal antibodies and with 3BNC117 (protocols MCA-835, MCA-866 and MCA-867), it is unlikely that administration of 3BNC117 will lead to cytokine release syndrome. However, a potential side effect of a monoclonal antibody can be the stimulation of a massive release of cellular cytokines, which can have profound effects on blood pressure, vascular integrity, and myocardial, lung, liver, and kidney functions. If cytokine release syndrome occurs, the volunteer may need to be treated with intravenous fluids, vasopressors, and high-dose corticosteroids and may require ventilatory support.

Study participants will be monitored for 1 hour post infusion in the site infusion unit. Access to a twenty-four hour on-call physician is available at all sites. The study sites are equipped with crash carts for immediate medical care. Supportive medications, including acetaminophen, diphenhydramine and glucocorticoids, will be available at both clinical sites for use if clinically indicated. In case of an emergency, after stabilization of the volunteer, he/she will be transferred to a tertiary care center for specialized medical care.

6.2.8 Family Planning Counseling

During screening and subsequent study visits, study personnel will counsel volunteers about the importance of prevention of pregnancies and the use of condoms, as well as other effective family planning methods. Condoms will be provided.

Participants will be required to use 2 effective forms of contraception (i.e. condom with spermicide, diaphragm with spermicide, progestin-only containing intrauterine device (IUD) (eg, Mirena, Implanon, Nuva Ring), non-estrogen containing formulations of hormonal birth control drugs with condom) for the study duration.

Pregnancy tests will be conducted at each clinic visit as outlined in the Time of Events Schedule (Appendix A). Should pregnancy be detected before administration of 3BNC117 or romidepsin, the volunteer will not receive the infusion. Should pregnancy be detected after any 3BNC117 or romidepsin infusion, a pregnant volunteer will be asked to return for follow up every 4-6 weeks until delivery. Should pregnancy occur, ART will not be discontinued or will be resumed as soon as the study investigators become aware of the pregnancy. Approximately 2-4 weeks after delivery, the baby will

be examined by a pediatrician of the participant's choosing to assess the health status of the baby. Financial assistance will be provided to pay for the visit if necessary. The outcome of the pregnancy and the health status of the baby will be reported to the Sponsor at the RU, the local IRBs, and the SMC.

6.2.9 Compensation

Study volunteers will be compensated according to local standards.

6.2.10 Safety Assessments

6.2.10.1 Solicited Adverse Events

Solicited adverse events in this study include presence of feverishness, chills, headache, nausea, vomiting, diarrhea, malaise, myalgia and arthralgia, as well as ocular complaints such as conjunctival erythema, excessive tearing or burning within 2 weeks of 3BNC117 and/or romidepsin administration, and will be collected prospectively by structured interviews on the 3BNC117 and romidepsin infusion and post-infusion follow up visits; recorded and graded according to pre-established criteria (see C). The CTCAE v4.03 grading scale will be used to grade infusion-related adverse events. The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0 will be used to grade all non-infusion-related adverse events.

Vital signs (pulse, respiratory rate, blood pressure and temperature) will be measured prior to 3BNC117 or romidepsin administration, at the end of infusion, at 30 minutes, and 1 hour after the infusion is completed, graded according to Appendix C and recorded. Similarly, the occurrence of adverse events will be assessed and graded. All medications required for treatment of adverse events will be recorded.

6.2.10.2 Other Adverse Events

Other adverse events will be recorded following an open question to volunteers, with the dates of commencement and resolution and any medication required. All adverse events will be followed to resolution. Serious adverse events will be collected during the entire study period. They will be graded as indicated in Appendix C.

Safety monitoring at each clinical site will be conducted by an external monitor and by an external Study Monitoring Committee (SMC). The RUH, AUH and UCH IRBs will conduct the initial review of the proposed study and will follow progress through annual reports and by immediate notification of serious and unanticipated adverse events. Any serious adverse events will be reviewed by the study investigators immediately. Site investigators will notify the local IRB and the sponsor at the Rockefeller University within 2 working days from the investigators being made aware of the event. The RU sponsor will notify the FDA, Danish Health Authority, PEI, and BfArm per 21 CFR 312 (Appendix G). The SMC will be available to the investigators for consultation and review of severe adverse events if needed.

6.2.10.3 Routine Laboratory Parameters

As outlined in the Time of Events Schedule, laboratory parameters will include CD4+ T cell counts and HIV-1 VLs, hematology, clinical chemistry, and urinalysis. ANA will be performed at screening.

Prior to each 3BNC117 or romidepsin infusion, pre-menopausal female volunteers will have serum beta-HCG assessed and at follow up visits they will have urine beta-HCG checked. The laboratory samples for these tests will be collected at the time points indicated in the Time of Events Schedule (Appendix A). In the event of an abnormal laboratory value, volunteers may be asked to have an additional sample collected at the discretion of the principal investigator or designee.

Volunteers will be screened for syphilis and viral hepatitis (HBsAg and HCV-RNA) at the Screening Visit.

6.2.11 Diagnostic work up in the event of graded elevations in total bilirubin

Any participant with a graded elevation in total bilirubin will undergo a diagnostic work up that includes right upper quadrant ultrasound, testing for gamma glutamyl transferase (GGT) HAV (IgM and IgG), HBV (hepatitis B surface antigen and IgM anti-hepatitis B core antigen), HCV (anti-hepatitis C antibody and HCV PCR), EBV (IgM and IgG VCA and EBNA antibodies), CMV (IgM and IgG), VZV (IgM and IgG) and HSV (IgM and IgG), and any other relevant laboratory tests as determined by the investigators. Participants will be referred for evaluation by a hepatologist in the event of ALT or AST increase equal to or greater than 3x the upper limit of normal with concurrent increase in total bilirubin equal to or greater than 2x the upper limit of normal, and if otherwise clinically indicated.

These evaluations will be of no cost to the participant.

6.2.12 Antiretroviral and Immunogenicity Assessments

HIV-1 levels will be assessed by (Appendix A):

1. Standard HIV-1 viral load assay (Cobas Taqman) (CLEP-certified) will be performed at a contracted laboratory, LabCorp (RUH site) and at the AUH and CUH clinical virology labs. The detection range of the assay is 20-10x10^6 copies/ml. HIV-1 viral load will be determined at multiple time points before and after 3BNC117 administration.

2. Transcription mediated amplification is a qualitative method to detect plasma HIV-1 RNA (Procleix Ultrio Plus, Genprobe). It has 50% sensitivity at 3.8 copies/mL and 95% sensitivity at 12 copies/mL. TMA results are considered binary and defined as positive or negative according to assay outcomes.

3. Single copy assay has a detection limit of 1-2 copies HIV-1 RNA/mL of plasma. This assay will be performed in the Laboratory of Molecular Immunology. This

assay will be performed on samples collected at baseline (week -2 and day 0), and 1 day after the second romidepsin infusion in each treatment cycle.

4. HIV-1 cell-associated unspliced HIV-1 RNA dd PCR assay. This assay provides an accurate quantification of HIV-1 transcriptional activity and will be performed at the AUH site. This assay has a limit of detection of 1 HIV-RNA copy per 1 million CD4+ T cells.

5. HIV-1 cell associated DNA levels in CD4+ T cells will be measured at the AUH site, before and after administration of 3BNC117. This assay has a limit of detection of 10 DNA copies per 10^6 CD4+ T cells. This assay will be performed at the AUH site.

6. The size of the functional HIV-1 reservoir will be determined by the number of infectious unit per 10^6 resting memory $CD4^+$ T cells (IUPM) using a viral outgrowth assay before (week -2) and after therapy, just before ATI (week 22).

Given the large number of cells required for this assay, viral outgrowth assays will not be performed at a later time point. The size of the reservoir in participants who remain virologically suppressed during ATI or are re-suppressed following ART resumption will be evaluated by levels of cell-associated HIV-1 DNA, performed at week 48.

In addition, the effects of 3BNC117 on host immune responses and on circulating HIV-1 strains will be evaluated by the following assays (Appendix A):

7. TZM-bl neutralization assay will performed in the laboratory of Dr. Michael Seaman of the Beth Israel Deaconess Hospital in Boston (a Core Laboratory sponsored by the Collaboration for AIDS Vaccine Discovery, CAVD). *In vitro* neutralization assays will be performed with serum from study subjects before and after administration of 3BNC117.

8. Phenotypic characteristics for T and NK cells using standard cell marker panels by flow cytometry (e.g. CD3, CD4, CD8, CD45RA, CCR7 for T cells and CD16/CD56 for NK cells) will be determined before and after each treatment cycle. These assays will be performed at the RUH and/or AUH sites.

9. Functional properties of cytotoxic T cells and NK cells before and after each treatment cycle will be investigated by analyzing cytokine secretion properties (e.g. IL-2, IFN-γ, TNF-α) and surface expression of CD107a/b as a surrogate marker of cytotoxic activities. CD69, CD161, NKp46, NKG2, and CD85J expression will be analysed on NK cells. In addition, change from baseline in the capacity of NK and CD8+ T cells to mediate inhibition of viral replication ex vivo will be analyzed. These assays will be performed at the RUH site and the laboratory of Dr. Richard Koup at the Vaccine Research Center (VRC) at NIH, a core lab of the Collaboration for AIDS Vaccine Development (CAVD).

10. Levels of inflammation markers, such as C-reactive protein, D-dimers, IL-6, and soluble CD14 will be performed in plasma or serum samples, prior to and after 3BNC117 infusions. These will be performed at the Laboratory of Molecular Immunology, or by clinical assays at LabCorp.

11. Sequencing – If latently infected virus can be isolated/cultured ex-vivo, sequencing and phylogenetic analysis of HIV-1 env will be performed in samples collected before and after the first and second treatment cycles and at the time of virologic rebound. These analyses will use similar approach to the reported in Caskey et al (2015) and Schoofs et al (2016). This will allow us to compare viruses grown from PBMCs collected from subjects while on ART to rebound viruses collected after treatment interruption and analyze the induction of escape mutations. This will be performed at the RUH and/or the UCH site.

12. Genotypic analysis of antiretroviral resistance in rebounding viral strains (with HIV-1 RNA levels > 400 copies/ml) will be performed by clinical assays at all sites.

13. Evaluation of HIV-1 integration sites by deep sequencing will be performed at the RUH site, before and after the first and second treatment cycles.

Pharmacokinetics and immunogenicity assays (Appendix A):

14. Measurement of 3BNC117 levels by validated sandwich ELISA using a murine anti-idiotype antibody to 3BNC117 and will be performed at Celldex Therapeutics. 3BNC117 levels will be measured in serum or plasma.

15. Anti-drug (3BNC117) antibody responses in serum or plasma. Validated Assays will be performed at Celldex Therapeutics Inc.

16. Measurement of romidepsin levels by validated sandwich ELISA will be performed on samples collected before, at the end of the infusion, and 1 day after each romidepsin infusion during treatment cycle 1.

Research samples collected at all clinical sites will be processed and stored locally, until samples are transferred to a pre-determined site for specific assays, as outlined above. Optimal sample collection, processing, cryopreservation, archiving and storage will be maintained. Additional studies will be performed as warranted at the discretion of the investigators.

6.2.13 Pharmacokinetic evaluations

Pharmacokinetic parameters will be calculated using standard non-compartmental analysis methods. Descriptive results will be presented for the pharmacokinetic parameters.

3BNC117 PK assessments will be performed on plasma or serum samples in Group A before the first 3BNC117 and at multiple time points as outlined in the Time of Events Schedule (Appendix A). Romidepsin PK assessments will be performed on plasma or serum samples. These measurements will be performed during the first treatment cycle at baseline, end of infusion, and 1 day after each romidepsin infusion.

7 Investigational Products

- 3BNC117 is manufactured by Celldex Therapeutics, Inc. 3BNC117 is a recombinant, fully human monoclonal antibody (mAb) of the IgG1κ isotype that specifically binds HIV envgp120. 3BNC117 is being investigated under USFDA IND 118,225.

- Romidepsin (Istodax®) is manufactured by Celgene Corporation. This histone deacetylase (HDAC) inhibitor is a bicyclic depsipeptide.

7.1 Regimen

- 3BNC117 will be administered intravenously at 30 mg/kg dose level on day 0 and day 56 (Group A only).

- Romidepsin will be administered intravenously at 5 mg/m^2 dose level on days 2, 9, 16, 58, 65, and 72 for Group A and days 0, 7, 14, 56, 63, and 70 for Group B.

7.2 Storage and Shipment of the Investigational Products

- 3BNC117 will be shipped from Celldex Therapeutics and will be stored in the site research pharmacy at 2- 8°C. 3BNC117 is a clear liquid, provided in single-use vials containing 5 ml of product at 20 mg/ml concentration. For further information refer to the 3BNC117 IB.

- Romidepsin will be provided by Celgene Corporation and will be stored in the site research pharmacy. At room temperature, romidepsin is a white powder. For further information refer to the romidepsin IB.

7.3 Dispensing and Handling of the Investigational Products

- 3BNC117 will be dispensed by the site research pharmacy. Trial personnel will ensure that the study ID number on the piggy-back matches the study ID assigned to the volunteer prior to administration.

3BNC117 will be provided in single-use vials containing 5 ml of 3BNC117 at a 20 mg/ml concentration. The appropriate dose will be calculated by the site research pharmacist according to subject's weight. 3BNC117 will be dispensed in a piggy-back, and diluted in normal saline (NaCl 0.9%), to a volume of 250 ml. It will be dispensed ready for administration by the study investigators and be good for infusion for 3 hours.

- Romidepsin will be dispensed by the site research pharmacy. Trial personnel will ensure that the study ID number on the piggy-back matches the study ID assigned to the volunteer prior to administration.

7.4 Accountability and Disposal of Used and Unused Investigational Product

The date, allocation number and location of storage of the vials will be recorded in a log at each study site. During the trial, the product accountability form, and the dispensing log will be monitored. At the end of the trial, unused 3BNC117 vials will be returned to Celldex Therapeutics or destroyed; unused romidepsin vials will be returned to Celgene Corporation or destroyed.

7.5 Concomitant and Prohibited Medications

- As per the manufacturer of romidepsin, the prophylactic use of antiemetics such as ondansetron is strongly encouraged.

- Any medications listed in Appendix E, which may cause QTc prolongation or induce torsades de pointes should not be used.

- Concomitant use of CYP3A4 or Pgp inhibitors with romidepsin should be avoided (excluding granisetron and ondansetron) to prevent potential increase in romidepsin exposure during concomitant treatment with these drugs. Should a patient already enrolled on this study require treatment with these drugs (as listed in Appendix F) romidepsin must be interrupted prior to starting these drugs and should not resume until a washout period of at least 5 half-lives has elapsed. All participants taking protease inhibitors, which are strong inhibitors of P450 3A4, will be switched to an integrase inhibitor prior to enrollment. In addition, participants on regimens that contain cobicistat (a CYP3A4 and Pgp inhibitor) will be switched to an integrase inhibitor-based regimen that does not include cobisistat.

- Any medications that have the potential to alter serum electrolytes (e.g., diuretics) should be monitored very closely for electrolyte abnormalities as these can contribute to the risk of QT prolongation and ventricular arrhythmias.

- Romidepsin can prolong PT and elevate INR in patients receiving warfarin. Patients on warfarin will be excluded from the study.

8 Data Analysis

8.1 Analysis of Antiretroviral effects, Safety and Pharmacokinetics

Primary Endpoint:

1. Days to viral rebound during ATI or days to reinitiation of ART in participants who restart ART before viral rebound. Viral rebound is defined as HIV-1 RNA $\geq$ 200 copies/ml on 2 consecutive measurements during ATI. If viral rebound occurs, the

date of the first measurement of HIV-1 RNA ≥ 200 copies/mL will be defined as "date of viral rebound." As primary analysis, we will use the Wilcoxon-Mann-Whitney test to compare the median time to viral rebound between the two study groups. As secondary analysis, we will use the Kaplan-Meier estimator and log-rank test to assess the significance of the difference between the survival curves in the two study arms.

Secondary and Exploratory Endpoints:

1. Safety evaluation:

The number and percentage of subjects experiencing one or more AEs will be summarized by relationship to study drug, and severity. AEs will also be summarized by severity grade and by relationship to study drug according to the CTCAE v4.03 and DAIDS v2.0 grading scale. Changes will be calculated relative to the values collected at baseline.

2. Size of the functional HIV-1 reservoir:

The size of the functional HIV-1 reservoir will be determined by the number of infectious unit per 10^6 resting memory $CD4^+$ T cells (IUPM) using a viral outgrowth assay before (week -2) and after therapy, just before ATI (week 22). Paired student t-test or paired Wilcoxon test will be used to determine changes in reservoir size from baseline to the pre-ATI time-point for each group.

Total HIV-1 DNA, episomal HIV-1 DNA (2-LTR), and unspliced HIV-1 RNA in circulating total $CD4^+$ T cells will also be determined at baseline (week -2, week 0), before and after each treatment cycle, at the pre-ATI time point (week 24), and at and the end of the study (week 48). A 95% repeated measures ANOVA F-test will be used to compare changes in these variables during the study.

3. Plasma HIV-1 RNA:

Plasma HIV-1 RNA levels will be measured by a routine clinical assay (Cobas Taqman; detection limit 20 copies/mL), a transcription mediated amplification (TMA)-based assay (detection limit 12 copies/mL) and/or a single copy assay (detection limit 1-2 copies/mL). Fishers exact or chi-square test will be used to compare the proportion of subjects in both groups with detectable viremia during each romidepsin treatment.

4. Host immune responses:

Functional properties of cytotoxic T cells and NK cells will be correlated to changes in total HIV-1 DNA and IUPM. Flow cytometry data will be evaluated by Boolean partitioning of NK and T cell responses into distinct responding populations (Lamoreaux et al., 2006).

Finally, linear regression will be used to identify predictors of log-transformed time to viral rebound in both arms. P values <0.05 will be considered statistically significant.

5. Other measurements:
The frequency and levels of anti-3BNC117 antibodies, after each 3BNC117 infusion, will be calculated and displayed in tables. Levels of romidepsin will similarly be calculated and displayed in tables. Pharmacokinetic parameters will be calculated using standard non-compartmental analysis methods, using WinNolin software, version 6.4. Pharmacokinetic parameters, including AUC, Cmax, T½, Tmax and others will be summarized.

Genotyping of HIV-1 isolates will be performed by reverse transcription followed by PCR amplification and sequencing of HIV-1 envelope genes. Sequence analysis to identify potential 3BNC117-induced escape mutations will be descriptive.

Continuous data will be summarized by descriptive statistics, including the sample size, mean, standard deviation, median and range. Categorical data will be summarized by the number and percentage of participants. If necessary Log_2 of variables will be used.

8.2 Sample Size Considerations

The sample size calculation is based on the primary analysis for the primary endpoint. We will compare days from day of ART interruption until day of viral rebound or day of reinitiation of ART without viral rebound in arm A to arm B (1:1 randomization) with the Wilcoxon-Mann-Whitney test. Given a standard deviation (SD) of 10 (days), enrolling 12 patients in each of the two arms, will have 80% power to detect ≥ 13 days difference in time to viral rebound at a 5% significance level (Davey et al., 1999; Hamlyn et al., 2012; Hill et al., 2014). The power calculation for this primary analysis was performed in G*power using the minimum Asymptotic Relative Efficiency method.

To accommodate for dropouts, we aim to enroll 30 study subjects in the study (15 in each arm). A dropout rate of ~20% is anticipated.

9 Data and Sample Storage

The Principal Investigator(s) will oversee how the data are collected, entered, and protected. All study data will be collected by the clinical study staff using designated source documents and entered onto the appropriate electronic case report forms (eCRFs). Clinical Trials Centre Cologne will provide a secure web-based database that will be used for data management. Data collection forms (DCFs) will be provided for use as source documents as appropriate. All study data must be verifiable to the source documentation.

All source documents will be kept in a locked facility at the clinical sites and remain separate from volunteer identification information (name, address, etc.) to ensure confidentiality. All data with volunteer identifiers will be kept in a locked facility and/or encrypted files. Source documentation will be available for review to ensure that the collected data are consistent with the eCRFs.

All eCRFs and laboratory reports will be reviewed by the site's clinical team, who will ensure that they are accurate and complete.

All research samples will have a unique identifier. The site PI will be responsible for ensuring project compliance, data analysis and entry, regulatory monitoring, and coordination of the activities of the entire study team. Standard GCP practices will be followed to ensure accurate, reliable and consistent data collection.

Source documents include, but are not limited to:
- Signed Informed Consent Documents
- Dates of visits including date of 3BNC117 and romidepsin infusions
- Documentation of any existing conditions or past conditions relevant to eligibility
- Reported laboratory results
- All adverse events
- Concomitant medications

10 Recruitment Plan

Both men and women ages 18 through 65 will be recruited for the study from the community at large and will be referred by physicians in the community. We will make every effort to recruit minorities and women. We project screening 60 subjects in order to achieve at least 30 evaluable subjects. Enrollment will be competitive across the three trial sites. In case of drop-outs an over-enrollment of 10% will be allowed.

- At RUH, the Clinical Research Support Office at the Rockefeller University Hospital (CRSO) will utilize the Volunteer Repository. Advertisements will also be placed: online (e.g. Craiglist, CenterWatch, etc.), in newspapers (Metro, AMNY) and on campus. In addition, participants will be recruited at Montefiore Medical Center. Recruitment fliers will be placed in the clinic, and interested participants will contact study recruiters at Montefiore. The pre-screening procedure will take place over the phone or in person at Montefiore clinic. Recruiters will collect participant's medical history and other relevant information and will provide the participant a brief description of the study. Potential participants will also have an opportunity to ask questions about the study. If participants show interest and agree to be contacted, their contact information will be shared with Rockefeller site investigators (via secure email) for scheduling of screening visit. Informed consent and all other study-related procedures will occur at the Rockefeller site.

- At AUH, written invitations to participate in the study will be sent to eligible HIV patients.

- At UCH, eligible HIV infected individuals will be invited by phone to participate in the study.

11 Potential Benefits to Subjects

It is unlikely that study subjects will benefit from participating in this study.

12 Potential risks to the subject

- This study entails moderate risk to subjects since 3BNC117 is an investigational new drug with limited human safety data and romidepsin has potential side effects. The study also includes a period of ART interruption. It has been shown that episodic ART guided by CD4+ count decline leads to increased risk of opportunistic infections as compared with continuous ART (Strategies for Management of Antiretroviral Therapy Study et al., 2006). However, different groups have now shown that short analytical treatment interruption is safe (Routy et al., 2012). ART will be resumed if plasma HIV-1 RNA levels increase to ≥ 200 copies/ml and are confirmed upon repeated measurement.

- If the HIV-1 viremia rebounds after ART is discontinued, absolute CD4+ counts might drop. However subjects will be followed very closely and ART will be resumed if the CD4+ cell count drops < 350 cells/µl and this is confirmed upon repeat measurement.

- During ART interruption, subjects might experience symptoms of acute retroviral syndrome, such as fever, rash, lymphadenopathy, headache, sore throat, nausea, vomiting. ART will be resumed if acute retroviral syndrome is suspected by study investigators.

- Resistant viral strains to previous ART medications might arise during the analytical treatment interruption.

- During the ART-interruption phase of the study subjects may be at increased risk of transmitting HIV to their partners, if they become viremic, and of HIV-1 superinfection from an HIV-infected partner. Therefore, subjects will be asked to use male or female condoms for the duration of ART interruption. In the event of a high-risk exposure to an HIV-infected partner, a subject may re-initiate ART as clinically indicated by his/her primary care physician.

- 3BNC117 has now been administrated to 63 volunteers and was generally safe and well tolerated in all doses tested. To date, 8 ART-treated HIV-infected individuals have received two 3BNC117 infusions, administered 3 weeks apart. This is the first time 3BNC117 will be administered in combination with romidepsin.

- While each mAb product has unique safety issues related to its mechanism of action, the major safety concern related to mAbs in general is an infusion/hypersensitivity reaction. These types of reactions are more common for mAbs that contain murine elements compared to human mAbs, such as 3BNC117. Passive administration of anti-HIV-1 antibodies has been evaluated in humans in the past. As observed with other monoclonal antibodies, anti-HIV-1 antibodies were generally safe and well tolerated and most adverse events observed were infusion-related events. (Mehandru et al., 2007b; Trkola et al., 2005b).

- Immunologic symptoms such as listed below are possible with administration of a monoclonal antibody and will be considered adverse events of interest. Potential allergic-type reactions during and immediately following the administration of 3BNC117 will be carefully monitored.
    - Constitutional symptoms, such as fever, rigors/chills;
    - Injection site reaction/extravasation changes, pruritus, urticaria;
    - Serum sickness like syndromes as evidenced by fever, rash, arthralgia, arthritis, nephritis;
    - Deposition of immune complexes in the kidneys leading to renal insufficiency;
    - Adult Respiratory Distress Syndrome, bronchospasm/wheezing, anaphylaxis;
    - Cytokine release syndrome/ acute infusion reaction.

- 3BNC117-resistant viral strains might arise following administration of 3BNC117. Development of 3BNC117 resistance might limit the future use of 3BNC117 by the study subject, if this monoclonal antibody is licensed for clinical use by the FDA.

- In the cross-reactivity study in human tissues, 3BNC117 was found to bind to cells in the conjunctival recesses. It is possible that this binding could lead to conjunctival toxicity. However, when rats and non-human primates were administered 3BNC117, conjunctival toxicity was not observed. Sixty-three participants have received 3BNC117 to date, and 12 participants reported mild ophthalmic complaints (such as pruritus, conjunctival erythema, increased lacrimation) during study follow up. In all instances symptoms resolved without specific treatment and ophthalmologic evaluations 5 months after 3BNC117 administration did not show changes from baseline.

- The adverse effects 3BNC117 administration would have in a fetus or unborn child are unknown.

- Most studies with romidepsin were performed in patients with severe haematological malignancies and used doses up to 15 mg/m^2. The most common adverse events associated with romidepsin involve the GI system (nausea, vomiting, diarrhea/constipation), hematologic condition (thrombocytopenia, leucopenia (neutro- and lymphopenia) and anemia), asthenic conditions (asthenia, fatigue, malaise and lethargy) and finally electrolyte abnormalities (hypomagnesiamia, hypokalemia and hypocalcemia), hyperglycaemia and pyrexia. Overall, the most common grade 3/4 events reported were anaemia, thrombocytopenia, neutropenia, leukopenia and fatigue.

- QT prolongation as well as several morphological changes in ECGs (including T-wave and ST segment changes) has been reported in clinical studies of romidepsin. Many of the ECG morphologic abnormalities were also observed at baseline. These ECG changes were transient and were not associated with functional cardiovascular changes or with symptoms. The clinical significance of these changes is unknown.

- In a pilot study in 6 HIV-1-infected participants on long-term ART, who received 3 infusions of 5 mg/m^2 of romidepsin over the course of 3 weeks, no serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSAR) was observed. Thirty-five AEs were considered related to romidepsin. All drug-related AEs were mild (grade 1, n=35) and resolved spontaneously within a few days. The most common romidepsin-related AEs were abdominal symptoms (e.g. nausea [n=11], borborygmia [n=4], abdominal pain [n=2]) and fatigue (n=5). Modest changes in white blood cell counts (WBC) and T cell counts were observed during the study. Neutrophil counts below 1000 cells/mm^3, CD4+ cell counts below 350 cells/mm^3, or platelet counts below 100,000 cells/mm^3 were not observed.

- 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. However in a study in HIV-infected participants who received panobinostat over a course of 8 weeks (another HDAC inhibitor), CMV DNA (in urine) and EBV DNA (in blood) were monitored and there was no evidence of unintended virus reactivation.

- Clinical data is not available with romidepsin during pregnancy. In this study, use of two contraceptive methods for both female and male study subjects is required for the duration of the study.

- Based on non-clinical findings in repeat-dose toxicity studies, romidepsin has the potential to affect male and female fertility. Testicular atrophy or degeneration occurred in rats at doses corresponding to 1.98 mg/m^2. In dogs, romidepsin caused hypospermia at doses corresponding to ≥ 20mg/m^2. In rats, at doses ≥ 0.1 mg/kg/week corresponding to 0.6 mg/m^2 or a mean steady state AUC0-∞ 4.9 nghr/mL, females exhibited atrophy in the ovary, uterus, vagina and mammary glands. Further, maturation arrest of ovarian follicles was observed in female rats at ≥ 0.3 mg/kg/week corresponding to 1.8 mg/m^2. It is not known if romidepsin can impair fertility in humans, although since the FDA approval of romidepsin in 2009, no cases of fertility-related adverse effects have been reported. If romidepsin does result in ovarian or testicular atrophy, symptoms related to decreased sex hormone production could also occur, such as early menopause, decreases in bone density or libido, and alterations in mood or body habitus. Until now, however, such symptoms have not been observed among HIV patients (n=23) receiving romidepsin at a dosing of 5 mg/m^2 in other experimental trials (Søgaard et al. 2015, Leth et al. 2016).

- Blood drawing and phlebotomy can be associated with pain, bruising, anemia or infection at the site of venipuncture. Rarely, fainting may follow phlebotomy.

13 Procedures to minimize risk

- As outlined above, this study will be an exploratory phase 2 trial of a combination of romidepsin and 3BNC117 in humans. Potential trial volunteers will be informed

about the possible risks of the monoclonal antibody administration and that there may be unknown risks.

- In the US, medical records and routine laboratory data will be handled with HIPAA compliance. Medical records will be protected by the rules and regulations of RUH, AUH and UCH.

- With any new medicine or monoclonal antibody, there is a possibility of totally unexpected side effects. Subjects will be monitored for 1 hour post 3BNC117 or romidepsin infusions in the site infusion unit. The study site infusion units are equipped for providing emergency medical interventions in the unlikely event of acute allergic or other reactions. In case of an emergency, after stabilization of the subject, he/she will be transferred to a tertiary care center, for specialized medical care.

- Subjects will be closely monitored for the development of symptoms of ocular disease (such as blurry vision, increased lacrimation, redness, dryness, pain). If subjects develop symptoms or signs of ocular disease, they will be referred to an ophthalmologist for diagnosis and management. These evaluations will be performed at no cost to the subject.

- During the treatment interruption phase of the study, plasma HIV-1 RNA levels will be monitored weekly and CD4+ T cell counts will be monitored every 2 weeks. ART regimen will be resumed if plasma HIV-1 RNA level is $\geq$ 200 copies/ml in 2 consecutive measurements or if CD4+ is found to be $<$ 350 cells/µl on two consecutive measurements, the participant becomes pregnant, or if otherwise clinically indicated.

- In order to minimize the risk of transmitting HIV to their partners if subjects become viremic, and of HIV-1 superinfection from an HIV-infected partner, subjects will be asked to use male or female condoms for the duration of ART interruption. In the event of a high-risk exposure to an HIV-infected partner, a subject may re-initiate ART as clinically indicated by his/her primary care physician.

- To minimize risks associated with phlebotomy, blood drawing will be performed by experienced phlebotomists. Should discomfort occur, they will provide appropriate treatment.

- To minimize risks associated with blood drawing, volunteers will be closely monitored for signs and symptoms of anemia.

- Females of childbearing potential and who participate in sexual activity that might lead to pregnancy will be advised to use two reliable forms of contraception (i.e. condom with spermicide, diaphragm with spermicide, progestin-only containing intrauterine device (IUD) (eg, Mirena, Implanon, Nuva Ring), non-estrogen containing formulations of hormonal birth control drugs with condom) for the study

duration. Romidepsin may interact with estrogen-based contraceptives and such agents may be unreliable in participants receiving romidepsin.

- In addition, a pregnancy test will be performed at screening, on the days of drug infusion, and throughout the course of the study. Males who are not anatomically sterile and who participate in sexual activity that might lead to pregnancy will be advised to use two reliable forms of contraception during the study to avoid pregnancy in a spouse or partner.

- Subjects will have regularly scheduled visits to the outpatient clinic and routine safety laboratories will be checked according to the Time of Events Schedule (Appendix A). HIV-infected individuals will have close monitoring of HIV-1 viral load and CD4 counts according to the Time of Events Schedule (Appendix A).

- In view of potential ECG changes associated with romidepsin, ECGs will be performed as described above (section 6.2.4). Serum potassium, magnesium and calcium will also be checked before each infusion. Any emergent ECG findings, including asymptomatic findings, will be assessed by a cardiologist and appropriate monitoring and/or management will be instituted as clinically indicated.

- Participants will be counseled during the informed consent process regarding the possible effects on fertility that may occur as a result of romidepsin. If requested, participants will be given information on centers where sperm or egg banking could be performed.

- Infusion-related adverse events including cytokine release syndromes will be monitored and graded using the CTCAE v4.03 grading scale ; all non-infusion-related adverse events will be graded using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0 (Appendix C).

- Adverse events will be managed by the study site investigators who will assess and treat the event as appropriate, including referral to an independent physician and/or department. Participants who develop graded elevations in total bilirubin will undergo a diagnostic workup at no cost to the participant that includes right upper quadrant ultrasound, testing for gamma glutamyl transferase (GGT), HAV, HBV, HCV, EBV, CMV, VZV and HSV serologies, and any other relevant laboratory tests as determined by the investigators.

- Safety monitoring at each clinical site will be conducted by an external monitor and by an external Study Monitoring Committee (SMC). The RUH, AUH and UCH IRBs will conduct the initial review of the proposed study and will follow progress through annual reports and by immediate notification of serious and unanticipated adverse events. Any serious adverse events will be reviewed by the study investigators immediately. Site investigators will notify the local IRB and the sponsor at the Rockefeller University within 2 working days from the investigators being made aware of the event. The RU sponsor will notify the FDA, Danish Health Authority,

PEI, and BfArm per 21 CFR 312. The SMC will be available to the investigators for consultation and review of severe adverse events if needed.

14 Alternative methods or treatments

This does not apply to this study.

15 Data and Safety Monitoring Plan

This is an exploratory Phase II study, which exposes the subjects to "moderate risk."

15.1 Protocol Safety Review Team

The Protocol Safety Review Team (PSRT) will include the available site PIs and co-investigators. Additional members could include senior clinical research nursing staff and site staff. The PSRT will meet on a weekly basis to review any adverse events; minutes will be recorded. For any AE Grade 3 or above deemed possibly, probably or definitely related to 3BNC117 and/or romidepsin, the site PI will notify the PSRT within 24 hours and the PSRT will convene within 1 business day to review these AEs. The PSRT will decide by consensus whether AEs should also be reviewed by the SMC.

15.2 Safety Monitoring Committee

A Study Monitoring Committee (SMC) will be established to monitor the study. The charter of the SMC is to provide an ongoing assessment of volunteer safety during the conduct of the study. The SMC will consist of three independent individuals who have no relationship to the Principal Investigators and Co-Investigators involved in the trial. No member of the SMC will have any direct responsibility for the clinical care of trial volunteers. No representative of Celldex Therapeutics, Celgene Corporation or the Rockefeller University, or their designees may be a member of the SMC. However, the SMC may invite the principal investigators (PI) or designee and a Celldex Therapeutics, Celgene Corporation and/or Rockefeller University representative to an open session of a SMC meeting to provide information on study conduct, present data, or to respond to the members' questions.

The names, university affiliation and title, area of expertise, and contact information of each of the SMC members are provided below:

Rajesh T. Gandhi, MD
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Phone: (514) 843-1558
Email: jean-pierre.routy@mcgill.ca
Expertise: treatment of HIV infection, therapeutic HIV vaccines.

At least two members of the SMC must be in attendance (phone, video, or in-person meetings) to constitute a quorum for an SMC meeting. SMC members may also review and comment by email, if scheduling cannot be worked out in a timely manner. One member of the SMC will be appointed as chair of the committee. The SMC chair (or his/her alternate) will be responsible for summarizing and communicating in writing SMC acknowledgments and recommendations to the PI within 5 business days following each SMC meeting and/or review.

All available safety data will be reviewed by the SMC three weeks after the first five participants receive the second 3BNC117 infusion, and every 6 months thereafter. The study will not pause, but following the review, SMC member(s) will make a recommendation to the principal investigator(s) regarding the continuation of the trial.

SAEs and unanticipated adverse events will be reported to the SMC within 2 working days of the site becoming aware of the event. If there is one grade 4 SAE judged as possibly, probably or definitely related to the administration of 3BNC117 or romidepsin by the principal investigator or designee, no additional enrollment will take place pending a review by at least two members of the SMC. Following this review, the SMC member(s) will make a recommendation to the principal investigator regarding the continuation of the trial.

All updated versions of the protocol will be provided to the SMC members. The review of trial data by the SMC will take place at least every 6 months. For these reviews, the study team will provide the SMC with updated records of all adverse events (AEs) of a grade 2 or greater toxicity.

The SMC will provide a written report to the sponsor at the RU and the site PIs after each evaluation. The PIs will, in turn, distribute these reports to the study team, the local IRBs and the FDA.

15.3 Monitoring

Safety monitoring at both sites will be conducted by the study investigators and by an external monitor. External monitoring reports will be reviewed and approved by the Sponsor. An external SMC will review SAE's and Unanticipated AEs and will be available to the study investigators for consultation. The RU, AU and UC IRBs will conduct the initial review of the proposed study and will follow progress through annual reports and by immediate notification of SAEs and UAEs. External monitoring will occur at least quarterly at all clinical sites.

15.4 Adverse Event Classification

The CTCAE v4.03 grading scale and DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0 will be used for all occurring adverse events (Appendix C). Serious adverse events are defined as those that result in death, are life threatening, require inpatient hospitalization, result in significant disability or incapacity, is a congenital anomaly or birth defect, or is judged by the investigators to be a significant medical event.

15.5 Reporting Adverse Events

All adverse events will be reported to the local IRBs at least annually. Serious Adverse Events, (SAEs) will be reported to the local IRBs and to the sponsor at the Rockefeller University according to policy, within two working days of identification of the SAE. The RU sponsor will report SAEs directly to the FDA, Danish Health Authority, PEI, and BfArm per 21 CFR 312 (Appendix G).

Expedited Reporting by Investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-XX-PI-###) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115

E-mail: drugsafety@celgene.com

15.6 Reporting Unanticipated AEs

Unanticipated Adverse Events (UAEs) will be reported to the local IRBs. UAEs that are related and greater than moderate severity must be reported to the local IRBs and to the sponsor at the Rockefeller University according to policy, within two working days of identification of the UAE. The RU sponsor will report UAEs to the FDA, Danish Health Authority, PEI, and BfArm per 21 CRF 312.

15.7 Clinical Laboratory Improvement Amendment/Clinical Laboratory Evaluation Program (CLIA/CLEP)

This study includes tests that are not CLIA/CLEP certified. The results of such tests will not be used in clinical decision-making or shared with subjects or their health care providers.

15.8 Study Pausing Rules

If the trial is placed on safety pause, all enrollment and infusions will be suspended pending review. The AEs that may lead to a safety pause or prompt PSRT AE review are summarized in Table 1.

Table 1 Adverse events that may lead to a safety pause

Event and relationship to study product	Severity	Occurrence	Action
SAE, related	Grade 3 or 4	First	Immediate pause until PSRT and SMC determination to resume enrollment
AE[1], related	Grade 3 or 4[2]	Second[3]	Immediate pause until PSRT and SMC determination to resume enrollment
ALT or AST increase > 3 x ULN with concurrent increase in total bilirubin > 2 x ULN, any relatedness	N/A	First	PSRT and SMC review to consider pause
Abnormality of ANC, platelet count, or hemoglobin, any relatedness	Grade 4	First	PSRT and SMC review to consider pause
AE[1], related	Grade 3 or 4[2]	First	PSRT review within 1 business day to consider pause

[1] Does not include subjective solicited symptoms (fatigue/malaise, myalgia, arthralgia, chills, headache, nausea).

[2] If no evidence of disease is present other than an abnormal laboratory value, the test must be repeated at least one time.

[3] PSRT and SMC will determine whether the reported related AE (Grade 3 or 4) is a second occurrence of a previously reported AE (Grade 3 or 4).

If a study pause is triggered, all enrollment and infusions will be held until review by the PSRT or SMC. Resumption of enrollment and study treatment may be determined by the PSRT or SMC (in consultation with the FDA, if required) following a cumulative review of the available safety data as outlined in the charter. If a decision to resume study enrollment and study treatment administration is made, the PSRT and/or SMC will record its judgment. As needed, the appropriate regulatory authorities will be informed in writing of the decision by the PSRT and/or SMC to resume or discontinue study activities. Sites are responsible for notifying their IRBs according to local standards and regulations.

Volunteers will be withdrawn from the study if: a) the study team feels that continued participation in the study would be harmful to the health of a subject; b) if the study volunteer fails to comply with the study procedures and/or fails to keep study visit

appointments; c) The RU, AU or UC IRBs decided to stop or cancel the study for any reason.

15.9 Futility Rule

If 10 participants in a single group rebound before week 26 (2 weeks following ATI), additional participants from that group will not undergo ATI. In the case in which the futility rule is applied to both arms and only 10 participants undergo ATI in each arm, there will be 80% power to detect ≥ 14 days difference in time to viral rebound at 5% significance.

16 Clinical Trial Registration

The proposed study involves testing of FDA regulated drugs or biologics and will be registered at www.ClinicalTrials.gov.

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