An Open Label, Phase 2 Study of the Safety and Antiretroviral Activity of 3BNC117 in HIV-Infected Individuals on Combination Antiretroviral Therapy

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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 regulations and ICH guidelines.

The Lead Principal Investigator (Protocol Chair) should sign Signature Page 1. A copy of this Signature Page 1 should be filed with the holder of the Regulatory documents and a copy should be maintained at the site.

Principal Investigator: _____
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Signed: _____ Date: _____
Name/Title

Signature Page 2

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 regulations and ICH guidelines.

The Investigator(s) of Record (signature(s) on 1572) from each participating clinical site should sign the Signature Page 2 as appropriate. This Signature Page 2 should be maintained at each site.

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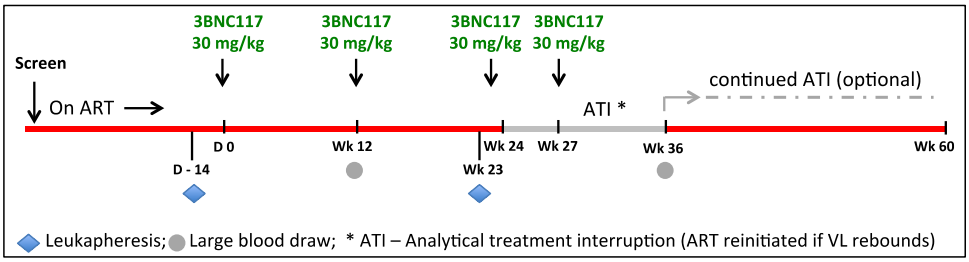
TABLE OF CONTENTS

List of Abbreviations

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
DC	Dendritic Cell
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
EOS	End of Study
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
gp120	HIV-1 Envelope Glycoprotein 120
HIPAA	Health Insurance Portability and Accountability Act
HIV-1	Human immunodeficiency virus
hu-mice	Humanized Mice
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 Participants 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
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
T cell	T lymphocyte
V3 loop	Third Variable Loop of the HIV-1 Virion Envelope Glycoprotein 120
WCMC	Weill Cornell Medical College

Protocol Summary

Title	An open label, phase 2 study of the safety and antiretroviral activity of 3BNC117 in HIV-infected individuals on combination antiretroviral therapy.
Short Title	3BNC117 mAb in HIV-infected individuals on combination antiretroviral therapy (ART)
Protocol Number	MCA-0866
Phase	Phase 2
IND Sponsor	The Rockefeller University
Study Center(s)	The Rockefeller University (RUH), New York, NY Weill Cornell Medical Center (WCMC), New York, NY
Principal Investigators	Marina Caskey, MD Leah Burke, MD
Study Design	The proposed study is a Phase 2, open label study to evaluate the safety, antiretroviral activity and pharmacokinetics of four infusions of 3BNC117 in HIV-infected individuals on combination ART and during a brief analytical treatment interruption (ATI) (Figure 1. Study Design). Fifteen study participants will receive four intravenous infusions of 3BNC117, administered at 30 mg/kg on day 0, week 12, week 24 and week 27. Antiretroviral therapy will be discontinued 2 days after the third 3BNC117 infusion (week 24), until week 36. The ART regimen will be resumed at week 36 or sooner if plasma HIV-1 RNA level is ≥ 200 copies/ml, CD4+ T cell count drops < 350 cells/µl, and results are confirmed upon repeat measurement during the next weekly scheduled visit. If plasma HIV-1 RNA level is ≥ 1,000 copies/ml, the participant will be asked to return for a repeat measurement prior to the next scheduled visit, and ART will be resumed if results are confirmed. ART will also be resumed early if the participant becomes pregnant or if otherwise clinically indicated. If ART is resumed before week 27, the fourth 3BNC117 infusion will not be administered. Participants will be followed weekly during the analytical treatment interruption phase for safety assessments and for monitoring plasma HIV-1 RNA levels. Participants may return to clinic between scheduled visits for additional VL measurements, if they desire to do so. CD4+ T cell counts will be monitored every 2 weeks during the analytical treatment interruption phase. If HIV-1 RNA remains undetectable at week 36, participants will be offered to continue off ART with close monitoring, in conjunction with the participant's primary medical provider, as long as HIV-1 viral rebound does not occur. ART resumption will follow same criteria as detailed above. All participants will be followed for a total of 60 weeks from enrollment.

Study Schema	**Figure 1. Study Design** 
Schedule of Procedures/ Evaluations	See Appendix A
Study Duration	15 months/per participant Total planned study duration: 30 months
Objectives	The primary objectives are: - Evaluate the effect of four infusions of 3BNC117 at 30 mg/kg in preventing or delaying virologic rebound during a short analytical treatment interruption. - Evaluate the safety and tolerability of four intravenous infusions of 3BNC117, dosed at 30 mg/kg, in HIV-infected individuals with suppressed viremia on ART and during interruption of ART. The secondary objectives are to evaluate the pharmacokinetics of four intravenous infusions of 3BNC117, dosed at 30 mg/kg in HIV-infected individuals with suppressed viremia on ART and during interruption of ART. Exploratory objectives include an evaluation of the effects of 3BNC117 in combination with standard ART on the size of the HIV-1 reservoir. In addition, a phylogenetic comparison of viruses grown from PBMCs collected from participants while on ART to rebound viruses collected after ART interruption and analysis of escape mutations that might arise after administration of 3BNC117 will be performed. HIV-1-specific immune responses and levels of chronic inflammation markers following 3BNC117 infusions will also be evaluated.
Outcomes	The primary outcomes are rate of virologic rebound (plasma HIV-1 RNA ≥ 200 copies/ml on two separate occasions) at week 36 (12 weeks post ART interruption), time to rebound following ART interruption, and frequency of adverse events and laboratory abnormalities. The secondary endpoints are serum elimination half-life, and decay kinetics, as well as other PK/PD measurements.
Number of Participants	15
Study Population	Adults, male and female, ages 18-65 with well-controlled HIV-1 infection on standard ART.
	Inclusion Criteria. • Informed consent obtained and signed. • Male and females, age 18 to 65. • HIV-1 infection confirmed by two independent methods. • Plasma HIV-1 RNA < 50 copies/ml for at least 12 months while on combination ART and < 20 copies/ml at the screening visit. [Note: One or two viral blips of < 200 copies/mL prior to enrollment are permitted if preceded and followed by test results

	showing VL less than or equal to 50 copies/ml on the same ARV regimen.] • CD4 cell count > 500 cells/µl. CD4 cell count nadir > 200 cells/µl. • If sexually active male or female, and participating in sexual activity that could lead to pregnancy, agrees to use an effective method of contraception throughout the study period. Participants should also agree to use male or female condoms while off ART. • If on an NNRTI-based regimen willing to switch for 4 weeks to a dolutegravir-based regimen. ***Exclusion Criteria*** • Have a history of AIDS-defining illness within 1 year prior to enrollment. • Have a history of resistance to two or more antiretroviral drug classes. • History of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the trial physician within the last 6 months. • Chronic hepatitis B or hepatitis C. • Participant report, or chart history, of significant coronary artery disease, myocardial infarction, percutaneous coronary intervention with placement of cardiac stents. • Participant report, or chart history, of diabetes type 1 or 2 and/or current use of insulin or oral hypoglycemic medications. • Uncontrolled hypertension, as defined by a systolic blood pressure > 180 and/or diastolic blood pressure > 120, in the presence or absence of anti-hypertensive medications. • Total cholesterol level > 240 mg/dl or LDL level > 190 mg/dl at screen. • Known family history of myocardial infarction or stroke in a first-degree relative aged < 60 years. • Any other clinically significant acute or chronic medical condition, such as autoimmune diseases, that in the opinion of the investigator would preclude participation. • Current cigarette use in excess of 1 pack per day. • Laboratory abnormalities in the parameters listed below: • Absolute neutrophil count ≤ 1,000 cells/µl • Hemoglobin ≤ 10 g/dL • Platelet count ≤ 125,000 cells/µl • ALT ≥ 2.0 x ULN • AST ≥ 2.0 x ULN • Total bilirubin ≥ 1.5 ULN • Creatinine ≥ 1.1 x ULN • Coagulation parameters ≥ 1.5 x ULN • Current antiretroviral regimen includes maraviroc or enfuvirtide. • Pregnancy or lactation. • Any vaccination within 14 days prior to 3BNC117 administration. • Receipt of monoclonal antibody therapy of any kind in the past. • History of severe reaction to drug infusions or history of severe allergic reactions. • 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 is a recombinant, fully human monoclonal antibody (mAb) of the IgG1κ isotype that specifically binds HIV-1 envgp120. Four intravenous infusions of 3BNC117 mAb will be administered on day 0, week 12, week 24 and week 27 via a peripheral vein over 60 minutes. Dose level to be tested: 30 mg/kg.

Statistical Methodology	A one-sided upper confidence interval will be constructed for the probability of rebound using the Clopper-Pearson method. As such, with a sample size of 15 HIV-infected individuals, the null hypothesis (p(rebound)=0.85) will be rejected with at least 80% power if at least 6 participants do not rebound (an effect size equal or higher than 0.32). Kaplan-Meier survival curves will be used to address the second variable, "time to rebound". If 10 or more participants experience viral rebound prior to week 29 [5 weeks after ART interruption and 2 weeks after last 3BNC117 infusion], additional participants will not undergo ATI. The number and percentage of participants 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 DAIDS AE Grading Table v2.0. The CTCAE v4.03 grading scale will be used for reporting and grading adverse events related to infusion reactions (Appendix B). Pharmacokinetic parameters will be calculated using standard non-compartmental analysis methods. A 95% repeated measures ANOVA F-test will be used to compare the levels of latently infected resting CD4+ T cells in peripheral blood; levels of plasma HIV-1 RNA by single copy assay; and levels of cell-associated HIV-1 RNA and DNA, at baseline and at weeks 12, 23 (or 24) and 36. For repeated measures ANOVA F-test, a sample size of 15 participants allows the detection of an effect size of 0.44, with 80% power and 95% confidence. Genotyping of HIV-1 isolates will be performed to phylogenetically compare viruses grown from PBMCs collected from participants while on ART to rebound viruses collected after treatment interruption, and to analyze the induction of escape mutations.

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2 LAY SUMMARY

Despite the major success of combination antiretroviral therapy (ART) in suppressing viral replication and preventing disease progression, HIV-1 infection persists. When combination ART is discontinued, viral load levels rebound within 2-3 weeks in most participants, due to persistence of HIV-1 in latent reservoirs. 3BNC117 is a highly neutralizing anti-HIV-1 monoclonal antibody isolated and cloned from an HIV-infected individual who is a viremic controller. In preclinical studies carried out in humanized mice and non-human primates, 3BNC117 alone or in combination with other neutralizing antibodies led to protection from HIV-1 or chimeric simian/human immunodeficiency virus (SHIV) infection, and also to sustained suppression of HIV-1 plasma viremia. Moreover, 3BNC117 in combination with other bNAbs and agents that reverse HIV-1 latency prevented viral rebound in HIV-infected humanized mice. In humans, 3BNC117 is being evaluated under protocol MCA-835 and to date has been generally safe. Moreover, a single infusion of 3BNC117 transiently decreases HIV-1 viral loads in HIV-infected individuals. The primary aims of this protocol are to evaluate 3BNC117's effects on preventing virologic rebound when ART is discontinued and the safety of four intravenous infusions of 3BNC117. In addition, the study will evaluate 3BNC117's effects on established HIV-1 reservoirs in humans, when given in combination with standard antiretroviral therapy to HIV-infected individuals who have achieved virologic suppression on ART alone.

3 Objectives and Rationale

3.1 Introduction

3.1.1 Background

Despite the major success of combination antiretroviral therapy in suppressing viral replication and preventing disease progression, HIV-1 infection persists in a latent state as integrated proviruses in resting memory CD4+ T cells (Eisele E *et al.* 2012)**.** The burden of daily medication regimens, toxicity, development of resistance and cost underscore the need for a continued search for additional complementary therapeutic modalities. Moreover, standard antiretroviral therapies do not fully restore health or a normal immune status in HIV-infected individuals and co-morbidities such as cardiovascular disease, bone disorders and cognitive impairment may occur (Deeks S *et al.* 2013**)**.

The latent reservoir is established very early during infection (Chun TW *et al.* 1998, Archin NM *et al.* 2012) and it is the major barrier to curing HIV-1 infection. The HIV-1 reservoir is maintained during ART by the long half-life of infected memory T cells, the homeostatic proliferation of these cells, and perhaps by low levels of cell-to-cell virus transfer (Barouch D Deeks S 2014). Although latently infected resting CD4+ T cells are largely nonpermissive for viral gene expression, it is believed that even on ART, a fraction of infected cells can intermittently produce virus (Bailey J *et al.* 2006, Tobin N *et al.* 2005).

When ART is discontinued, virological rebound occurs within 2-3 weeks in most subjects (Davey RT *et al.* 1999; Papasavvas E *et al.* 2004, El-Sadr WM *et al.* 2006, Rothenberger M et al. 2015). Even in the context of suppressive ART, HIV-1 infection is characterized by persistent immune activation, and levels of HIV-1 viremia and cell-associated HIV-1 remain relatively stable (Palmer S *et al.* 2008; Deeks S *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 M *et al.* 2014; Dinoso JB *et al.* 2009; McMahon D *et al*, 2010).

A fraction of HIV-infected individuals (10 – 30%) mount a serologic response that can neutralize a broad spectrum of HIV-1 isolates (Simek M *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 (Mascola J *et al.* 1999, Moldt B *et al.* 2012, Shingai M *et al.* 2013). Broadly neutralizing antibodies might also play a role in the treatment of HIV-1 infection.

Broadly neutralizing antibodies (bNAbs) differ from other therapeutic modalities for HIV-1 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 immunity to HIV-1. In addition a subset of bNAbs can inhibit cell-to-cell transmission of HIV-1 at very low concentrations (Malbec M *et al.* 2013). Experiments in humanized mice and non-human primates indicate that bNAbs can lead to rapid virological suppression that is sustained for as long as mAb levels are maintained above a certain threshold (Klein F *et al.* 2012, Horwitz T *et al.* 2013, Shingai M *et al.* 2013, Barouch D *et al.* 2013).

In SHIV-infected nonhuman primates 3BNC117 induces rapid viral suppression as monotherapy (Shingai M *et al.* 2013, Barouch D *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 untreated humanized mice (hu-mice), a single neutralizing antibody, *i.e.* 3BNC117, controlled infection when plasma HIV-1 RNA levels were initially suppressed by antiretroviral therapy. Hu-mice that received ART normally rebounded immediately after the drugs were terminated, whereas a single antibody was sufficient to maintain virologic control after ART interruption in 50-86% of the hu-mice, for as long as antibody concentrations remained therapeutic (Horwitz J *et al.* 2013). 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 antibodies. Of interest, cell-

associated HIV-1 DNA levels declined in plasma and lymphoid tissue following therapy with bNAbs alone or in combination with conventional ART in non-human primates or hu-mice (Barouch D *et al.* 2013, Horwitz J *et al.* 2013). Therefore, antibody monotherapy may be sufficient as a maintenance regimen, when combinations of antiretroviral drugs and/or antibodies initially suppress viremia.

In addition to suppressing plasma viremia, broadly neutralizing antibodies can also interfere with the establishment of the reservoir in hu-mice by Fc-FcR mediated mechanisms. When hu-mice where administered bNAbs carrying Fc region mutations that abrogate Fc-receptor binding, bNAbs initially suppressed viremia at the same rate as the unmutated bNAbs, but more than half of the animals showed viral rebound within 6 weeks after last antibody infusion, which demonstrates that bNAbs *in vivo* activity is at least partially dependent on Fc-mediated effector functions, such as ADCC (Halper-Stromberg A *et al.* 2014).

Experiments in humanized mice also showed that bNAbs have effects on established HIV-1 viral reservoirs. HIV-1 infected hu-mice were treated with a tri-mix of bNAbs in combination with one or three agents that induce viral transcription from latently infected cells (vorinostat, I-BET151, and α-CTLA4 mAb). When 23 mice that initially suppressed viremia on antibody therapy were treated with the combination of three inducers and followed for 62-105 days after the last antibody injection, 57% of mice failed to rebound. Moreover, proviral DNA could not be detected at the terminal time point in the majority of mice that did not rebound, whereas the majority of mice that did rebound had detectable HIV-1 DNA at the end of follow up. These results show that combination therapy with antibodies and inducers of viral transcription can significantly alter the latent HIV-1 reservoir in hu-mice (Halper-Stromberg A *et al.* 2014). Even in the absence of latency reversing agents, bNAbs have the potential to eliminate infected cells that intermittently produce viruses despite ART by Fc-mediated mechanisms, such as ADCC. Therefore, bNAbs in combination with ART might deplete the reservoir over time.

Eliminating the HIV-1 reservoir in chronic infection is essential to eradicating HIV-1 infection, but direct measurement of the latent reservoir to evaluate therapeutic eradication strategies remains difficult (Siliciano J *et al.* 2014). Quantitative viral outgrowth assays and PCR-based assays of integrated DNA yield conflicting results (Eriksson G *et al.* 2013), in part because PCR cannot distinguish between inactive and permanently disabled proviruses, while outgrowth assays underestimate reservoir size (Ho YC *et al.* 2013). Time to viral rebound after ART is discontinued may prove to be a useful measurement to evaluate strategies that aim to decrease the size of the reservoir (Siliciano J *et al.* 2014). It is possible that data generated in this study will allow us to examine if 3BNC117 potential effects on the reservoir (measured by the assays above) correlate with delayed time to viral rebound, particularly if participants who do not experience viral rebound by week 12 remain off ART until 3BNC117 levels are no longer detected.

The SMART randomized trial demonstrated that episodic ART, guided by drop in CD4+ count (ART reinitiated if CD4+ 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 (El-Sadr W *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 (continuous ART or episodic ART). In addition, the difference in risk of opportunistic diseases and major cardiovascular, renal, and hepatic diseases between the two groups occurred predominantly after 16 weeks and increased over time. Recent evidence suggests that short analytical treatment interruption (ATI; limited to a maximum of 16 weeks), in patients with preserved CD4 count and virologic suppression, is safe and is an accepted tool to evaluate new therapeutic modalities (Rothenberger M *et al.* 2015; Routy JP *et al.* 2012; Kutzler MA *et al.* 2008). 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.

Passive administration of less potent, earlier generation anti-HIV-1 bNAbs has been evaluated in ART-interruption settings in humans, but not in combination with ART. 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. One of the administered antibodies (2G12) seemed to delay viral rebound in some participants. This effect was rather limited, as 2G12 did not neutralize subject's viral isolates with sufficient potency (Mehandru S *et al.* 2007, Trkola A *et al.* 2005). However both studies found some correlation between the baseline sensitivity of the subject's virus to 2G12 and delay in viral rebound. Therefore, in this study we will test the sensitivity of the participant's provirus to 3BNC117 at baseline (day 0) and will correlate the effects on viral rebound and on the HIV-1 reservoir with baseline 3BNC117 sensitivity.

Since highly potent second generation bNAbs have not been evaluated before in the setting of ART-interruption in humans, it is not known which serum antibody levels will be required to prevent viral rebound. In hu-mice, levels of 3BNC117 decreased to levels as low as 0.5 μg/ml (10 times the IC_{50} value for the HIV-1 strain used) before viral rebound occurred during ART-interruption (Horwitz et al., 2013). In the setting of antibody monotherapy in nonhuman primates, 3BNC117 serum levels above 1-10 μg/ml (10-100 times the IC_{50} value for the respective strain) were required to prevent rebound. In this study, an additional infusion of 3BNC117 will be administered 3 weeks into the ATI period in order to maintain 3BNC117 serum levels above 50-100 μg/ml, for at least 6 weeks after ART is discontinued. This will allow us to investigate the ability of 3BNC117 to prevent viral rebound beyond the period of 2-3 weeks, during which rebound usually occurs after ART is discontinued (Davey RT *et al.* 1999; Papasavvas E *et al.* 2004, El-Sadr WM *et al.* 2006, Rothenberger M et al. 2015).

This study aims to evaluate the effects of 3BNC117, one of the most highly potent and broadly neutralizing anti-HIV-1 antibodies, on preventing or delaying viral rebound after ART is discontinued. In addition, the study will evaluate the safety of four infusions of 3BNC117, and its effects on established HIV-1 reservoirs in humans, when given in combination with standard antiretroviral therapy to HIV-infected individuals who have

achieved viral suppression on ART alone. Lastly, pharmacokinetic evaluations will be performed.

Analytical interruption of ART is included in this protocol to evaluate if 3BNC117 alone can maintain viral suppression and delay viral rebound. ART will be interrupted for 12 weeks only in order to avoid negative outcomes as observed in the SMART trial (discussed above). However, participants who do not experience viral rebound by week 12, will have the option to remain off ART with continued weekly follow up. Since viral rebound occurs between weeks 2-3 in most individuals, we expect to be able to measure an effect of 3BNC117 should viral rebound not occur until week 12.

3.1.2 The Investigational Product, 3BNC117

3BNC117 is a broadly neutralizing and highly potent anti-HIV-1 antibody. 3BNC117 was initially cloned from B cells isolated from a volunteer infected with HIV-1 clade B, who controls his HIV-1 infection without antiretroviral therapy. The initial study was conducted under protocol MNU-0628. 3BNC117 targets the CD4 binding site (CD4bs) within HIV-1 envelope gp-120. 3BNC117 showed an average IC_{80} on a combined group of 95 tier 2 viruses of 1.4 µg/ml (Scheid J *et al.* 2011) when evaluated by *in vitro* neutralization assays. 3BNC117 also showed *in vivo* activity in HIV-1 or SHIV-infected 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 J *et al.* 2013; Shingai M *et al.* 2013; Barouch D *et al.* 2013). Moreover, the combination of 3BNC117 with two other bNAbs and latency reversing agents prevented viral rebound in HIV-infected humanized mice (Halper-Stromberg A *et al.* 2014).

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. 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.

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-1 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, C *et al.* 2011).

Several monoclonal antibodies that target HIV-1 gp120 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 C *et al.* 2002; Armbruster C *et al.* 2004). The antibodies were administered intravenously at 0.5 to 1 gm 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 individuals. Another neutralizing antibody KD-247, which targets the V3 loop, was evaluated in viremic HIV-infected individuals. The antibody was administered as 3 weekly infusion administered as doses ranging from 4 to 16 mg/kg. KD-247 was well tolerated at the doses tested and showed some virologic activity at the higher dose levels (Matsushita S *et al*. 2015).

Two other studies included HIV-infected individuals on combination ART and plasma viral levels < 50 copies/ml (Trkola, A *et al.* 2005), n = 14; Mehandru M *et al.* 2007), n =10). The antibodies were administered intravenously at doses ranging from 1 to 2 gm for each antibody; 13-16 antibody infusions were given weekly. ART was interrupted following 1 or 4 antibody infusions. Antibody infusions were well tolerated in most individuals; 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-1 in humanized mice (Poignard et al., 1999).

3.1.3 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 NOAEL (no observable adverse effect level) was determined to be the high dose of 60 mg/kg twice a week for four weeks.

3.1.4 Clinical Experience with 3BNC117

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

In protocol MCA-835, study participants 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 17 Aug 2015, total of 55 individuals were enrolled in the study (22 HIV-uninfected, 19 viremic HIV-infected and 14 HIV-infected individuals on ART). Five subjects (HIV-uninfected) have received two doses of 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. To date, no serious adverse events (SAEs) were reported during study follow up and no dose-limiting toxicities (DLT's) deemed possibly, probably or definitely related to 3BNC117 have occurred.

Preliminary PK data show that 3BNC117's half-life is approximately 17.6 days in HIV-uninfected and 9.6 days in viremic HIV-infected individuals. PK data from ART-treated participants, with VLs < 20 copies/ml, who received a single 3BNC117 infusion of 10 mg/kg show that 3BNC117's $t_{1/2}$ in this setting is similar to HIV-uninfected individuals.

In HIV-uninfected individuals, dosed at 30 mg/kg, 3BNC117 levels were maintained around 75 μg/ml for 3-4 weeks after infusion and around 5 μg/ml for 12 weeks after a single 3BNC117 infusion. In addition, 3BNC117 decay rate following first and second 10 mg/kg infusions were similar in HIV-uninfected individuals who received two 3BNC117 infusions at 10 mg/kg, administered 12 weeks apart.

In this study, we expect that 3BNC117 serum trough levels will be around 5 μg /ml during the 3BNC117 dosing period, while ART is maintained. Since 3BNC117 has not yet been tested in the setting of ATI, the decay rate of 3BNC117 in this setting is not yet known and may be relatively faster than seen in HIV-uninfected or ART-treated HIV-

infected individuals.

A transient decline in HIV-1 viremia, of approximately 0.5 log_{10}, occurred following the administration of 3 mg/kg of 3BNC117 to three HIV-infected individuals with detectable viremia. Of the 2 individuals off ART receiving the 10 mg/kg dose of antibody, 1 responded with a 1.36 log_{10} decline in viremia and the other did not respond. The individual that did not respond was infected with 3BNC117-resistant virus (IC_{50} > 20µg/ml at baseline). All nine individuals that received the 30mg/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. Interestingly, emergence of resistant viral strains was variable, with some individuals remaining sensitive to 3BNC117 for a period of 28 days after infusion (Caskey, Klein et al. 2015). Virologic data will continue to be analyzed under protocol MCA-835, as additional HIV-infected individuals are enrolled.

In protocol MCA-867, HIV-infected individuals on suppressive cART are administered two 30 mg/kg intravenous infusions of 3BNC117 at week 0 and week 3. cART is discontinued 2 days after the first 3BNC117 infusion. Subjects are followed weekly and cART is resumed if viral rebound occurs or CD4+ T cell counts decline to < 350 cells/mm^3. As of 17 August 2015, 8 individuals have been enrolled. 3BNC117 infusions have been well tolerated. Most reported AEs were transient, of grade 1 severity, and include headache, fatigue and myalgia.

3.2 Hypothesis

The administration of four infusions of 3BNC117 (30 mg/kg) will be safe, well tolerated, and will prevent or delay the return of HIV-1 viremia during a brief analytical treatment interruption. In addition, 3BNC117 infusions in combination with standard ART might be associated with a decrease in the size of the HIV-1 reservoir in ART-treated HIV-infected individuals.

3.3 Aims

Primary Objectives:

- Evaluate the effect of four infusions of 3BNC117 at 30 mg/kg in preventing or delaying virologic rebound during a short analytical treatment interruption.

- Evaluate the safety and tolerability of four intravenous infusions of 3BNC117, dosed at 30 mg/kg, in HIV-infected individuals with suppressed viremia on ART and during interruption of ART.

Secondary Objectives:

- Evaluate the pharmacokinetics profile of four intravenous infusions of 3BNC117, dosed at 30 mg/kg, in HIV-infected individuals with suppressed viremia on ART and during interruption of ART.

Exploratory Objectives:

- Evaluate the effects of 3BNC117 in combination with standard ART on the size of the HIV-1 reservoir. The reservoir will be measured by:

1) Quantitative PCR-based assays to measure cell-associated HIV-1 DNA;

Viral outgrowth assays that measure infectious units per million (IUPM) in CD4+ resting T cells.

- Correlate baseline 3BNC117 sensitivity of participant's proviruses to the observed effects on viral rebound and on the HIV-1 reservoir.

- Evaluate HIV-1-specific immune responses and chronic inflammation markers following 3BNC117 infusions.

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

3.4 Primary Outcome(s)

- Rate of viral rebound (plasma HIV-1 RNA ≥ 200 copies/ml on two separate occasions) post ART interruption by plasma HIV-1 RNA levels at week 36 (12 weeks after ART is discontinued).
- Time to viral rebound post ART interruption by plasma HIV-1 RNA levels.
- Safety will be evaluated by frequency of adverse events and laboratory abnormalities.

3.5 Secondary Outcome(s)

- PK will be evaluated by serum elimination half-life, and decay kinetics, as well as other PK/PD measurements.

Other evaluations:

- Levels of latently infected CD4+ resting T cells measured by viral outgrowth assay at baseline and week 23.
- Levels of cell-associated HIV-1 DNA determined in PBMCs at baseline and at week 24.
- Levels of cell-associated HIV-1 RNA determined in PBMCs at baseline and at week 24.
- Levels of HIV-1 RNA determined by single copy assay when HIV-1 RNA is < 20 copies/mL by standard clinical assay at baseline and at week 24.
- Phylogenetic comparison of viruses grown from PBMCs collected from participants while on ART to rebound viruses collected after treatment interruption.
- Analysis of 3BNC117-induced escape mutations.
- Compare 3BNC117 effects on preventing or delaying viral rebound (rate and time to rebound) and on the HIV-1 reservoir (decrease in IUPM in CD4+ resting T cells) between subjects with baseline 3BNC117 IC_{50} against autologous viruses of < 2 μg/ml or ≥ 2 μg/ml.
- Evaluate the effects of 3BNC117 on serum levels of inflammation markers, such as C-reactive protein, D-dimers, IL-6 and soluble CD14, at baseline and week 24.

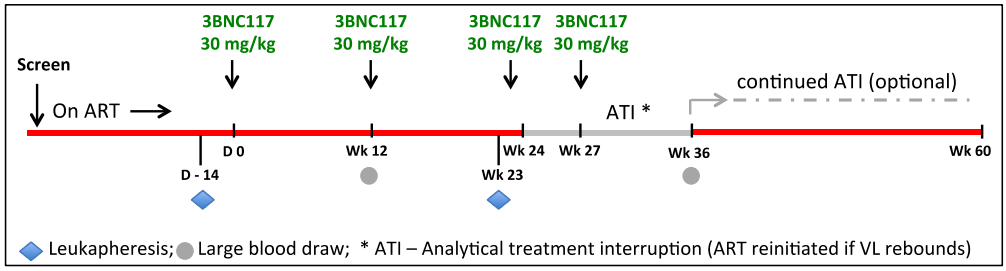
- Evaluate HIV-1 specific T and B cell immune responses following administration of 3BNC117, including CD8+ T cell expression of immune activation markers, such as HLA-DR, CD38 and PD-1, at baseline and week 24.

4 Study Design

The proposed study is an exploratory Phase 2, open label study to evaluate the safety and antiretroviral activity of four infusions of 3BNC117 in HIV-infected individuals on combination ART and during a brief analytical treatment interruption (Figure 2. Study Design). PK assessments are also included.

After meeting enrollment criteria, fifteen participants with 3BNC117-sensitive virus will be enrolled sequentially and will receive four intravenous infusions of 3BNC117, administered at 30 mg/kg on day 0, week 12, week 24 and week 27. ART will be continued for 2 days after the third 3BNC117 infusion to allow for initial redistribution of the antibody, and will then be discontinued. Based on PK data from study MCA-835 we expect this dosing regimen to maintain 3BNC117 serum levels above 50-100 µg/ml for at least 6 weeks. This exceeds the typical period of viral rebound after ATI, which ranges from 2-3 weeks (Davey RT *et al.* 1999; Papasavvas E *et al.* 2004, El-Sadr WM *et al.* 2006, Rothenberger M et al. 2015).

Figure 2. Study Design



Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have longer elimination half-lives than other antiretroviral classes. In order to avoid the risk of inadvertent monotherapy, which can select NNRTI resistant strains, if the participant's ART regimen includes an NNRTI, the NNRTI will be switched to dolutegravir (an integrase inhibitor), 4 weeks prior to discontinuing all other antiretroviral drugs. Dolutegravir will be provided to the participants for that time period.

Participants will be followed weekly during the analytical treatment interruption (ATI) phase of the study for safety assessments and for monitoring plasma HIV-1 RNA levels. Participants may return to clinic between scheduled visits for additional VL measurements, if they desire to do so. CD4+ T cell counts will be measured every other week.

The same ART regimen will be resumed at week 36. ART will be resumed sooner if plasma HIV-1 RNA level is ≥ 200 copies/ml) or CD4+ T cell count drops < 350 cells/µl and either value is confirmed upon repeat measurement, during the next weekly scheduled visit. If plasma HIV-1 RNA level is ≥ 1,000 copies/ml, the participant will be asked to return for a repeat measurement prior to the next scheduled visit and ART will be resumed if results are confirmed. ART will also be resumed early if the participant becomes pregnant or if otherwise clinically indicated. If ART is resumed before week 27, the fourth 3BNC117 infusion will not be performed.

If HIV-1 RNA remains undetectable at week 36, participants will be offered to continue off ART through week 60 with close monitoring, in conjunction with the participant's primary medical provider, as long as viral rebound does not occur. In the continued ATI phase of the study, participants will return for follow up every week while off ART. ART resumption will follow same criteria as detailed above. After ART is resumed, study participants will return for follow up according to the Main Schedule (i.e. wk 40, 48 and 60) (Appendix A).

Study investigators will provide non-research laboratory results as well as other relevant clinical information to the participant's primary care physician during all phases of the study. The participant's primary care physician will be consulted on any changes in treatment.

All participants will be followed for a total of 60 weeks from enrollment.

Safety and PK assessments will be performed at multiple time points following 3BNC117 infusions (see Appendix A). The effects of 3BNC117 on the HIV-1 reservoir will be evaluated by several assays. These evaluations will occur at baseline (day -14), prior to second (week 12) and third (week 23 or 24) 3BNC117 infusions, and at week 36) if viral rebound did not occur.

We expect that enrollment will be completed in 6 – 18 months.

5 Study Population

Adults, males and females, ages 18-65 with well-controlled HIV-1 infection on standard ART.

5.1 Inclusion Criteria

The participant must meet all of the following inclusion criteria to participate in this study:

- Informed consent obtained and signed.
- Males and females, age 18 to 65.
- HIV-1 infection confirmed by two independent methods.
- Plasma HIV-1 RNA < 50 copies/ml for at least 12 months while on combination ART and < 20 copies/ml at the screening visit. [Note: One or two viral blips of < 200

copies/mL prior to enrollment are permitted if preceded and followed by test results showing VL less than or equal to 50 copies/ml on the same ARV regimen.]

- CD4 cell count > 500 cells/µl. CD4 cell count nadir > 200 cells/µl.
- If sexually active male or female, and participating in sexual activity that could lead to pregnancy, agrees to use an effective method of contraception throughout the study period. Participants should also agree to use a male or female condom while off ART.
    - Female study participants of reproductive potential are defined as pre-menopausal women who have not had a sterilization procedure (e.g. hysterectomy, bilateral oophorectomy, tubal ligation or salpingectomy). Women are considered menopausal if they have not had a menses for at least 12 months and have a FSH of greater than 40 IU/L or if FSH testing is not available, they have had amenorrhea for 24 consecutive months.
    - Acceptable forms of contraception must include one of the following: condoms (male or female) with or without a spermicidal agent, diaphragm or cervical cap with spermicide, IUD, or hormone-based contraceptive.
- If on an NNRTI-based regimen willing to a switch for 4 weeks to a dolutegravir-based regimen.

5.2 Exclusion Criteria

Participants meeting any exclusion criterion at baseline will be excluded from study participation:

- Have a history of AIDS-defining illness within 1 year prior to enrollment.
- Have a history of resistance to two or more antiretroviral drug classes.
- History of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the trial physician within the last 6 months.
- Chronic hepatitis B or hepatitis C.
- Participant report, or chart history, of significant coronary artery disease, myocardial infarction, percutaneous coronary intervention with placement of cardiac stents.
- Participant report, or chart history, of diabetes type 1 or 2 and/or current use of insulin or oral hypoglycemic medications.
- Uncontrolled hypertension, as defined by a systolic blood pressure > 180 and/or diastolic blood pressure > 120, in the presence or absence of anti-hypertensive medications.
- Total cholesterol level > 240 mg/dl or LDL level > 190 mg/dl at screen.
- Known family history of myocardial infarction or stroke in a first-degree relative aged < 60 years.
- Any other clinically significant acute or chronic medical condition, such as autoimmune diseases, that in the opinion of the investigator would preclude participation.
- Current cigarette use in excess of 1 pack per day;
- Laboratory abnormalities in the parameters listed below:
    - Absolute neutrophil count ≤ 1,000 cells/µl
    - Hemoglobin ≤ 10 g/dL
    - Platelet count ≤ 125,000 cells/µl
    - ALT ≥ 2.0 x ULN

  - AST ≥ 2.0 x ULN
  - Total bilirubin ≥ 1.5 ULN
  - Creatinine ≥ 1.1 x ULN
  - Coagulation parameters ≥ 1.5 x ULN.
- Current antiretroviral regimen includes maraviroc or enfuvirtide.
- Pregnancy or lactation.
- Any vaccination within 14 days prior to 3BNC117 administration.
- Receipt of monoclonal antibody therapy of any kind in the past.
- History of severe reaction to drug infusions or history of severe allergic reactions.
- 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 post-3BNC117 visits are performed either at The Rockefeller University Hospital (RUH) outpatient clinic or the Weill Cornell Medical Center (WCMC). 3BNC117 infusion visits will only be performed at RUH.

6.1.1 Pre-Screening

Potential participants will first undergo pre-screening by telephone to assess medical history, 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 Outpatient Clinic or at the WCMC Clinical Trials Unit.

6.1.2 Screening Visit

Screening Visit:

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 a reliable form of contraception for the duration of the trial (as described in **section 5.1 Inclusion Criteria**).
2. Risk reduction counseling. Sexually active males and females will be asked to use condoms during ART interruption due to the risk of intermittent viremia.
3. One must assume that no improvement in control of HIV-1 infection will occur given the experimental nature of this monoclonal antibody.
4. Participants agree to stopping their antiretroviral medications as planned in the protocol and agree to return for weekly follow up visits for monitoring of plasma viremia levels.

If the volunteer consents to participate, site personnel will:

- Obtain a complete medical history (including concomitant medications);
- Review participant's previous HIV-1 viral load and CD4/CD8 measurements (HIV-1 viral load measurements should be available for at least 1 year prior to screening);
- 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/CD8 counts.
- Perform a pregnancy test for all female volunteers (excluding those who are post-menopausal).

If the screening visit occurs more than 49 days prior to the date of the first 3BNC117 mAb infusion, then study procedures for the screening visit must be repeated. The most recent set of procedures will be used if there is a discrepancy.

6.1.3 Pre-Infusion Visit

- Participants will have an ophthalmologic assessment (including slit lamp exam), at no cost to the participant.

6.1.4 3BNC117 Infusion Visits

3BNC117 infusions (day 0, week 12, week 24 and week 27) and assessments 1 day post each 3BNC117 infusion will occur at the Rockefeller University Hospital (RUH). Other visits will occur at the original study site (the RUH or WCMC).

Prior to drug infusion, site personnel will:

- Answer any questions about the study;
- Review interim medical history (including concomitant medications);
- Review safety laboratory data;
- Review the informed consent form administered at screening visit with the volunteer;
- 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;
- 3BNC117 will be prepared for administration according to the Rockefeller University Pharmacy Standard Operating Procedures;
- 3BNC117 mAb will be administered via a peripheral vein by slow intravenous infusion.

- The infusion will take approximately 60 minutes. Participants will be closely observed for 4 hours after drug infusion in the inpatient unit of the RUH. Vital signs (pulse, respiratory rate, blood pressure and temperature) will be monitored at end of infusion, 30 (+/- 5 minutes), 2 (+/- 10 minutes), and 4 hours (+/- 10 minutes) post infusion. Presence or absence of adverse events will be recorded at 30 – 45 minutes and at 4 hours. The study staff will record solicited and unsolicited adverse events during clinic visits as shown in Time of Events Schedule (Appendix A).
- 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 inpatient unit for use if clinically indicated. Infusion may be reinitiated after symptoms improve, and the remaining dose will be administered over 3 hours.

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

6.1.5 Post-3BNC117 Administration Visits

Study participants will be followed through week 60.

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

- Review of interim medical history and use of concomitant medications;
- If symptoms are present, perform a symptom-directed physical examination;
- Solicited and unsolicited adverse events will be assessed;
- Pregnancy counseling and pregnancy testing;
- Safe sex counseling;
- Vital Signs;
- Collect blood and urine specimens for all tests as indicated in the Time of Events Schedule (Appendix A);
- At post-infusion study visits, participants will be asked about symptoms of ocular disease (such as blurry vision, increased lacrimation, redness, dryness, pain) and the study investigators will perform a directed exam of the eyes. If participants develop symptoms or signs of ocular disease, they will be referred to an ophthalmologist for diagnosis and management;
- Participants will have a scheduled ophthalmologic assessment at week 48.
- 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.

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

Any abnormalities (adverse events) attributed to study drug, including laboratory abnormalities, should be subsequently followed until the event or its sequelae resolve or stabilize.

6.1.6 ART interruption and re-initiation of combination ART

ART regimen will be discontinued 2 days after the third 3BNC117 infusion, at week 24 (last dose of ART will be taken on day 169).

NNRTIs have longer elimination half-lives (> 20 hours) compared with most nucleoside reverse transcriptase inhibitors (NRTIs). In order to avoid a period of NNRTI monotherapy, which can lead to the development of resistance, if the participant's ART regimen includes an NNRTI, the NNRTI will be switched to dolutegravir (an integrase inhibitor) at week 20, 4 weeks before all other antiretroviral drugs are discontinued. Dolutegravir will be provided to the participants for that time period.

The same ART regimen will be resumed at week 36. ART regimen will be resumed sooner if plasma HIV-1 RNA level is ≥ 200 copies/ml or CD4+ T cell count drops < 350 cells/μl, and either result is confirmed upon repeat measurement, during the next weekly scheduled visit. If plasma HIV-1 RNA level is ≥ 1,000 copies/ml, the participant will be asked to return for a repeat measurement prior to the next scheduled visit and ART will be resumed if results are confirmed. ART will also be resumed early if the participant becomes pregnant, or if otherwise clinically indicated. If ART regimen is resumed before week 27, the fourth 3BNC117 infusion will not be administered.

Participants will be followed weekly during the analytical treatment interruption phase of the study for safety assessments and for monitoring plasma HIV-1 RNA levels. Participants may return to clinic between scheduled visits for additional VL measurements, if they desire to do so. CD4+ T cell counts will be measured every other week.

If HIV-1 RNA remains undetectable at week 36, participants will be offered to continue off ART with close monitoring, as long as HIV-1 viral rebound does not occur. In the continued ATI phase of the study participants will return for follow up every week, while off ART. ART resumption will follow same criteria as detailed above. After ART is resumed, study participants will return for follow up according to the Extension Schedule – Off ART Follow up (i.e. wk 40, 48, 56 and 60) (Appendix A).

The participant's primary care physician will be consulted on any changes in treatment.

During the ART-interruption phase of the study participants may be at increased risk of transmitting HIV-1 to their partners if they become viremic, and of HIV-1 superinfection from an HIV-infected partner. Therefore, participants 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, the participant will be advised to seek evaluation by his/her primary care provider to determine the need to reinitiate ART.

6.1.7 Final Visit/Early termination Visit

End of study (EOS) visit procedures will occur according to the Time of Events Schedule (Appendix A). Any participant who is withdrawn from the study should be seen for an EOS visit (Appendix A) as soon as possible. The study team will ensure the participant has appropriate follow-up with his/her primary care physician.

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

6.1.8.1 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.

6.1.8.2 Discontinuation of further 3BNC117 infusions

Volunteers will be discontinued from further 3BNC117 infusions for any of the following reasons:

1. If ART regimen is resumed before week 27 due to viral rebound. ART regimen is resumed if plasma HIV-1 RNA level is ≥ 200 copies/ml or if CD4+ count drops < 350 cells/µl and either result is confirmed upon repeat measurement, during the next weekly scheduled visit; or if plasma HIV-1 RNA level is ≥ 1,000 copies/ml, and confirmed by a repeat measurement prior to the next scheduled visit.
2. A disease, 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.
3. An abnormal laboratory event based on the following criteria:
   - For a grade 2 laboratory event, the laboratory test must be repeated and the event determined to be resolved or improved in the opinion of the principal investigator or designee prior to 3BNC117 infusion;
   - For a grade 3 or greater laboratory abnormality, even if resolved, the SMC must be consulted before making a decision to administer 3BNC117.
4. Any immediate hypersensitivity reaction (such as urticarial rash; bronchospasm; laryngeal edema; anaphylaxis; syncope).
5. Life threatening medical event following 3BNC117 unless not related to the investigational product.
6. Intercurrent use of immunosuppressive medication considered significant by the trial physician (e.g., systemic corticosteroids).
7. Pregnancy.
8. Participant's request to discontinue further 3BNC117 infusions.

6.1.8.3 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 participant.
4. Participant 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 or investigator.

6.1.8.4 Follow up after withdrawal from 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 the requested termination visit procedures (EOS visit procedures) will be performed according to 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 Safety Monitoring Committee (SMC), the Clinical Research Office and the IRB. Whenever possible, volunteers who are withdrawn from the study will be followed until the time of their final planned visit.

A pregnant volunteer will not receive 3BNC117 infusions. If pregnancy occurs after any 3BNC117 infusion, the volunteer will be asked to return for follow up every 4-6 weeks until delivery (see **section 6.2.8 Family Planning Counseling**).

6.2 Study Procedures

6.2.1 Consent Procedure

Prior to the initiation of any study related procedures, the potential participants will be given a copy of the most recent IRB stamped and 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, alternative treatments, benefits, risks, confidentiality etc. in a comprehensible (non-scientific) manner, using language readily understandable by the participant. Participants 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 participant.

A private, confidential setting will be provided for the potential participant to read and discuss the informed consent free from coercion, undue influence or constraints of time. All participants 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 participant and the person conducting the consenting process signs and dates the consent, the participant 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 participant.

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 participant. This method is used to assess comprehension and retention of protocol requirements, adverse event information, risks and benefits, and the participant's rights described in the Informed Consent process.

Spanish-speaking volunteers may be enrolled in the study. For these potential volunteers, a certified Spanish translation of the IRB-approved informed consent form (ICF) will be used. For unexpected or isolated volunteers who are candidates for this study, who are native speakers of other languages, a telephonic interpreting service (such as Pacific Interpreters) will be used to facilitate the explanation of the study. The investigator will send the interpreter a copy of the study’s ICF and a Short Form in the language that needs to be interpreted. The consenting process will be conducted by reading the English ICF while the interpreter repeats the words in the language of choice. The interpreter will also translate questions and answers that occur during the informed consent discussion. At the end of the consenting process, if the participant agrees, he/she will sign the Short Form in his/her native language in the presence of the investigator. The interpreter will sign both the IRB-approved ICF and Short Form as a witness, and will fax or email the signed copies to the investigator. The investigator will sign the IRB-approved ICF as the person conducting the consent discussion.

6.2.2 Study Assignment

This is an open-label study and participants will be enrolled sequentially as they meet enrollment criteria. The RUH pharmacist will dispense 3BNC117 in a piggy-back, diluted in sterile normal saline, ready for use. This study is open-label, both study investigators and volunteers will know the study allocation.

6.2.3 3BNC117 Infusions

3BNC117 will be provided in single-use vials containing 5 ml of the product at a concentration of 20 mg/ml. The volume of 3BNC117 to be administered will be calculated by the RUH research pharmacist, according to study assignment. The appropriate volume of 3BNC117 will be administered as a slow intravenous infusion over 60 minutes in the inpatient unit of the RUH. The calculated dose of 3BNC117 will be diluted in sterile normal saline to a volume of 250 ml.

A maximum of two participants will receive a 3BNC117 infusion per day. Infusions will not be given simultaneously.

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 20ml of Normal Saline to ensure all the medication has been delivered.

Volunteers will be closely observed for 4 hours 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 in the RUH inpatient unit 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 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 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 weight, vital signs, examination of infusion site, and any further examination indicated by history or observation.

6.2.5 Laboratory Evaluations

Venous blood will be collected at every study visit, usually from the antecubital fossa, according to the Time of Events Schedule (Appendix A). At no time will the total volume of blood collected exceed 550 mL over an 8-week period. Two large blood draws (250-300 ml) will occur in the study: on weeks 12 and 36. At all other study visits, total blood volume collected will not exceed 100 ml. Participants will undergo a leukapheresis procedure on day -14 and week 23.

All specimens will be handled according to SOPs that were developed in the GLP-like-Processing Lab within the Laboratory of Molecular Immunology.

6.2.5.1 Specimen Shipment Preparation, Handling and Storage

- Safety labs: Specimens collected for safety labs at RUH will be transported to Memorial Sloan Kettering Cancer Center laboratory (MSKCC) via a courier. At the Cornell site, safety labs will be processed at the local laboratory. Specimens for LabCorp will be picked up by LabCorp staff at both clinical sites.

- Research labs:
Specimens collected at the Rockefeller and Cornell Sites will be transported to the Sample Processing lab in the Laboratory of Molecular Immunology by laboratory staff. The buildings are adjacent to each other and are connected by an underground tunnel.

1. Peripheral Blood Mononucleated Cells (PBMC) (isolated from ACD tubes or from

leukapheresis): PBMC isolation will be performed at the Laboratory of Molecular Immunology. PBMCs are isolated using density gradient centrifugation with Histopaque. The isolated PBMC layer is washed twice with Hanks Balanced Salt Solution before a final wash in R10. Cells are counted with a Vi-cell XR (Beckman Coulter) before being frozen at a concentration of 1 x 10^7 cells per aliquot. PBMCs will be stored in liquid nitrogen freezer.

PBMC samples will be shipped to the laboratory of Dr. Richard Koup and the laboratory of Dr. Daniel Kaufman, who will perform monitoring of cellular immune responses. Samples will also be shipped to the laboratory of Dr. Robert Siliciano for viral outgrowth assays. The remaining aliquots will be stored in a liquid nitrogen freezer located in the Lab. of Molecular Immunology.

2. Plasma: Samples will be collected from ACD tubes after an initial centrifugation step, prior to PBMC isolation. The collected plasma sample goes through a second centrifugation step and is aliquoted in 1 or 10 ml volumes and stored at -80 degrees Celsius.

Plasma samples will be shipped to the Laboratory of Dr. David Montefiori for monitoring of humoral immune responses. The remaining aliquots will be stored in the Lab. of Molecular Immunology.

3. Serum: Samples will be collected in Serum Separation Tubes (SST). Following centrifugation, serum from multiple tubes, from the same volunteer, will be pooled, divided in 1ml aliquots and stored at -80 degrees Celsius.

Serum samples will be shipped to Celldex Therapeutics in Needham, Massachusetts and to the laboratory of Dr. Michael Seaman in Boston. Serum samples will be used for measurement of 3BNC117 levels, anti-3BNC117 antibodies and for in vitro neutralization assays. The remaining aliquots will be stored in the Lab. of Molecular Immunology.

All infectious specimens will be transported using packaging mandated in the Code of Federal Regulations, 42 CFR Part 72. Member carriers such as FedEx will accept or reject packages of dangerous goods on strict adherence to the International Air Transportation Association (IATA) Dangerous Goods Regulations (DGR). Shipments will be compliant with IATA DGR requirements.

6.2.5.2 Biohazard Containment

As the transmission of HIV-1 and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

6.2.6 Leukapheresis

Leukapheresis will be performed for all study participants. The procedure will occur at day -14 and week 23 in the RUH inpatient unit. Collected samples will be used for viral outgrowth assays to measure levels of latently infected resting CD4+ T cells.

Stat PT/PTT and CBC with differential will be sent prior to the procedure.

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 (protocol MCA-835), 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 closely monitored for 4 hours post infusion in the RUH inpatient unit. Access to a twenty-four hour on-call physician is available. The RUH outpatient and inpatient units and the WCMC Clinical Trial Unit 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 the neighboring tertiary care center, New York Presbyterian Hospital (Cornell) 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.

Pregnancy tests will be conducted at follow up visits as outlined in the Time of Events Schedule (Appendix A).

Should pregnancy occur, a pregnant volunteer will not receive 3BNC117 infusions. If pregnancy occurs after any 3BNC117 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, a pediatrician will examine the baby to assess her/his health status. The outcome of the pregnancy and the health status of the baby will be reported to the local IRBs, Clinical Research Office at the RUH, the SMC and the Antiretroviral Pregnancy Registry.

6.2.9 Compensation

There will be no compensation for the screening visit. Each study volunteer will be compensated $200 for each 3BNC117 infusion visit, $ 200 for each leukapheresis and $50 for each ophthalmologic evaluation. They will be compensated $60 dollars for each post infusion follow up visit and for weekly visits during the ART interruption phase. For late follow up visits, they will be compensated $100. In total, participants will be compensated $2,660, if all study visits are completed.

Volunteers that agree to remain off ART after week 36 will return to clinic every week for follow up. These volunteers will be compensated $50 for each of these additional visits, up to $1,200. In total, these volunteers may receive up to $3,860 if they remain off ART until the final study visit at week 60.

If volunteers are asked to return for an unscheduled visit, they will be compensated $25 each time.

Compensation is provided to help cover travel expenses, as well as child care and time lost from gainful employment. Volunteers will be compensated only for the visits they complete.

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, malaise, myalgia and arthralgia, as well as ocular complaints such as conjunctival erythema, excessive tearing or burning, and will be collected prospectively by structured interviews on 3BNC117 infusion and post-infusion follow up visits; recorded and graded according to pre-established criteria (see Appendix B). The DAIDS AE Grading Table v2.0 will be used to grade adverse events. In addition, the CTCAE v4.03 grading scale will be used for reporting and grading adverse events related to infusion reactions and cytokine release syndromes.

Vital signs (pulse, respiratory rate, blood pressure and temperature) will be monitored at end of infusion, 30 (+/- 5 minutes), 2 (+/- 10 minutes), and 4 hours (+/- 10 minutes) post infusion. 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 recorded during the entire study period. They will be graded as indicated in Appendix B.

6.2.10.3 Routine Laboratory Parameters

Laboratory parameters will routinely include CD4+ and CD8+ T cell counts and HIV-1 viral loads (VL), hematology (WBC and differential, RBC, hemoglobin/hematocrit, platelets), clinical chemistry (Na, K, Cl, Ca, Creatinine, Glucose, Total and Direct

bilirubin, Alkaline phosphatase, AST and ALT), and urinalysis. ANA will be performed at screening, day 0 and at week 60, and as clinically indicated. Coagulation tests (PT and PTT) will be performed at screening.

At screening and prior to each 3BNC117 infusion, female volunteers (except post-menopausal women) 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 Viral Sensitivity, Antiretroviral and Immunogenicity Assessments

Sensitivity of the participant's virus to 3BNC117 will be assayed by:

1. Viral outgrowth assay to evaluate the sensitivity of autologous viruses to 3BNC117 will be performed in the Laboratory of Molecular Immunology.

   Briefly, autologous viruses will be outgrown from participant's PBMCs in co-cultures with healthy donor PBMCs, and 3BNC117's neutralizing activity against culture supernatants containing autologous viruses will be determined by TZM.bl assay. The presence of HIV-1 in supernatant will be determined by p24 ELISA. $TCID_{50}$s will be determined for all HIV-1 containing supernatant and the 3BNC117 IC_{50}s determined in a TZM.bl neutralization assay, which will be 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) (Laird et al., 2013, Caskey, Klein et al, 2015).

Plasma HIV-1 RNA levels will be assessed by:

1. Standard HIV-1 viral load assay (CLEP-certified) will be performed at a contracted laboratory, LabCorp. 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 administrations.

The HIV-1 reservoir will be evaluated by the following assays:

2. Single copy HIV-1 viral load assay. This is a more sensitive assay with a limit of detection of 1 copy of HIV-1 RNA/ml of plasma. These assays will be performed in the laboratory of Dr. Frank Maldarelli (NCI/NIH).

3. Viral outgrowth assay for latency. The levels of latently infected resting CD4+ T cells (measured as infectious units per million CD4+ resting T cells) will be

evaluated by a viral outgrowth assay, performed in the Laboratory of Dr. Robert Siliciano from Johns Hopkins University. This assay requires large number of PBMCs, and samples will be collected at day -14 and weeks 12, 23 and 36 (if virologic rebound does not occur by week 36).

4. HIV-1 cell associated DNA and RNA levels in PBMCs will be determined in the Laboratory of Molecular Immunology, at baseline and weeks 12, 24 and 36 (if virologic rebound does not occur by week 36).

The effects of 3BNC117 on host immune responses and on infecting HIV-1 strains will be evaluated by the following assays:

5. TZM-bl neutralization assay will be 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 participants before and after administration of 3BNC117 against a panel of HIV-1 env pseudoviruses representing multiple clades.

6. T cell assays - HIV-1 Env and Gag specific responses will be evaluated in PBMC's by multiparametric cytokine flow cytometry. Phenotypic analysis, specifically the expression of immune activation/exhaustion markers on CD8+ T cells will also be evaluated. These assays will be performed at the Laboratory of Molecular Immunology, 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), and the laboratory of Dr. Daniel Kaufman at the University of Montreal.

7. B cell assays – HIV-1 Env and Gag specific binding antibody responses will be evaluated in serum or plasma samples in the laboratory of Dr. Georgia Tomaras (Duke University, a core laboratory of the CAVD).

8. 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 MSKCC or LabCorp.

9. Genotyping – Viral strains will be isolated/cultured ex-vivo and sequencing of HIV-1 env will be performed in samples collected at baseline and after 3BNC117 infusions, at the time of virologic rebound. Genotyping will be performed in the Laboratory of Molecular Immunology by reverse transcription followed by PCR amplification and sequencing of HIV-1 envelope genes. This will allow us to analyze the induction of escape mutations, if virologic rebound occurs. Results will be descriptive.

____Genotypic analysis of antiretroviral resistance in rebounding viral strains (samples

with HIV-1 RNA levels > 400 copies/ml) will be performed by a CLEP-certified assay at LabCorp.

10. Resistance testing of amplified HIV-1 envelope genes will be performed as previously described (Klein F et al., 2012). Amplified HIV-1 envelope genes will be cloned and expressed as pseudoviruses followed by evaluation of resistance to 3BNC117 in TZM-bl neutralization assays. Envelope gene amplification and cloning will be performed in the Laboratory of Molecular Immunology, TZM-bl neutralization assays in the laboratory of Dr. Michael Seaman. Results will be descriptive.

11. Evaluation of HIV-1 integration sites by deep sequencing will be performed in the Laboratory of Molecular Immunology, before and after administration of 3BNC117.

The pharmacokinetics and immunogenicity of 3BNC117 will be evaluated by the following assays:

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

13. Anti-drug (3BNC117) antibody responses in serum or plasma. Assays will be performed by Celldex Therapeutics.

Adherence to ART interruption will be confirmed at weeks 27 and 32, and at selected later study visits if participants remain off ART beyond week 36 (Appendix A) by the following assays:

14. Levels of antiretroviral medications (i.e. NNRTI's or PI's) will be measured by CLEP-certified assays performed at a contract laboratory (LabCorp).

15. TZM-bl infection with HIV-1 pseudotyped with murine leukemia virus, 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). This is not a standardized assay. However, negative controls and positive controls with sera from patients treated with representative drug classes will be used.

All immune responses and antiretroviral activity will be evaluated for proportion of responders and the mean responses will be compared. Research samples collected at the RUH and WCMC will be processed and stored in the Laboratory of Molecular Immunology. Optimal sample collection, processing, cryopreservation, archiving and storage will be maintained. Additional studies will be performed as warranted at the discretion of the investigators.

6.2.12 Pharmacokinetic evaluations

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

PK assessments will be performed on plasma or serum samples before 3BNC117 administration, at the end of each 3BNC117 infusion, 1 day, 1 week and 4 weeks after each infusion, at the time of viral rebound and at later time points, as outlined in the Time of Events Schedule (Appendix A). Pharmacokinetic parameters to be assessed will include maximum concentration (Cmax) elimination half-life (t1/2), clearance (CL/F), volume of distribution (Vz/F), AUC and decay curve.

3BNC117 serum or plasma levels will be measured by a sandwich ELISA using a murine anti-idiotype antibody to 3BNC117. The assays will be performed at Celldex Therapeutics.

7 Investigational Product

- Investigational Drug Name: 3BNC117

3BNC117 is a recombinant, fully human monoclonal antibody (mAb) of the IgG1κ isotype that specifically binds HIV envgp120.

- Manufacturer of study drug: Celldex Therapeutics, Inc.
- FDA Approved: No
- IND Number: 118,225
- IND Sponsor: Sarah Schlesinger, MD

7.1 Regimen

3BNC117 will be administered intravenously at 30 mg/kg dose level, on day 0, week 12, week 24 and week 27.

7.2 Study Product Formulation and Preparation

3BNC117 will be provided by Celldex Therapeutics in single-use vials containing 5 ml of the product at a concentration of 20 mg/mL.

The volume of 3BNC117 to be administered will be calculated by the RUH research pharmacist. 3BNC117 will be diluted in sterile normal saline to a volume of 250 mL, and administered as a slow intravenous infusion over 60 minutes.

7.3 Dispensing and Handling of Investigational Product

3BNC117 will be shipped from Celldex Therapeutics and will be stored in the RU Pharmacy at 2 - 8°C. 3BNC117 will be dispensed by the RU Hospital 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.

The appropriate dose will be calculated by the RU pharmacist according to participant'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 study investigators.

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. During the trial, the product accountability form, and the dispensing log will be monitored. At the end of the trial, unused vials will be returned to Celldex Therapeutics or destroyed.

7.5 Assessment of Participant Adherence with Study Product

Not applicable. Participants will be administered 3BNC117 in the inpatient unit of the RUH.

7.6 Concomitant Medications and Procedures

Use of concomitant medications will be reviewed at each study visit. Each participant will have a medication reconciliation record. It will be updated if schedule or dose level changes, and if new medications are initiated.

Participants will continue their ART regimen until week 24. If ART regimen includes an NNRTI, the NNRTI will be switched to dolutegravir 4 weeks prior to ART interruption. The participant's primary care physician will be consulted on any changes in treatment.

7.7 Permitted Medications and Procedures

We do not anticipate significant drug interactions with the study product at this time, therefore, if clinically necessary, volunteers can be initiated on other medications for intercurrent illnesses that might occur during their study participation.

7.8 Prohibited Medications and Procedures

We do not anticipate significant drug interactions with the study product at this time. Participants that enroll in the study agree to not participate in other studies of investigational drugs. In addition, they should not participate in studies that require frequent blood sample collection.

7.9 Precautionary Medications and Procedures

We do not anticipate significant drug interactions with the study product at this time. Participants that enroll in the study agree to not participate in other studies of investigational drugs. In addition, they should not participate in studies that require frequent blood sample collection.

7.10 Required Medications

Volunteers will continue their ART regimen until week 24. Volunteers on an NNRTI-based regimen will be switched to dolutegravir for 4 weeks prior to stopping all other antiretroviral medications. Dolutegravir will be provided to participants during that time period.

7.11 Rescue Medications

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 inpatient unit for use if clinically indicated. Infusion may be reinitiated after symptoms improve, and the remaining dose will be administered over 3 hours.

8 Data Analysis

8.1 Design

The proposed study is an exploratory phase 2, open label study to evaluate the antiretroviral activity and safety of four 3BNC117 infusions in HIV-infected individuals on combination antiretroviral therapy and during a brief analytical treatment interruption. The study will also obtain additional data on 3BNC117's effects on the HIV-1 reservoir.

Study participants will be administered four intravenous infusions of 3BNC117, (administered at 30 mg/kg). Antiretroviral therapy will be discontinued 2 days after the third 3BNC117 infusion, at week 24. We project screening 50 participants in order to achieve 15 evaluable participants. An over-enrollment of 2 participants will be allowed if participants do not complete all four 3BNC117 infusions. Participants that do not receive the fourth infusion because viral rebound occurred prior to week 27 will not be replaced. Additional participants will be enrolled after study withdrawal is confirmed.

The same ART regimen will be resumed at week 36 or sooner if plasma HIV-1 RNA level is $\geq$ 200 copies/ml or CD4+ T cell count drops $<$ 350 cells/μl, during the next weekly scheduled visit. If plasma HIV-1 RNA level is $\geq$ 1,000 copies/ml, the participant will be asked to return for a repeat measurement prior to the next scheduled visit, and ART will be resumed if results are confirmed. ART will also be resumed early if the participant becomes pregnant or if otherwise clinically indicated. If ART regimen is resumed before week 27, the fourth 3BNC117 infusion will not be administered. Volunteers will be followed weekly during the analytical treatment interruption phase for safety assessments and for monitoring plasma HIV-1 RNA levels. CD4+ T cell counts will be monitored every 2 weeks. (Appendix A).

Volunteers will be followed for 60 weeks from enrollment.

8.2 Analysis of Antiretroviral effects, Safety and Pharmacokinetics

Primary Objective:

1. 3BNC117's effect on virologic rebound:

A one-sided upper confidence interval will be constructed for the probability of rebound using the Clopper-Pearson method (Clopper, C. et al., 1934). Kaplan-Meier estimator will be used to address the second variable, "time to rebound" (Kaplan, E. et al., 1958).

2. Analysis of safety

The number and percentage of participants experiencing one or more AEs will be summarized by relationship to study drug, and severity. AEs will be summarized by the number and percentage of participants who experienced the event, according to system organ class (SOC) and preferred term. AEs will also be summarized by severity grade and by relationship to study drug according to the DAIDS AE Grading Table v2.0 (see Appendix B). The CTCAE v4.03 grading scale will be used for reporting and grading adverse events related to infusion reactions and cytokine release syndromes.

The changes in hematology, chemistry, and other laboratory values will be summarized descriptively. Changes will be calculated relative to the values collected at baseline.

Secondary and Exploratory Objectives:

1. Pharmacokinetics:

Pharmacokinetic parameters will be calculated using standard non-compartmental analysis methods, using WinNolin software, version 6.3. Pharmacokinetic parameters, including AUC, Cmax, T½, Tmax and others will be summarized. Pharmacokinetic parameters will be examined to correlate exposure with safety and pharmacodynamic parameters, and variance based on population intrinsic factors such as weight and gender will be explored.

2. 3BNC117 effects on the size of the HIV-1 reservoir:

A 95% repeated measures ANOVA F-test will be used to compare the following variables, before each infusion for all participants and at week 36, for participants that do not rebound:

- levels of latently infected resting CD4+ T cells in peripheral blood;
- levels of cell-associated HIV-1 RNA and DNA in PBMCs;
- levels of plasma HIV-1 RNA by single copy assay.

3. Host immune responses:

A 95% repeated measures ANOVA F-test will be used to compare the following variables, at baseline, at 4 weeks after each infusion and at week 36.

- serum levels of inflammation markers, such as: C-reactive protein, D-dimers, IL-6 and soluble CD-14.
- CD8+ T cell expression of activation markers such as: HLA-DR, CD38 and PD-1.

- HIV-1 gag and env-specific T and B cell immune responses will be evaluated by intracellular cytokine staining and multiplex ELISA.

4. Other measurements:
The frequency and levels of anti-3BNC117 antibodies, after each 3BNC117 infusion, will be calculated and displayed in tables.

Genotyping of HIV-1 isolates will be performed in the Laboratory of Molecular Immunology by reverse transcription followed by PCR amplification and sequencing of HIV-1 envelope genes. This will allow us to phylogenetically compare viruses grown from PBMCs collected from participants while on ART to rebound viruses collected after treatment interruption, and analyze the induction of escape mutations. In addition, amplified HIV-1 envelope genes will be cloned and produced in pseudoviruses in order to test for resistance to 3BNC117 by TZM-bl neutralization assay. Results will also be descriptive.

A Fisher exact test will allow us to contrast the rate of rebound between participants with baseline 3BNC117 IC_{50} against autologous viruses of < 2 μg/ml or ≥ 2 μg/ml. The Kruskal–Wallis one-way analysis of variance will be used to compare the mean time to rebound and mean reduction in infectious units per million (IUPM) in CD4+ resting T cells according to baseline 3BNC117 sensitivity of autologous viruses ($IC_{50} < 2$ μg/ml or ≥ 2 μg/ml). For both tests a 95% significance level will be assumed.

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.

8.3 Sample Size Considerations

In this pilot study we intend to enroll a convenient sample size of 15 evaluable participants.

A one-sided upper confidence interval will be constructed for the probability of rebound using the Clopper-Pearson method. As such, a sample size of 15 HIV-infected individuals will allow the rejection of the null hypothesis (rate=0.85) with 80% power for an effect size equal or higher than 0.32, if at least 6 participants do not rebound. The one-sided 95% Clopper-Pearson confidence intervals calculated for a varying number of observed rebounds are presented in Table 1.

Number of Rebounds	UCI
0	0.1810
1	0.2794
2	0.3634
3	0.4398
4	0.5108
5	0.5774
6	0.6404
7	0.7000

8	0.7563
9	0.8091
10	0.8583
11	0.9033
12	0.9432
13	0.9758
14	0.9966
15	1.0000

Table 1. Upper bound Confidence Interval for a sample size of n=15, calculated using binom.test R function, package stats

If 10 or more participants experience viral rebound prior to week 29 [5 weeks after ART interruption and 2 weeks after last 3BNC117 infusion], additional participants will not undergo ATI.

The safety population will include all participants who receive a 3BNC117 infusion. A baseline measurement and at least one laboratory, vital sign, or other safety-related measurement obtained after at least one dose of study treatment may be required for inclusion in the analysis of a specific safety parameter. With sample size of 15, if none of the participants experience a grade 2 adverse event related to 3BNC117, the 95% upper confidence bound for the rate of adverse events in the population is 21.8%.

This study also aims at evaluating possible effects of 3BNC117 on the HIV-1 reservoir. A 95% repeated measures ANOVA F-test will be used to compare levels of latently infected resting CD4+ T cells in peripheral blood; levels of plasma HIV-1 RNA by single copy assay; and levels of cell-associated HIV-1 RNA and DNA, at baseline and at weeks 12, 23 (or 24) and 36, if viral rebound does not occur. For repeated measures ANOVA F-test, a sample size of 15 participants allows to detect a Cohen f^2 effect size (Cohen, J, 1988) of 0.44, with 80% power and 95% confidence. The detectable effect size is common for all the variables since it depends on power, significance level and sample size. The detectable change will depend on the observed standard deviation of each variable.

8.4 Enrollment/Stratification/Randomization/Blinded Procedures:

This will be an open-label, single-arm study. Patients will be enrolled sequentially as they meet enrollment criteria for study participation.

8.5 Participant Enrollment and Follow-Up

The total number of enrolled participants in the study will be 15.

An over-enrollment of 2 participants will be allowed if participants do not complete all four 3BNC117 infusions. Participants that do not receive the fourth infusion because viral rebound occurred prior to week 27 will not be replaced. Additional participants will be enrolled after study withdrawal is confirmed. If a participant drops out after receiving 1 or more infusions of the study drug, he/she will be followed for safety.

We expect it will take up to 18 months to recruit 15 participants and they each will be followed for a total of 60 weeks.

9 Data and Sample Storage

The site Principal Investigator 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). Data collection forms (DCFs) will be provided by EMMES 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 site and remain separate from volunteer identification information (name, address, etc.) to ensure confidentiality. All medical records (when not being reviewed by the research team) will be kept under lock and key in the Medical Record Department of the hospital with access limited to the appropriate RUH personnel. At the Cornell site, source documents will be kept in a locked office in the WCMC Clinical Trials Unit. 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 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 dates of 3BNC117 infusions
- Documentation of any existing conditions or past conditions relevant to eligibility
- Reported laboratory results
- All adverse events
- Concomitant medications

Study records will be kept for five years after completion of the study.

9.1 Quality Control and Quality Assurance

Quality control checks (manually and automated) will be run on the EMMES generated database. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

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 50 participants in

order to achieve 15 evaluable participants. An over-enrollment of 2 participants will be allowed if participants do not complete all four 3BNC117 infusions.

- Advertisements – The Clinical Research Support Office at the Rockefeller University Hospital (CRSO) will utilize the Volunteer Repository. Advertisements will also be placed: online (e.g. Craigslist, Centerwatch, etc), in newspapers (Metro, AMNY) and on campus.

- Centralized Call Management – The CRSO will conduct telephone screenings of selected Volunteer Repository members, and of volunteers who call 1800-RUCARES, to facilitate screening efficiently. Based on IRB approved eligibility criteria, potentially eligible candidates pre-screened by CRSO staff will be referred to the study coordinator/investigator for further evaluation.

Participants may also be referred by physicians in the community.

10.1 Participant Retention

This study requires frequent follow up visits, which can be challenging to participants. The study staff will review the study schedule in detail with potential participants in advance of enrollment and attempt to facilitate transportation to the clinical site, if needed. Frequent visits allow ongoing communication between study investigators and participants and can decreased the risk of participants being lost to follow up. Participants will be contacted by phone or email (whichever is preferred to the participant) prior to their next appointment, not more than 3-5 days in advance. Study investigators will consult participant's primary care physician on any changes in treatment, which can also improve participant retention.

11 Potential Benefits to Participants

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

12 Potential Risks to Participants

- This study entails moderate risk to participants since 3BNC117 is an investigational new drug with limited human safety data. 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 (El-Sadr W *et al.* 2006, SMART trial). However, different groups have now shown that short analytical treatment interruption is safe (Rothenberger M et al. 2015; Routy JP *et al.* 2012). ART will be resumed if plasma HIV-1 RNA levels increase to ≥ 200 copies/ml and confirmed upon repeated measurement (performed within 1 week of first measurement).

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

- During ART interruption, participants might experience symptoms of acute retroviral syndrome, such as fever, rash, swollen glands, 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 participants may be at increased risk of transmitting HIV-1 to their partners, if they become viremic, and of HIV-1 superinfection from an HIV-infected partner.

- 3BNC117 has now been administrated to 63 volunteers and was generally safe and well tolerated in all doses tested. Ten HIV-uninfected individuals have received two 3BNC117 infusions at 10 mg/kg (n=5) or 30 mg/kg dose levels (n=5), administered 12 weeks apart. This study will for the first time evaluate the safety of four infusions of 3BNC117, as well as the safety of administering two infusions three weeks apart. The risk of repeated 3BNC117 infusions is not yet known.

- 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.

- 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;
    - Infusion 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 participant, 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. 63 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.

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

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

- Leukapheresis is a well-tolerated procedure, which is commonly used for blood cell donations. The risks associated with a leukapheresis are mild pain or discomfort with catheter insertion (common) in both arms, temporary numbness of lips or extremities (occasionally), ecchymosis, nausea, chills, transient numbness and infection (rare). The best method to obtain the number of cells needed for this research is leukapheresis.

13 Procedures to minimize risk

- As outlined above, this study will be an exploratory phase 2 trial of 3BNC117 in humans. Potential trial volunteers will be informed about the possible risks of the monoclonal antibody and that there may be unknown risks.

- Medical records and routine laboratory data will be handled with HIPAA compliance and protected by the rules and regulations of the RUH and WCMC, JCAHO-approved institutions.

- With any new medicine or monoclonal antibody, there is a possibility of totally unexpected side effects. Participants will be closely monitored for 4 hours post infusion in the RUH inpatient unit. The RUH inpatient unit is 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 participant, he/she will be transferred to the neighboring tertiary care center, New York Presbyterian Hospital (Cornell) for specialized medical care.

- Participants will be closely monitored for the development of symptoms of ocular disease (such as blurry vision, increased lacrimation, redness, dryness, pain) and the study investigators will perform a directed exam of the eyes. If participants 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 participant.

- 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 other week.

Participants may return to clinic between scheduled visits for additional VL measurements, if they desire to do so.

- ART regimen will be resumed if plasma HIV-1 RNA level is ≥ 200 copies/ml, CD4+ T cell count drops < 350 cells/μl, and either result is confirmed upon repeat measurement, during the next weekly scheduled visit. If plasma HIV-1 RNA level is ≥ 1,000 copies/ml, the participant will be asked to return for a repeat measurement prior to the next scheduled visit, and ART will be resumed if results are confirmed. ART will also be resumed early if the participant becomes pregnant copies/ml, or if otherwise clinically indicated. If ART regimen is resumed before week 27, the fourth 3BNC117 infusion will not be administered (Appendix A).

- In order to minimize the risk of resistance to the previous ART regimen, all antiretroviral drugs will be stopped simultaneously and ART will be resumed if plasma HIV-1 RNA level is ≥ 200 copies/ml and confirmed upon repeat measurement. Non-nucleoside reverse transcriptase inhibitors have longer elimination half-lives than other antiretroviral classes. Therefore, in order to avoid the risk of inadvertent monotherapy, which can select NNRTI resistant strains, if the participant's ART regimen includes an NNRTI, the NNRTI will be switched to dolutegravir (an integrase inhibitor) 4 weeks prior discontinuing all other antiretroviral drugs. Dolutegravir will be provided to the participants for that time period.

- In order to minimize the risk of transmitting HIV-1 to their partners and of HIV-1 superinfection from an HIV-infected partner, participants 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, participant may re-initiate ART as clinically indicated by his/her primary care physician.

- Since the safety profile of 3BNC117 is not fully known and since interruption of ART has been associated in the past with increased risk of cardiovascular complications, participants with certain co-morbid conditions (such as coronary artery disease, uncontrolled hypertension, diabetes, auto-immune diseases) will be excluded to ensure a healthy population of participants are selected.

- 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.

- Female study volunteers of reproductive potential who participate in sexual activity that might lead to pregnancy will be advised to use a reliable form of contraception for the duration of the study. In addition, a pregnancy test will be performed at screening, on the day of each 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 condoms from screening throughout the duration of the study to avoid pregnancy in a spouse or partner. Condoms will be provided.

- Participants will have regularly scheduled study visits and Routine safety laboratories [CBC, clinical chemistries, liver function tests, and urinalysis] will be checked according to the Time of Events Schedule (Appendix A). HIV-1 viral load and CD4/CD8 counts will be closely monitored according to the Time of Events Schedule (Appendix A).

- Adverse events will be monitored and graded using the DAIDS AE Grading Table v2.0. The CTCAE v4.03 grading scale will be used for reporting and grading adverse events related to infusion reactions and cytokine release syndromes (Appendix B).

- Adverse events will be managed by the clinical trial team who will assess and treat the event as appropriate, including referral to an independent physician and/or department.

Safety monitoring at both clinical sites will be conducted both by the International AIDS Vaccine Initiative (IAVI) and by an external Study Monitoring Committee (SMC). The RUH and WCMC IRBs will conduct the initial review of the proposed study and will follow progress through annual reports and by immediate notification of serious adverse events.

Any serious and unanticipated 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, per 21 CFR 312. The SMC will be available to the investigators for consultation and review of grade 3 or greater toxicity 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 2 study which exposes the participants to “moderate risk”. A Study Monitoring Committee (SMC) will be established to monitor the study.

15.1 Safety Monitoring Committee

The charter of the SMC is to provide an ongoing assessment of volunteer safety during the conduct of the study. The SMC consists of three independent individuals who have no relationship to the Principal Investigator 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, 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, 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:

Michael Keefer, MD
Professor of Medicine
University of Rochester Medical Center School of Medicine and Dentistry
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Michael_Keefer@urmc.rochester.edu
Clinical expertise: infectious diseases, vaccines, HIV vaccines.

Karolina Palucka, MD
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Clinical expertise: immunotherapy, cancer vaccines

Eric Daar, MD
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EDaar@LABioMed.org
Clinical expertise: clinical management of HIV infection

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.

In addition, the SMC will review all safety data in the event of two or more adverse events graded as grade 3 or greater toxicity, and deemed at least possibly related to 3BNC117. Further enrollment or 3BNC117 infusions will not occur until SMC review. Enrollment will stop but participants will continue to be monitored by the study investigators. 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 SAE judged as possibly,

probably or definitely related to the administration of 3BNC117 by the principal investigator or designee, no additional enrollment or 3BNC117 infusions 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, investigator's brochure, and related documents will be provided to the SMC members and the DAIDS Medical Officer (MO) and DAIDS Program Officer (PO). 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 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 in turn will distribute these reports to the study team and the local IRBs and the DAIDS MO and DAIDS PO.

15.2 Safety Review

Participants will be closely monitored for 4 hours post infusion in the RUH inpatient unit. The RUH inpatient unit is equipped for providing emergency medical interventions in the unlikely event of acute allergic or other reactions. RU Hospital outpatient and inpatient units and the WCMC Clinical Trials Unit are equipped with crash carts for immediate medical care, should the need arise. In case of an emergency, after stabilization of the volunteer, he/she will be transferred to the neighboring tertiary care center, New York Presbyterian Hospital (Cornell) for specialized medical care.

The study investigators will review and grade AE's on an ongoing basis for the duration of the study. Safety monitoring will be conducted by IAVI, which will review clinical records and adverse events.

15.3 Clinical Site Monitoring

Safety monitoring at both sites will be conducted by the study investigators and by IAVI. An external SMC will review SAEs and Unanticipated AEs and will be available to the study investigators for consultation. The RU and WCMC 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.

Prior to initiation of clinical activities at both Rockefeller and Cornell sites, a site initiation visit (SIV) will take place to discuss protocol-specific procedures with study investigators, pharmacy, nursing and laboratory staff. IAVI monitors will be present at both SIVs. SIV reports will be distributed to the DAIDS MO and DAIDS PO. Furthermore, DAIDS may opt to conduct a site visit prior to initiation of clinical activities, in part to ensure deficiencies identified during the SIV have been rectified.

IAVI Monitors will verify that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

Monitoring reports will be provided to the study investigators and IRB once every 6-10 weeks plus or minus 2 weeks. Monitoring reports will be submitted to the DAIDS MO and DAIDS PO. Each clinical trial site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring by IAVI, and inspection by local and regulatory authorities. IAVI is primarily responsible for site monitoring but DAIDS may follow-up directly with the site to ensure issues are resolved and/or write directly to the sites if DAIDS identifies issues that were not raised by IAVI.

15.4 Adverse Event Classification

The DAIDS AE Grading Table will be used for grading of AEs, The CTCAE v4.03 grading scale will be used for reporting and grading adverse events related to infusion reactions and cytokine release syndromes (Appendix B).

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, the DAIDS medical officer (DAIDS MO) and DAIDS program officer (DAIDS PO), and to the RU sponsor according to policy, within two working days of identification of the SAE. The RU sponsor will report SAEs to the FDA, per 21 CFR 312.

15.6 Reporting Unanticipated AEs

Unanticipated Adverse Events (UAEs) will be reported to the local IRBs. UAEs that are related and greater than grade 2 severity will be reported to the local IRBs, the DAIDS MO and DAIDS PO, and to the RU sponsor according to policy, within two working days of identification of the UAE. The RU sponsor will report UAEs to the FDA, 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 participants or their health care providers.

15.8 Toxicity Management and Stopping Rules

A dose limiting toxicity (DLT) will be defined as any adverse event of grade 3 or greater toxicity, if the study investigators recognize a possible, probable or definite attribution to 3BNC117.

Investigators at WCMC will promptly notify the PI and Sponsor at the Rockefeller

University in the event of any DLT. Both clinical sites will also notify the DAIDS MO and DAIDS PO of the occurrence of a DTL.

In case of two or more DLTs, further enrollment or 3BNC117 infusions will not occur until investigators and SMC review the event and all available safety data. Enrollment will stop but participants will continue to be monitored by the study investigators. The SMC member(s) will make a recommendation to the principal investigator(s) regarding the continuation of the trial (see **section 15.1 Safety Monitoring Committee**).

Participants will be withdrawn from the study for the reasons listed in **section 6.1.8.3 Withdrawal from the study (Early Termination)**.

15.9 Other Disease Events

Adverse events will be followed until resolved or considered stable during each scheduled study visit or during unscheduled study visits if warranted. If adverse events deemed related to the study agents are not resolved at the time of final study visit, participants will be referred for appropriate medical care until the symptoms resolve or the participant's condition becomes stable.

15.10 Critical Event Reporting

All critical events, as defined by the DAIDS Critical Events Manual, will be reported to DAIDS as per the Critical Events Manual.

16 Clinical Trial Registration

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

17 Study Discontinuation

The study may be discontinued at any time by the IRB, NIAID, the FDA or other government entities as part of their duties to ensure that research participants are protected.

In the event that the study is discontinued, 3BNC117 infusions will be halted and volunteers will be followed to ensure resolution of all adverse events. It is not applicable in this study to have participants continue therapy elsewhere as the investigational product does not provide the volunteers any direct benefit. In addition, the study does not have placebo recipients.

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