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A phase 2, open label study of the safety, antiretroviral activity and pharmacokinetics of 3BNC117 during a short analytical treatment interruption in HIV-infected subjects

IND Sponsor:
The Rockefeller University (Sarah Schlesinger, MD)
IND # 118225

Principal Investigator/Protocol Chair:
Marina Caskey MD

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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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Investigator(s) of Record: _____
Print/Type
Signed: _____ Date: _____
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Additional Investigators: _____
Print/Type
Signed: _____ Date: _____
Name/Title

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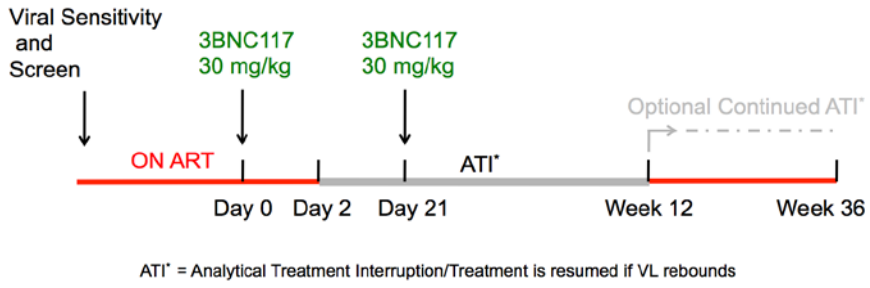
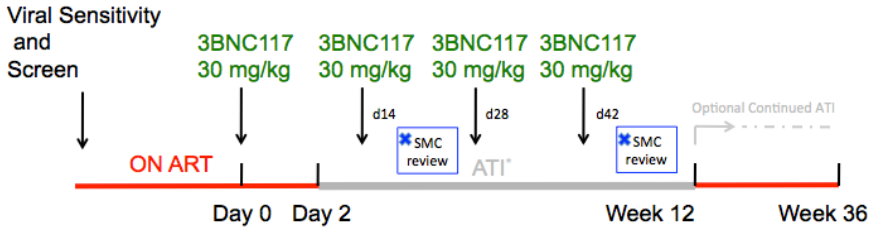
List of Abbreviations

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
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 Subjects Research
PBMC	Peripheral Blood Mononuclear Cell
PI	Principal Investigator
RU	The Rockefeller University
RUH	The Rockefeller University Hospital
QA	Quality Assurance
QC	Quality Control
RNA	Ribonucleic Acid
SAE	Serious Adverse Event/Serious Adverse Experience
S.C.	Subcutaneously
SHIV	Chimeric Simian/Human Immunodeficiency Virus
SOP	Standard Operating Procedure
T cell	T lymphocyte
V3 loop	Third Variable Loop of the HIV-1 Virion Envelope Glycoprotein 120

Study Schema

Title	A phase 2, open label study of the safety, antiretroviral activity and pharmacokinetics of 3BNC117 during a short analytical treatment interruption in HIV-infected subjects
Short Title	3BNC117 mAb in HIV-infected subjects during treatment interruption
Protocol Number	MCA-0867
Phase	Phase 2
IND Sponsor	The Rockefeller University (Sarah Schlesinger, MD)
Study Center(s)	The Rockefeller University (RUH), New York, NY
Principal Investigator	Marina Caskey, MD
Study Design	The proposed study is a Phase II, open label study to evaluate the safety and antiretroviral activity of two and four infusions of 3BNC117 in HIV-infected subjects on combination ART during a brief analytical treatment interruption (**Figure 1**, Study design). PK assessments are also included. The subject's viral sensitivity to 3BNC117 will be tested by outgrowing the subject's virus followed by a TZM-bl assay as previously described (Trkola et al., 2005a) (Mehandru et al., 2007a). After meeting enrollment criteria sixteen subjects with 3BNC117 sensitive virus (<2μg/ml IC_{50}) will receive two (Group A) or four (Group B) intravenous infusions of 3BNC117, administered at 30 mg/kg as shown below (Figure 1) Enrollment in Group B will start with a mini cohort of three subjects. These 3 subjects will receive 2 doses of 3BNC117, administered 2 weeks apart. Following the week 3 visit for the third subject, the Safety Monitoring Committee (SMC) will review all available safety data. The SMC will then provide a recommendation regarding administration of a third dose. If the SMC determines it is safe to proceed, the third dose will be administered 2 weeks following the second dose and the fourth dose will follow two weeks later. Two weeks after the third subject in Group B receives the fourth dose, all available safety data will be reviewed by the SMC. If the SMC determines it is safe to proceed, additional subjects will be enrolled to receive 4 doses at 2-week intervals. In both dosing groups, antiretroviral therapy will be discontinued 2 days after the first 3BNC117 infusion (day 2) until week 12. ART regimen will be resumed sooner 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. 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 completion of 3BNC117 infusions, further 3BNC117 infusions will not be performed. All subjects will be followed weekly until week 12 for safety assessments and for monitoring plasma HIV-1 RNA levels. CD4+ T cell counts will be monitored every 2 weeks until week 12. After week 12 subjects will be followed as outlined in the Time of Events Schedule (Appendix A). Subjects will be offered a continuation of the treatment interruption through week 36 in conjunction with their primary care physician as long as viral rebound does not occur (Extension

	Phase). In the extension phase of the study, subjects will return for follow up every week, while off ART. ART resumption will follow same criteria as detailed above. Safety and PK assessments will be performed at multiple time points following 3BNC117 infusions (see Appendix A). Subjects will be followed for 36 weeks from enrollment.
	Figure 1. Study Design: Group A  ATI* = Analytical Treatment Interruption/Treatment is resumed if VL rebounds Group B  ATI* = Analytical Treatment Interruption/Treatment is resumed if VL rebounds ✖ = SMC review on d21 and d56 in mini cohort (n=3)
Study Duration	36 weeks
Objectives	- The primary objectives of the study are to evaluate the effect of two and four infusions of 3BNC117 at 30 mg/kg in delaying virologic rebound and maintaining viral suppression during a short analytical treatment interruption; and to evaluate its safety, tolerability and pharmacokinetic profile in HIV-infected subjects with suppressed viremia during a short analytical treatment interruption. - The secondary objective is to determine the range of 3BNC117 serum levels at which virologic rebound occurs and to compare the effect of two and four infusions of 3BNC117 at 30 mg/kg in delaying virologic rebound and maintaining viral suppression during a short analytical treatment interruption. - Exploratory objectives are to phylogenetically compare viruses grown from PBMCs collected from subjects while on ART to rebound viruses collected after treatment interruption and analyze the induction of escape mutations that might arise after administration of 3BNC117. Furthermore, we plan to evaluate HIV-1 specific T and B cell immune responses following administration of 3BNC117 and the effect of 3BNC117 on cell associated HIV DNA and RNA.
Number of Subjects	16

Study Population	Adults, male and female, ages 18-65 with well-controlled HIV-1 infection on standard ART.
Inclusion and Exclusion Criteria	Inclusion Criteria: o Age 18 to 65 o HIV-1 infection confirmed by ELISA and immunoblot. o 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.] o 3BNC117 sensitivity (IC50 < 2 μg/ml) of subject derived HIV-1 virus isolates. These are isolated under protocol MCA-823 by co-culture of subject PBMCs with HIV-uninfected donor PBMCs followed by in vitro neutralization assays as previously described (Mehandru et al., 2007a) (Trkola et al., 2005a). o Current CD4 cell count > 500 cells/μl and no prior CD4 cell count < 200 cells/μl. o Willing to interrupt antiretroviral treatment for 12 weeks, or until viral rebound occurs. o If sexually active male or female, and participating in sexual activity that could lead to pregnancy using an effective method of contraception throughout the study period. Subjects should also agree to use a male or female condom during the time of pausing their HIV medication. o If on an NNRTI-based regimen willing to switch for 4 weeks to dolutegravir. Exclusion Criteria: o Have a history of AIDS-defining illness within 1 year prior to enrollment o History of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the trial physician within the last 6 months; o Chronic hepatitis B or hepatitis C; o Patient report, or chart history, of significant coronary artery disease, myocardial infarction, percutaneous coronary intervention with placement of cardiac stents; o Patient report, or chart history, of diabetes type 1 or 2 and/or current use of insulin or oral hypoglycemic medications; o 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; o Any other clinically significant acute or chronic medical condition, such as autoimmune diseases, that in the opinion of the investigator would preclude participation; o Current cigarette use in excess of 1 pack per day; o Laboratory abnormalities in the parameters listed below: o Absolute neutrophil count ≤ 1,000 o Hemoglobin ≤ 10 gm/dL o Platelet count ≤ 125,000 o ALT ≥ 2.0 x ULN o AST ≥ 2.0 x ULN o Total bilirubin ≥ 1.5 ULN o Creatinine ≥ 1.1 x ULN o Coagulation parameters ≥ 1.5 x ULN;

	○ Current antiretroviral regimen includes either maraviroc or enfuvirtide; ○ Pregnancy or lactation; ○ Any vaccination within 14 days prior to 3BNC117 administration; ○ Receipt of any monoclonal antibody therapy of any kind in the past; ○ Participation in another clinical study of an investigational product currently or within past 12 weeks, or expected participation during this study; ○ History of resistance to two or more antiretroviral drug classes;
Study Product, Dose, Route, Regimen	3BNC117 is a recombinant, fully human monoclonal antibody (mAb) of the IgG1κ isotype that specifically binds HIV envgp120. It is composed of 1,318 amino acids with a calculated molecular weight of 146,280 Dalton. In Group A, one intravenous infusion of 3BNC117 mAb will be administered on day 0 and a second infusion on day 21 via a peripheral vein over 60 minutes. In Group B, four intravenous infusions of 3BNC117 mAb will be administered on day 0, day 14, day 28 and day 42. Dose level to be tested: 30 mg/kg.
Statistical Methodology	In this study "occurrence of rebound during treatment interruption" and "time from treatment interruption until rebound occurs" are response variables. A one sided less Binomial Test with Clopper-Pearson confidence interval at 95% for proportion of rebound will allow us to determine the population probability for the first variable, "occurrence of rebound", with 95% of statistical significance level. As such, a sample size of 8 HIV-infected individuals will allow us to reject the null hypothesis (p(rebound)=1) with at least 80% power for any effect size of 0.18, which means the null hypothesis will be rejected with desired power, if at least 4 out of 8 subjects enrolled in study group B do not rebound by week 8 (2 weeks after last 3BNC117 infusion). If 5 or more participants in **group B** experience viral rebound prior to study week 6 [2 weeks after the third 3BNC117 infusion], additional participants will not undergo ATI. Kaplan-Meier survival curves will be used to address the second variable, "time to rebound". The number and percentage of subjects experiencing one or more AEs will be summarized by relationship to study drug, and severity. AEs will also be summarized by severity grade and by relationship to study drug according to the DAIDS AE Grading Table. 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). Changes will be calculated relative to the values collected at baseline. Pharmacokinetic parameters will be calculated using standard non-compartmental analysis methods. The time to rebound and the concentration of 3BNC117 at the time of rebound will be determined and summarized using confidence intervals. A 95% repeated measures ANOVA F-test will be used to compare the following variables, before the first infusion and at 8 weeks after the first infusion if viral rebound does not occur: • levels of plasma HIV-1 RNA by single copy assay; • levels of cell-associated HIV-1 RNA and DNA;

	The frequency and levels of anti-3BNC117 antibodies will be calculated and displayed in tables. Genotyping of HIV isolates will be performed to phylogenetically compare viruses grown from PBMCs collected from subjects while on ART to rebound viruses collected after treatment interruption. Amplified HIV envelope genes will be cloned and expressed in pseudoviruses in order to test for resistance to 3BNC117 in TZM-bl assays. These results will be descriptive.

1 Key Roles

1.1 Institutions

Study Sites:
- The Rockefeller University Hospital, New York NY
1230 York Ave.
New York, NY 10065
Contact Person: Marina Caskey, MD
Phone Number: (212) 327-7396
Fax Number: (212) 327-7234
E-mail: mcaskey@mail.rockefeller.edu

Clinical Laboratories:
- Memorial Sloan Kettering Cancer Center
1275 York Avenue
NY, NY 10065

- LabCorp
330 W 58th St
New York, NY, 10019

Funder: The Bill and Melinda Gates Foundation

Data Management:
EMMES Corporation
401 N. Washington St. Suite 700
Rockville, MD 20850

Independent Safety Monitoring:
International AIDS Vaccine Initiative (IAVI)
125 Broad Street, 9th Floor
New York, NY 10004

1.2 Individuals

Principal Investigator: Marina Caskey, MD Assistant Professor of Clinical Investigation The Rockefeller University 1230 York Avenue, NY, NY 10065 Phone Number: 212 327-7396 Fax Number: 212 327-7234 E-mail: mcaskey@mail.rockefeller.edu
Co-Investigators: Johannes Scheid, MD, PhD Sarah Schlesinger, MD Michel Nussenzweig, MD, PhD Florian Klein, MD Leah Burke, MD Yehuda Cohen, MD Allison Settler, ANP Sonya Hadrigan, ANP Arlene Hurley, ANP Irina Shimeliovich, MD, PhD Maggi Pack, PhD Sivan Ben Avraham Shulman, MPH Rebeka Levin, RN, BSN
Collaborators: Mike Seaman, PhD Frank Maldarelli, MD Richard Koup, MD Georgia Tomaras, PhD / David Montefiori, PhD Consultants: Roy Gulick, MD, MPH

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 subjects. 3BNC117 is a potent neutralizing anti-HIV antibody isolated and cloned in Dr. Nussenzweig's laboratory. 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 or chimeric simian/human immunodeficiency virus (SHIV) infection, and also to sustained suppression of HIV plasma viremia. Moreover, 3BNC117 alone prevented rebound of viral load after ART was discontinued in humanized mice. The aims of this protocol are to evaluate the effect of two and four infusions of 3BNC117 at 30 mg/kg in delaying virologic rebound and maintaining viral suppression during a short analytical treatment interruption. In addition, the study will evaluate the safety of 3BNC117 infusions during a brief analytical ART interruption.

3 Objectives and Rationale

3.1 Introduction

3.1.1 Background

Transmission of HIV continues at staggering rates in many areas of the world and AIDS is a major source of human morbidity and mortality worldwide. Despite intense research for over 30 years, an effective vaccine against HIV-1 remains elusive, and there are no vaccine candidates approaching licensure.

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

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

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

In SHIV-infected nonhuman primates 3BNC117 induces rapid viral suppression as monotherapy (7). 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(10). While antibody monotherapy did not control HIV-1 infection in viremic, untreated hu-mice, a single neutralizing antibody, *i.e.* 3BNC117, was able to sustain undetectable viral loads after initial suppression by antiretroviral therapy. Whereas hu-mice that received ART normally rebounded immediately after the drugs were terminated, continuing a single antibody was sufficient to maintain control after ART interruption in 50-86% of the hu-mice, for as long as antibody concentrations remained therapeutic (Horwitz et al., 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 antibody.

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 (Strategies for Management of Antiretroviral Therapy Study et al., 2006). While structured treatment interruptions (STIs) have traditionally been avoided given safety concerns, it should be noted that, in the first 16 weeks following randomization into the SMART study, there were no deaths in either treatment group – those that received continuous ART or those that received episodic ART guided by CD4 count. In addition, the differences in risk of opportunistic diseases and major cardiovascular, renal, and hepatic diseases between the two groups occurred predominantly after 16 weeks, increased over time and were strongly associated with low CD4 counts as well as increased viral loads. Recent evidence suggests that short analytical treatment interruption (limited to a maximum of 16 weeks), in individuals with preserved CD4 count and virologic suppression, is safe and is an accepted tool to evaluate new therapeutic modalities(Kutzler and Jacobson, 2008).

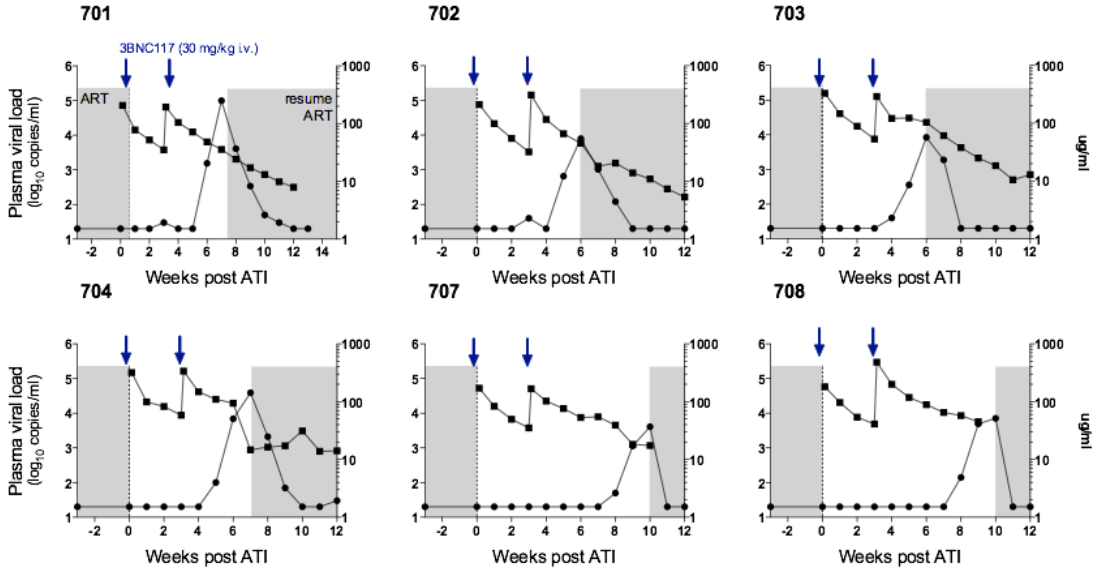
Passive administration of less potent, first generation anti-HIV-1 bNAbs has been evaluated in ART-interruption settings in humans. In these studies, 13-16 antibody infusions were administered intravenously at doses ranging from 0.5 to 2 g and were generally found to be safe and well tolerated. Furthermore, one of the antibodies (2G12) seemed to delay viral rebound in several participants. This effect was rather limited, as

2G12 did not neutralize the donor's virus isolates with sufficient potency(Trkola et al., 2005a) (Mehandru et al., 2007a). However, both studies found some correlation between the baseline sensitivity of the subject's virus to the antibody 2G12 and this antibody's ability to delay viral rebound. Therefore, we will test for the sensitivity of the subject's virus to 3BNC117 before the screening visit (under protocol MCA-823). Based on previous data (Scheid et al., 2011) sensitivity to 3BNC117 will be defined by an IC_{50} titer < 2μg/ml. The sensitivity testing will be repeated on day 0, after 3BNC117 infusions, and after viral rebound. It will be performed as previously described (Trkola et al., 2005a) (Mehandru et al., 2007a) (Laird et al., 2013) by outgrowing the subject's virus at the Laboratory of Molecular Immunology, followed by a TZM-bl assay in the laboratory of Dr. Michael Seaman.

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 humanized mice, levels of 3BNC117 decreased to levels as low as 0.5 μg/ml (10 times the IC_{50} value for the HIV strain used) before viral rebound occurred during ART-interruption (Horwitz et al., 2013). In the setting of antibody monotherapy in macaques, 3BNC117 serum levels above 1-10μg/ml (10-100 times the IC_{50} value for the respective strain) were required to prevent rebound (Shingai et al., 2013). Based on the PK data from the first clinical trial with 3BNC117, MCA-835 (Caskey et al., 2015) we designed the first group of this trial, Group A, to maintain 3BNC117 serum levels above 50 μg/ml (25 times the IC_{50} value of the respective patient virus) for at least 5 weeks after starting ATI. This allows us to investigate the ability of 3BNC117 to prevent viral rebound beyond the period of 2-3 weeks, during which rebound usually occurs in the setting of ATI (Davey et al., 1999; SMART Study et al., 2006; Rothenberger et al., 2015).

Eight subjects have enrolled in this protocol to date (Group A). Preliminary results show that the administration of 3BNC117 at 30mg/kg in the setting of an ATI is safe. Most reported adverse events were transient and considered of grade 1 severity. Participants did not report symptoms consistent with acute retroviral syndrome. To date, seven subjects have received the second 3BNC117 infusion (MCA867-701, -702, -703, -704, -706, -707, -708). Viral rebound has occurred in all seven participants; it occurred at week 9 in participants MCA867-707 and -708, at week 6 in participants MCA867-701 and -704, at week 5 in participants -702 and -703, and at week 4 in participant -706 (of note, this participant's viral load was 50 copies/ml at day 0). ART reinitiation led to rapid decrease in viral loads in all participants with measurements after ART reinitiation. Compared to historic controls who did not receive antibody treatment and showed viral rebound after 2-3 weeks after ART interruption, two infusions of 3BNC117 appear to delay viral rebound (Davey et al., 1999; SMART Study et al., 2006, Rothenberger et al., 2015).

Figure 2. Plasma HIV-1 RNA Levels and 3BNC117 serum levels in Participants Enrolled in Study Group A*.



* MCA867-705 and -706 viral loads were not fully suppressed at day 0 and are not displayed in this graph.

According to preliminary results in Group A of MCA-867, serum levels of 3BNC117 can decrease to levels as low as 66 µg/ml at week 5 (**Figure 2**). Experiments in mice and macaques suggest that antibody levels 10-100 times the IC_{50} value against infecting viral strains are necessary to control viral rebound. 3BNC117 levels achieved with Group A's dosing regimen, therefore, might only be sufficient to suppress viremia up to week 5. This might explain why viral rebound occurred at 4 to 9 weeks in the first 7 participants enrolled in this protocol.

In order to test if viral suppression can be further prolonged by 3BNC117 alone, we propose an amendment to this protocol to modify and optimize the dosing regimen. Enrollment in Group A will be closed. Additional participants will enroll in a new study group (Group B) and will receive four 3BNC117 infusions at 30mg/kg on day 0, day 14, day 28 and day 42. By decreasing the interval between 3BNC117 infusions and adding 2 infusions, we expect to maintain higher levels of 3BNC117 over a longer time period and, therefore, achieve continued viral suppression during the 3BNC117-dosing period and maintain viral suppression. Given the safety profile of 3BNC117 to date, we believe this modification does not significantly increase the risk to trial participants, while it enhances our ability to evaluate if 3BNC117 can maintain viral suppression during a brief analytical treatment interruption. However, as 3BNC117 has not been administered four times to single individuals to date, enrollment in Group B will be staggered, as described in **Section 4. Study Design.**

One of the aims of this study is to evaluate the effect of two or four 3BNC117 infusions on delaying viral rebound in subjects infected with 3BNC117-sensitive virus, when ART is discontinued. In addition the study will evaluate if viral suppression can be maintained with four infusions of 3BNC117 given at 14-day intervals. Finally, we will determine the

range of 3BNC117 serum levels at which viral rebound occurs and which escape mutations mediate viral rebound. Lastly, safety and pharmacokinetic evaluations will be performed.

3.1.2 The Investigational Product, 3BNC117

3BNC117 is a broadly neutralizing and highly potent anti-HIV-1 antibody. 3BNC117 was initially cloned from one B cell isolated from a volunteer infected with HIV-1 clade B, who controls his HIV-1 infection without antiretroviral therapy. The initial study was conducted under protocol MNU-0628. 3BNC117 targets the CD4 binding site (CD4bs) within HIV-1 envelope gp-120. It showed an average IC_{80} on a combined group of 95 tier 2 viruses of 1.4 μg/ml when evaluated by *in vitro* neutralization assays (Scheid et al., 2011). 3BNC117 also showed *in vivo* activity in experiments in both humanized mice and non-human primates. In chronically infected animals, passive administration of 3BNC117 alone or in combination with other potent neutralizing antibodies suppressed plasma viremia to levels below detection (Shingai et al., 2013) (Barouch et al., 2013). Moreover, 3BNC117 administration protected both humanized mice (Gruell et al., 2013) and rhesus macaques (Shingai et al., 2013) from challenge with HIV-1 and tier 2 SHIVs, respectively.

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

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

Passive administration of anti-HIV-1 antibodies has also been evaluated in humans. HIV Immune Globulin (HIVIG) was in clinical use in the 1990s before the advent of highly effective ART. HIVIG was also evaluated in HIV-infected pregnant females and their newborns in a phase III trial to assess whether HIVIG plus single dose nevirapine given to mothers and infants would provide additional benefit over single dose nevirapine alone for prevention of peripartum HIV transmission. While there was no demonstrable difference in treatment efficacy, the study showed that that there were no significant differences in mortality or serious AEs between the two arms of the trial (Onyango-Makumbi et al., 2011).

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

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

3.1.3 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 NOEL (no observable 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 subjects (protocol MCA-835). Study subjects are administered one or two intravenous infusions of 3BNC117 at increasing dose levels (1 mg/kg, 3 mg/kg, 10 mg/kg or 30 mg/kg), and are followed for 24 weeks after last infusion. As of 13 September 2015, 55 subjects (22 HIV-uninfected, 19 viremic HIV-infected and 14 ART-treated HIV-infected individuals) have enrolled in the study. Five HIV-uninfected individuals have received two infusions of 3BNC117 at 30mg/kg, 12 weeks apart. Twenty-three subjects (3 HIV-uninfected and 19 HIV-infected) have been administered one dose of 30 mg/kg.

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

Preliminary PK data show that 3BNC117's half-life is 17.6 days in HIV-uninfected and 9.6 days in viremic HIV-infected individuals. Peak serum concentration of 3BNC117 is reached at the end of infusion with a mean concentration of 563.6 μg/ml (range 410.2 – 976.4 μg/ml) after a single 30 mg/kg infusion in HIV-infected individuals. In these individuals, 3BNC117 serum levels range from 13 to 65 μg/ml (mean 41.6 +/- 12.5 μg/ml) three weeks after infusion. In addition, 3BNC117 decay rates following first and second 10 mg/kg infusions in HIV-uninfected individuals are similar.

A transient decline in HIV-1 viremia, of approximately 0.5 log, occurred following the administration of 3mg/kg of 3BNC117 to three HIV-infected subjects with detectable viremia. Of the 3 individuals receiving the 10mg/kg dose of antibody, only 2 responded with a decrease in viremia of 0.69 and 1.36 $\log_{10}$. The individual that did not respond was infected with 3BNC117-resistant virus that (2C4; IC_{50} > 20μg/ml at baseline). All ten viremic 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, but could be as long as 21 days. Interestingly, emergence of resistant viral strains was variable, with some individuals remaining sensitive to 3BNC117 for a period of 28 days after infusion (Caskey et al., 2015). Virologic data will continue to be analyzed under protocol MCA-835, as additional HIV-infected subjects are enrolled.

In addition, seven of the eight subjects enrolled in this study (protocol MCA-867) have received two 3BNC117 infusions at 30mg/kg at days 0 and 21. One subject's baseline

(day 0) HIV-1 viral load was found to be 8,730 copies/ml (subject -705). The subject was withdrawn from active study (second 3BNC117 dose was not administered), however he continues to be followed for safety as he received the first 3BNC117 dose. Most reported adverse events were transient and considered of grade 1 severity. Participants did not report symptoms consistent with acute retroviral syndrome. 3BNC117's peak mean serum concentration was 578.6 μg/ml (range 383.6 – 823.8 μg/ml) after first infusion and 613.4 μg/ml (range 456 – 757.6 μg/ml) after second infusion. The decay rate appears similar after first and second infusions, although follow up data is still being generated. 3BNC117 levels decreased to levels as low as 66 μg/ml at week 5 (66 – 123 μg/ml), two weeks after the second infusion. Seven participants enrolled (-701, -702, -703, -704, -706, -707, -708) experienced viral rebound at week 4 to 9 (**Figure 2**). ART was reinitiated in all subjects and has led to rapid decrease in viral loads in all cases.

3.2 Hypothesis

The administration of two or four infusions of 3BNC117 (30 mg/kg) will be safe, well tolerated, and will delay the return of HIV-1 viremia during a brief analytical treatment interruption.

3.3 Aims

Primary Objectives:

- Evaluate the effect of two and four infusions of 3BNC117 at 30 mg/kg in delaying virologic rebound and maintaining viral suppression during a short analytical treatment interruption.
- Evaluate the safety, tolerability and pharmacokinetic profile of two and four intravenous infusions of 3BNC117 at 30 mg/kg in HIV-infected subjects with suppressed viremia during a short analytical treatment interruption.

Secondary Objectives:

- Determine the range of 3BNC117 serum levels at which virologic rebound occurs.
- Compare the effect of two and four infusions of 3BNC117 at 30 mg/kg in delaying virologic rebound and maintaining viral suppression during a short analytical treatment interruption.

Exploratory Objectives:

- Phylogenetically compare viruses grown from PBMCs collected from subjects while on ART to rebound viruses collected after treatment interruption.
- Determine the viral escape mutations that might arise after administration of 3BNC117.
- Evaluate HIV-1 specific T and B cell immune responses following administration of 3BNC117.
- Evaluate the effects of 3BNC117 on serum levels of inflammation markers.
- Evaluate the effect of 3BNC117 on cell associated HIV DNA and RNA levels.

3.4 **Primary Outcome(s)**

- The rate of virologic rebound at 8 weeks post ART interruption (plasma HIV-1 RNA ≥ 200 copies/ml on two separate occasions).
- Time to rebound following ART interruption.
- The rate of signs, symptoms and laboratory abnormalities, in addition to systemic reactogenicity events following two 3BNC117 infusions at 30 mg/kg.
- 3BNC117 serum levels and anti-drug (3BNC117) antibody responses in serum or plasma at multiple time points following 3BNC117 intravenous administrations.

3.5 Secondary Outcome(s)

- The plasma level of 3BNC117 at the time of viral rebound.

Other evaluations:

- Phylogenetic comparison of viruses grown from PBMCs collected from subjects while on ART to rebound viruses collected after treatment interruption.
- Analysis of 3BNC117-induced escape mutations
- Evaluate the effects of 3BNC117 on serum levels of inflammation markers, such as C-reactive protein, D-dimers, IL-6 and soluble CD14.
- 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.
- Evaluate the effect of 3BNC117 on cell associated HIV DNA and RNA levels

4 Study Design

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

The subject's viral sensitivity to 3BNC117 will be tested by outgrowing the subject's virus at the Laboratory of Molecular Immunology, followed by a TZM-bl assay in the laboratory of Dr. Michael Seaman as previously described (Trkola et al., 2005a) (Mehandru et al., 2007a) (Laird et al., 2013). The initial testing will be performed under the protocol MCA-823. Based on previous data (Scheid et al., 2011) sensitivity to 3BNC117 will be defined by an IC_{50} titer < 2μg/ml.

After meeting enrollment criteria, eight subjects with 3BNC117 sensitive virus (< 2μg/ml IC_{50}) enrolled in Group A to receive two intravenous infusions of 3BNC117, administered at 30 mg/kg on day 0 and day 21. Eight additional subjects with 3BNC117 sensitive virus (< 2μg/ml IC_{50}) will receive four intravenous infusions of 3BNC117, administered at 30 mg/kg on day 0, day 14, day 28 and day 42 (Group B).

As 3BNC117 has not been administered four times to single individuals to date, Group B will be started with a mini cohort (n=3). The SMC will review all available safety data up to day 21 (1 week after second infusion) of the first 3 subjects enrolled in group B. The SMC will then provide a recommendation regarding administration of a third dose. If the

SMC determines it is safe to proceed, the third dose will be administered 2 weeks following the second dose (day 28) and the fourth dose will follow two weeks later (day 42). Two weeks after the third subject in Group B receives the fourth dose, all available safety data will be reviewed by the SMC. If the SMC determines it is safe to proceed, additional subjects (n = 5) will be enrolled to receive 4 doses at 2-week intervals.

On day 0 the sensitivity assay will be repeated in order to confirm the baseline sensitivity at the time of first infusion. Based on previous PK data from study MCA-835 and preliminary data from MCA-867 we expect that 3BNC117 serum levels will be maintained above 70 μg/ml for at least 8 weeks in Group B (Caskey et al., 2015). This significantly exceeds the typical period of viral rebound after ATI, which ranges from 2-3 weeks.

Antiretroviral therapy will be discontinued 2 days after the first 3BNC117 infusion (day 2). Non-nucleoside reverse transcriptase inhibitors have longer elimination half-lives than other antiretroviral classes. They are typically cleared in 2-4 weeks. Therefore, in order to avoid the risk of inadvertent monotherapy, which can select NNRTI resistant strains, if the subject's ART regimen includes an NNRTI, the NNRTI will be switched to dolutegravir (an integrase inhibitor) 4 weeks prior discontinuing all antiretroviral drugs. Dolutegravir will be provided to the subjects for that time period.

The original ART regimen will be resumed at week 12. The ART regimen will be resumed sooner 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. 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 completion of all 3BNC117 infusions, further 3BNC117 infusions will not be performed.

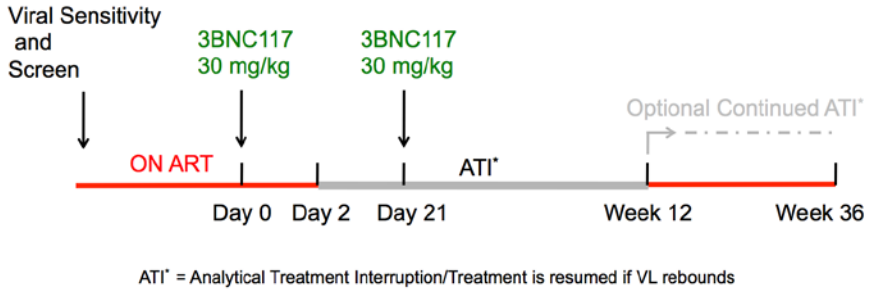
All subjects will be followed weekly until week 12 for safety assessments and for monitoring plasma HIV-1 RNA levels. CD4+ T cell counts will be monitored every 2 weeks until week 12. After week 12 subjects will be followed as outlined in the Time of Events Schedule (Appendix A).

Subjects will be offered a continuation of the treatment interruption through week 36, coordinated with their primary care physician as long as viral rebound does not occur. In the extension phase of the study subjects will return for follow up every week, while off ART. ART resumption will follow same criteria as detailed above. After ART is resumed, study subjects will return for follow up according to the Main Schedule (i.e. wk 14, 24 and 36) (Appendix A).

Safety and PK assessments will be performed at multiple time points following 3BNC117 infusions (see Appendix A). Subjects will be followed for 36 weeks from enrollment.

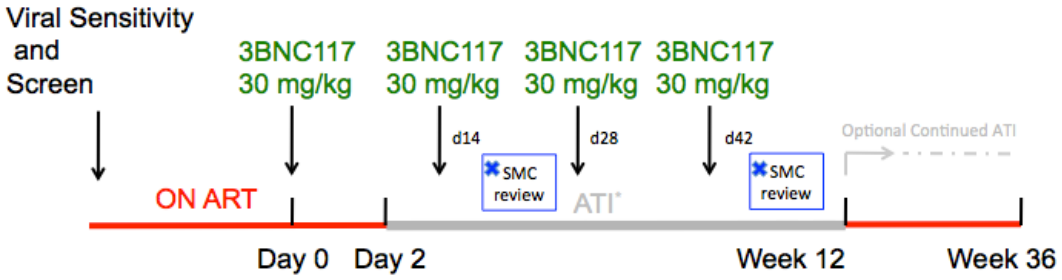
Figure 3. Study Design

Group A



ATI* = Analytical Treatment Interruption/Treatment is resumed if VL rebounds

Group B



ATI* = Analytical Treatment Interruption/Treatment is resumed if VL rebounds

✖ = SMC review on d21 and d56 in mini cohort (n=3)

5 Study Population

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

5.1 Inclusion Criteria:

- Age 18 to 65
- HIV-1 infection confirmed by ELISA and immunoblot.
- 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.]
- 3BNC117 sensitivity (IC_{50} < 2 µg/ml) of subject derived HIV-1 virus isolates. These are isolated under protocol MCA-823 by co-culture of subject PBMCs with HIV-uninfected donor PBMCs followed by in vitro neutralization assays as previously described (Mehandru et al., 2007a) (Trkola et al., 2005a).
- Current CD4 cell count > 500 cells/µl and no prior CD4 cell count < 200 cells/µl.
- Willing to interrupt antiretroviral treatment for 12 weeks, or until viral rebound occurs.

- If sexually active male or female, and participating in sexual activity that could lead to pregnancy using an effective method of contraception throughout the study period. Subjects should also agree to use a male or female condom during the time of pausing their HIV medication.
- If on an NNRTI-based regimen willing to switch for 4 weeks to dolutegravir.

5.2 Exclusion Criteria:

- Have a history of AIDS-defining illness within 1 year prior to enrollment
- 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;
- Patient report, or chart history, of significant coronary artery disease, myocardial infarction, percutaneous coronary intervention with placement of cardiac stents;
- Patient 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;
- 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
  - Hemoglobin ≤ 10 gm/dL
  - Platelet count ≤ 125,000
  - 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 either maraviroc or enfuvirtide;
- Pregnancy or lactation;
- Any vaccination within 14 days prior to 3BNC117 administration;
- Receipt of any monoclonal antibody therapy of any kind in the past;
- Participation in another clinical study of an investigational product currently or within past 12 weeks, or expected participation during this study.
- History of resistance to two or more antiretroviral drug classes

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 at The Rockefeller University Hospital (RUH) outpatient clinic. 3BNC117 infusion visits will be performed at RUH.

6.1.1 Pre-Screening Questionnaire

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

The sensitivity of subject's viral isolates to 3BNC117 will be evaluated under protocol MCA-823. This will be performed with a viral outgrowth assay followed by a validated in vitro TZM-bl neutralization assay as previously described (Mehandru et al., 2007a) (Trkola et al., 2005a) (Laird et al., 2013). Based on previous data (Scheid et al., 2011) sensitivity to 3BNC117 will be defined by an IC_{50} titer < 2μg/ml. The viral outgrowth assay will be performed in the Laboratory of Molecular Immunology, the in vitro neutralization assay will be performed in Dr. Michael Seaman's laboratory.

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 insure 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.
2. Risk reduction counseling. Sexually active males and females will be asked to use condoms during the short analytical treatment interruption due to the risk of intermittent viremia.
3. One must assume that no protection or improvement in control of HIV infection will occur given the exploratory nature of this study.
4. Subjects agree to stopping their antiretroviral medications as planned in the protocol and agree to return for weekly follow up visits for monitoring of plasma virus levels.

If the volunteer consents to participate, site personnel will:

- Obtain a complete medical history (including concomitant medications and cardiovascular history);
- Review subject's previous HIV-1 viral load and CD4/CD8 measurements (records 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.

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 3BNC117 Infusion Visits

3BNC117 infusions and assessments on the day after the infusions will occur at the Rockefeller University Hospital (RUH).
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 with the volunteer the informed consent form administered at screening visit;
- 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. Subjects will be closely observed for 1.5 hour after drug infusion in the inpatient unit of the RUH. Vital signs (pulse, respiratory rate, blood pressure and temperature) will be monitored at the end of infusion, 30 (+/- 5 min) minutes, 1 (+/- 10 min), and 1.5 hrs (+/- 10 min) post infusion. Presence or absence of reactogenicity events, as well as any other event that occurs, will be recorded at 30 – 45 minutes and at 1.5 hrs. The study staff will record reactogenicity events during clinic visits as shown on 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 clinic visit are illustrated in the Time of Events Schedule (Appendix A).

6.1.4 Post-3BNC117 Administration Visits

Study subjects will be followed through week 36.

During ART interruption follow up visits will be performed on a weekly basis for 12 weeks (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;
- Systemic reactogenicity, as well as other 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, subjects 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 subjects develop symptoms or signs of ocular disease, they will be referred to an ophthalmologist for diagnosis and management; expenses resulting from the evaluation will be covered by the study.
- 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.

6.1.5 ART interruption and reinitiation of combination ART

ART regimen will be discontinued for 12 weeks after the first 3BNC117 infusion.

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 subject's ART regimen includes an NNRTI, the NNRTI will be switched to dolutegravir (an integrase inhibitor) 4 weeks before all other antiretroviral drugs are discontinued. Dolutegravir will be provided to the subjects for that time period.

The original ART regimen will be resumed at week 12. ART regimen will be resumed sooner 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. 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 completion of 3BNC117 infusions, further 3BNC117 infusions will not be performed.

All subjects will be followed weekly until week 12 for safety assessments and for monitoring plasma HIV-1 RNA levels. CD4+ T cell counts will be monitored every 2 weeks until week 12. After week 12 subjects will be followed as outlined in the Time of Events Schedule (Appendix A).

Subjects will be offered a continuation of the treatment interruption through week 36, coordinated with their primary care physician as long as viral rebound does not occur. In the extension phase of the study subjects will return for follow up every week, while off ART. ART resumption will follow same criteria as detailed above. After ART is resumed, study subjects will return for follow up according to the Main Schedule (i.e. wk 14, 24 and 36) (Appendix A).

Safety and PK assessments will be performed at multiple time points following 3BNC117 infusions (see Appendix A). Subjects will be followed for 36 weeks from enrollment.

The subjects' primary care physician will be consulted on any changes in antiretroviral treatment. In addition, non-research results will be communicated to the subjects' primary care physician after each study visit during all phases of the study.

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

6.1.6 Final Visit/Early termination Visit

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

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

6.1.7.1 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.

6.1.7.2 Discontinuation from subsequent 3BNC117 infusions

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

1. A disease or condition or an adverse event that may develop, regardless of relationship to 3BNC117, if the principal investigator or designee is of the opinion that another 3BNC117 infusion will jeopardize the safety of the volunteer.
2. If ART regimen is resumed before completion of 3BNC117 infusions 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.
3. An abnormal laboratory event based on the following criteria:
   - For a moderate 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 severe or very severe 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. Subject's request to discontinue further 3BNC117 infusions.

6.1.7.3 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 subject.
4. Subject judged by the investigator to be at significant risk of failing to comply with the protocol in a manner that might lead to harm to self or seriously interfere with the validity of the study results.
5. At the discretion of the FDA or investigator.

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

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

At the time of withdrawal, provided the volunteer is willing, all the requested termination 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 SMC, the Clinical Research Office and the IRB. Volunteers who are withdrawn from the study (early termination) and received any 3BNC117 infusion will not be replaced, but, wherever possible, will return for safety assessments every 4-6 weeks until the time of their final planned visit.

A pregnant volunteer will not receive a 3BNC117 infusion. If pregnancy occurs after any 3BNC117 infusion, the volunteer will be asked to return for follow up every 4-6 weeks until delivery. Approximately 2-4 weeks after delivery, the baby will be examined by a pediatrician to assess the health status of the baby. The health status of the baby will be reported to the local IRBs, Clinical Research Office at the Rockefeller University Hospital and the SMC.

6.2 Study Procedures

6.2.1 Consent Procedure

Prior to the initiation of any study related procedures, the potential subjects will be given a copy of the most recent IRB 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 or device, alternative treatments, benefits, risks, confidentiality etc. in a comprehensible (non-scientific) manner, using language readily understandable by the subject. Subjects will be told that participation is voluntary and that, if they do not consent, they will not be penalized. The person consenting will assure the voluntariness of the subject.

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

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

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

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

Subjects for whom English is not a primary language will not be included in this study. The study investigators do not wish to discriminate against non-English speakers. However, investigators cannot risk having to depend on a translator service in the case of an emergency.

6.2.2 Study Assignment

This is an open-label study. Subjects will be enrolled sequentially as they meet enrollment criteria. Enrollment in Group A is closed. The target enrollment in Group B is of 8 participants. Enrollment will be staggered, 3 participants will be enrolled first, and further enrollment will be contingent upon review of safety data by the SMC.. 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 Administration Procedure

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. 3BNC117 will be administered as a slow intravenous infusion over 60 minutes in the RUH inpatient unit. 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 1.5 hour after drug infusion. If volunteers develop acute infusion reaction during 3BNC117 administration, the infusion will be held. Rescue medications, including acetaminophen, diphenhydramine and glucocorticoids will be available 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 injection site, and any further examination indicated by history or observation.

6.2.5 Blood Collection and Shipment

Venous blood will be collected at every study visit, usually from the antecubital fossa, according to the Time of Events Schedule (Appendix A). Total volume collected at each study visit will range from 50-150 ml. Given the close follow up with weekly visits during the first 12 weeks of the study, the total blood volume collected may reach up to 575 ml in an 8-week period during the ATI phase of the study.

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

Frozen PBMCs, plasma and serum will be processed and stored at the Laboratory of Molecular Immunology.

6.2.6 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. To date, 63 individuals have been administered 3BNC117 without complications. 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 1.5 hours post infusion in the RUH inpatient unit. Access to a twenty-four hour on-call physician is available. The Rockefeller University Hospital outpatient and inpatient units
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.

6.2.7 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 each clinic visit as outlined in the Time of Events Schedule (Appendix A). Should pregnancy be detected before administration of 3BNC117, the volunteer will not receive the 3BNC117 infusion. Should pregnancy be detected after any 3BNC117 infusion, a pregnant volunteer will be asked to return for follow up every 4-6 weeks until delivery Approximately 2-4 weeks after delivery, a pediatrician to assess the health status of the baby will examine the baby. The health status of the baby will be reported to the local IRBs, Clinical Research Office at the Rockefeller University Hospital and the SMC.

6.2.8 Compensation

Group A: There will be no compensation for the screening visit. Each study volunteer will be compensated $200 for each 3BNC117 infusion visit. They will be compensated $60 dollars for weekly visits during ART interruption phase. For each of the three follow up visits after week 12 they will be compensated $100. In total, these subjects will be compensated up to $ 1,360 if all study visits are completed. Subjects that agree to remain off ART after week 12 will return every week for follow up, up to 12 visits (week 36). These subjects will be compensated up to $1200 for the additional visits. In total, these subjects will be compensated up to $2,260 for study participation. Subjects will be compensated $25 for each unscheduled visit.

Group B: There will be no compensation for the screening visit. Each study volunteer will be compensated $200 for each 3BNC117 infusion visit. They will be compensated $60 for the visits during the ART interruption phase, up to and including week 12. For each of the three follow up visits after week 12 they will be compensated $100. In total, these subjects will be compensated up to $1,880 if all study visits are completed. Subjects that agree to remain off ART after week 12 will return every week for follow up, up to 12 visits (week 36). These subjects will be compensated $50 per visit, up to $1200 for the additional visits. In total, these subjects will be compensated up to $2,780 for study participation. Subjects will be compensated $25 for each unscheduled visit.

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

6.2.9 Safety Assessments

6.2.9.1 <u>Reactogenicity Events</u>

Reactogenicity events will be collected prospectively by structured interviews on the 3BNC117 infusion and post-infusion follow up visits; recorded and graded according to pre-established criteria (see Appendix B). The DAIDS AE Grading Table 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 measured prior to 3BNC117 administration at 30 - 45 minutes and 1.5 hour after the infusion is completed, graded according to Appendix B and recorded. Similarly, feverishness, chills, headache, nausea, vomiting, malaise and myalgia, arthralgia and rash will be assessed and graded. All medications required for treatment of adverse events will be recorded.

6.2.9.2 Other Adverse Events

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

6.2.9.3 Routine Laboratory Parameters

As outlined in the Time of Events Schedule, laboratory parameters will include CD4 and VL, hematology (WBC and differential, RBC, hemoglobin/hematocrit, platelets), clinical chemistry (Na, K, Cl, Ca, CO2, Creatinine, Glucose, Total and Direct bilirubin, Alkaline phosphatase, AST and ALT), and urinalysis. ANA will be performed at day 0, at week 36, and as clinically indicated. Immediately prior to each 3BNC117 infusion, pre-menopausal female volunteers will have serum beta-HCG assessed and at follow up visits they will have urine beta-HCG checked. The laboratory samples for these tests will be collected at the time points indicated in the Time of Events Schedule (Appendix A). In the event of an abnormal laboratory value, volunteers may be asked to have an additional sample collected at the discretion of the principal investigator or designee.

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

6.2.10 Viral Sensitivity, Antiretroviral and Immunogenicity Assessments

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

1. Viral outgrowth assay, performed at the Laboratory of Molecular Immunology as previously described (Laird et al., 2013), followed by a TZM-bl neutralization assay, 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).

HIV-1 levels will be assessed by:

2. 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 administration.

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

3. 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. This assay will be performed in the laboratory of Dr. Frank Maldarelli (NCI/NIH).

4. HIV-1 cell associated DNA and RNA levels in PBMCs will be determined in the Laboratory of Molecular Immunology, before and after administration of 3BNC117.

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

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

6. T cell assays - HIV-1 Env and Gag specific responses will be evaluated in PBMC's by IFNγ-ELISpot and/or 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 and the laboratory of Dr. Richard Koup at the Vaccine Research Center (VRC) at NIH, a core lab of the Collaboration for AIDS Vaccine Development (CAVD).

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 – If circulating viral strains can be isolated/cultured ex-vivo, sequencing and phylogenetic analysis of HIV-1 env will be performed in samples collected before and after the administration of 3BNC117, at the time of virologic rebound. This will allow us to compare viruses grown from PBMCs collected from subjects while on ART to rebound viruses collected after treatment interruption and analyze the induction of escape mutations. Genotyping of HIV isolates will be performed in the Laboratory of Molecular Immunology by reverse

transcription followed by PCR amplification and sequencing of HIV envelope genes. Results will be descriptive.

Genotypic analysis for antiretroviral resistance will be performed by a clinical assay (LabCorp) if viral rebound occurs.

10. Resistance testing of amplified HIV envelope genes will be performed as previously described (Klein et al., 2012). Amplified HIV envelope genes will be cloned and expressed as pseudovirus 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 validated sandwich ELISA will be performed at Celldex Therapeutics. 3BNC117 levels will be measured in serum or plasma.

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

The adherence to the treatment interruption will be confirmed at week 8 by the following assay:

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

15. Additionally, antiretroviral activity of serum against HIV 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.

Research samples collected at the RUH will be processed and stored at 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.

6.2.11 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 3BNC117 infusions, 1 day and 1 week after the infusions, 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 validated sandwich ELISA using a murine anti-idiotype antibody to 3BNC117. The assays will 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 and day 21 in Group A, and on day 0, 14, 28 and 42 in Group B.

7.2 Storage and Shipment of the Investigational Product

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

7.3 Dispensing and Handling of Investigational Product

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.

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

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.

8 Data Analysis

8.1 Design

The proposed study is a Phase II, open label study to evaluate the antiretroviral activity and safety of two and four 3BNC117 infusions in HIV-infected subjects on combination antiretroviral therapy, during a brief analytical treatment interruption. The study will also obtain additional data on its pharmacokinetic profile.

After meeting enrollment criteria eight subjects with 3BNC117 sensitive virus (< 2μg/ml IC_{50}) enrolled in Group A to receive two intravenous infusions of 3BNC117, administered at 30 mg/kg on day 0 and day 21 (Group A). Eight additional subjects with 3BNC117 sensitive virus (< 2μg/ml IC_{50}) will be enrolled to receive four intravenous infusions of 3BNC117, administered at 30 mg/kg on day 0, day 14, day 28 and day 42 (Group B). As 3BNC117 has not been administered four times to single individuals to date, Group B will be started with a mini cohort (n=3). Safety will be assessed by the SMC 1 week after the second dose, as well as 2 weeks after the fourth dose in the mini cohort, before proceeding with further infusions and enrollment.

Antiretroviral therapy will be discontinued on day 2 for 12 weeks after the first 3BNC117 infusion (week 12). We project screening 50 subjects in order to achieve 16 evaluable subjects. In case of drop-outs an over-enrollment of 10% will be allowed.

The same ART regimen will be resumed at week 12. ART regimen will be resumed sooner 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. 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 completion of 3BNC117 infusions, further 3BNC117 infusions will not be performed. All subjects will be followed weekly until week 12 for safety assessments and for monitoring plasma HIV-1 RNA levels. CD4+ T cell counts will be monitored every 2 weeks until week 12. After week 12 subjects will be followed as outlined in the Time of Events Schedule (Appendix A).

Subjects will be offered a continuation of the treatment interruption through week 36, coordinated with their primary care physician as long as viral rebound does not occur. In

the extension phase of the study subjects will return for follow up every week, while off ART. ART resumption will follow same criteria as detailed above.

The subjects' primary care physician will be consulted on any changes in antiretroviral treatment. In addition, non-research results will be communicated to the subjects' primary care physician after each study visit during all phases of the study. Safety and PK assessments will be performed at multiple time points following 3BNC117 infusions (see Appendix A). Subjects will be followed for 36 weeks from enrollment.

8.2 Analysis of Antiretroviral effects, Safety and Pharmacokinetics

Primary Objectives:

1. 3BNC117's effect on virologic rebound:

A one sided less Binomial Test with Clopper-Pearson confidence interval at 95% for rate of rebound will allow us to determine the population probability for the "occurrence of rebound", with 95% of statistical significance level (Clopper, C.; Pearson, E. S. (1934)).

Kaplan-Meier estimator will be used to address the second variable, "time to rebound" (Kaplan, E. L.; Meier, P. (1958).

2. 3BNC117's safety and tolerability profile in HIV-infected subjects with suppressed viremia during an analytical treatment interruption:

The number and percentage of subjects 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 subjects 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 (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 in all groups.

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

3. 3BNC117's pharmacokinetic profile in HIV-infected subjects with suppressed viremia during an analytical treatment interruption:

Pharmacokinetic parameters will be calculated using standard non-compartmental analysis methods. Pharmacokinetic parameters, including AUC, Cmax, T½, Tmax and others will be summarized. A 95% two tails matched pairs T-test will be used to compare 3BNC117 serum levels before and after each antibody infusion. Pharmacokinetic parameters will be examined to correlate exposure with safety and pharmacodynamic parameters. Variance based on population intrinsic factors such as weight and gender will be explored.

Secondary and Exploratory Objectives:

1. The range of 3BNC117 serum levels at which virologic rebound occurs:

For each participant the time to rebound and the concentration of 3BNC117 at the time of rebound will be determined and summarized using confidence intervals.

2. Compare the rate and time to rebound between groups:

A Fisher exact test will allow us to contrast the rate of rebound between groups and Kruskal–Wallis one-way analysis of variance will be used to compare the mean time to rebound. For both tests a 95% significance level will be assumed.

3. Host immune responses:

A 95% repeated measures ANOVA F-test will be used to compare the following variables, at baseline, 2 weeks after the last infusion, at weeks 12 and 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 gag and env-specific T and B cell immune responses will be evaluated by intracellular cytokine staining and ELISA.

4. Antiretroviral effects:

A 95% repeated measures ANOVA F-test will be used to compare the following variables, before as well as 8 weeks after the first infusion if viral rebound does not occur:

- levels of plasma HIV-1 RNA by single copy assay;
- levels of cell-associated HIV-1 RNA and DNA;

5. Other measurements:

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

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

Continuous data will be summarized by descriptive statistics, including the sample size, mean, standard deviation, median and range. Categorical data will be summarized by the number and percentage of subjects. If necessary Log2 of variables will be used.

8.3 Sample Size Considerations

The confidence interval calculation is based on one of the primary objectives of this study "Evaluate the effect of two or four infusions of 3BNC117 at 30 mg/kg in delaying virologic rebound and maintaining viral suppression during a short analytical treatment interruption". As such, the primary outcome is the occurrence of rebound during treatment interruption.

In study group A, 5 out 7 participants who received 2 infusions of 3BNC117 have experienced viral rebound to date. Eight participants will be enrolled in the new study group B and will be administered four 3BNC117 infusions at days 0, 14, 28 and 42.

A one-sided upper confidence interval will be constructed for the probability of rebound in study group B using the Clopper-Pearson method. As such, a sample size of 8 HIV-infected individuals will allow the rejection of the null hypothesis (rate = 1) with 80% power for an effect size equal or higher than 0.18, if at least 4 out of 8 participants enrolled in study group B do not experience viral rebound by week 8. The one-sided 95% Clopper-Pearson confidence intervals calculated for a varying number of observed rebounds are presented in **Table 1**. If 5 or more participants in group B experience viral rebound prior to study week 6 [2 weeks after the third 3BNC117 infusion], additional participants will not undergo ATI.

Table 1. Upper bound Confidence Interval
for a sample size of n=8 (Study Group B)

Number of Rebounds	UCI
0	0.3694
1	0.5265
2	0.6509
3	0.7551
4	0.843
5	0.9148
6	0.9682
7	0.9968
8	1

We will compare days from date of ART interruption to viral rebound in group A to group B. Given a standard deviation (SD) of 10 (days), enrolling 7 or 8 patients in each of the two arms, will have 80% power to detect ≥ 15 days difference in time to viral rebound at a 5% significance level (Davey et al., 1999, Rothenberger et al., 2015).

The safety population will include all subjects 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.

All adverse events will be reported, grouped as to whether or not they qualify as SAEs, their severity grading, and their relationship to the antibody, as judged by the study

investigators. If none of the subjects experiences a moderate adverse event related to 3BNC117 (n=16), the 95% upper confidence bound for the rate of adverse events in the population is 20.6%.

Two tail matched pairs T- test will be used to compare 3BNC117 serum levels before and after each antibody infusion. For two tail matched pairs T- Test, a sample size of 16 subjects in the group allows to detect an effect size of 0.75, with 80% power and 95% confidence.

For repeated measures ANOVA F-test, a sample size of 16 subjects in the group allows to detect an effect size of 0.46, with 80% power and 95% confidence. (to compare variables of antiretroviral effects and immune responses, before first infusion, at 2 weeks after last infusion, at week 12 and week 36.

9 Data and Sample Storage

The 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^{TM} 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. 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 date of 3BNC117 infusions
- Documentation of any existing conditions or past conditions relevant to eligibility
- Reported laboratory results
- All adverse events
- Concomitant medications

10 Recruitment Plan

Both men and women ages 18 through 65 will be recruited for the study from the community at large and will be referred by physicians in the community. We will make every effort to recruit minorities and women. We project screening 50 subjects in order to achieve 16 evaluable subjects. In case of drop-outs an over-enrollment of 10% will be allowed.

- Protocol MCA-823 - Subjects that already participated in protocol MCA-823, were found to have 3BNC117-susceptible strains, and agreed to be contacted for future studies will be contacted by study investigators.

- 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. Craiglist, CenterWatch, etc.), in newspapers (Metro, AMNY) and on campus.

Subjects may also be referred by physicians in the community.

11 Potential Benefits to Subjects

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

12 Potential risks to the subject including to the fetus

- This study entails moderate risk to subjects 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.* NEJM 2006, SMART trial). However, different groups have now shown that short analytical treatment interruption is safe (Routy et al., 2012). ART will be resumed if plasma HIV-1 RNA levels increase to $\geq$ 200 copies/ml and are 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 subjects will be followed very closely and ART will be resumed if the CD4+ cell count drops < 350 cells/μl and this is confirmed upon repeat measurement.

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

- 3BNC117 has now been administered to 63 volunteers (55 under protocol MCA-835 and 8 under this protocol – study group A) and it was generally safe and well tolerated in all doses tested. Sixteen volunteers have been administered 2 doses of 3BNC117 and 7 of these received the doses 3 weeks apart. This study will for the first time evaluate the safety of four infusions of 3BNC117 administered 2 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. Grade I partial thromboplastin time (PTT) prolongations were also noted in one study that tested a combination of three anti-HIV monoclonal antibodies (Mehandru et al., 2007b; Trkola et al., 2005b).

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

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

- In the cross-reactivity study in human tissues, 3BNC117 was found to bind to cells in the conjunctival recesses. It is possible that this binding could lead to conjunctival toxicity. However, when rats and non-human primates were administered 3BNC117,

conjunctival toxicity was not observed. Fifty-five participants have received 3BNC117 in protocol MCA-835. 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. To date, ophthalmic complaints have not been reported under this protocol.

- 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.

13 Procedures to minimize risk

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

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

- With any new medicine or monoclonal antibody, there is a possibility of totally unexpected side effects. Subjects will be closely monitored for 1.5 hours post infusion in the RUH inpatient unit. The Rockefeller University Hospital 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 subject, he/she will be transferred to the neighboring tertiary care center, New York Presbyterian Hospital (Cornell) for specialized medical care. So far, 3BNC117 has been administered to 55 individuals in protocol MCA-835 and 8 in this protocol (MCA-867) without any acute unexpected events. A maximum of two participants will receive a 3BNC117 infusion per day. Infusions will not be given simultaneously.

- Subjects 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 subjects develop symptoms or signs of ocular disease, they will be referred to an ophthalmologist for diagnosis and management. These evaluations will be performed at no cost to the subject.

- During the treatment interruption phase of the study, plasma HIV-1 RNA levels will be monitored weekly and CD4+ T cell counts will be monitored every other week. ART regimen will be resumed if plasma HIV-1 RNA level is $\geq$ 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 $\geq$ 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 completion of 3BNC117 infusions, further 3BNC117 infusions will not be performed.

- 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 according to the above criteria. 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 subject's ART regimen includes an NNRTI, the NNRTI will be switched to dolutegravir (an integrase inhibitor) 4 weeks prior discontinuing all antiretroviral drugs. Dolutegravir will be provided to the subjects for that time period.

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

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

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

- Females of childbearing potential and who participate in sexual activity that might lead to pregnancy will be advised to use a reliable form of contraception for the duration of the study. In addition, a pregnancy test will be performed at screening, on the days of drug infusion, and throughout the course of the study. Males who are not anatomically sterile and who participate in sexual activity that might lead to pregnancy will be advised to use condoms from screening throughout the duration of the study to avoid pregnancy in a spouse or partner. Condoms will be provided.

- Subjects will have regularly scheduled visits to the outpatient clinic 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-infected individuals will have close monitoring of HIV-1 viral load and CD4/CD8 counts according to the Time of Events Schedule (Appendix A).

- Adverse events will be monitored and graded using the DAIDS AE Grading Table. The CTCAE v4.03 grading scale will be used for reporting and grading adverse events related to infusion reactions and cytokine release syndromes in all groups (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 IRB will conduct the initial review of the proposed study and will follow progress through annual reports and by immediate notification of serious and unanticipated adverse events. Any serious adverse events will be reviewed by the study investigators immediately. Site investigators will notify the local IRB and the sponsor at the Rockefeller University within 2 working days from the investigators being made aware of the event. The RU sponsor will notify the FDA, per 21 CFR 312.The SMC will be available to the investigators for consultation and review of severe adverse events if needed.

14 Alternative methods or treatments

This does not apply to this study.

15 Data and Safety Monitoring Plan

This is an exploratory Phase II study which exposes the subjects to "moderate risk". 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 will consist of three independent individuals who have no relationship to the Principal Investigators and Co-Investigators involved in the trial. No member of the SMC will have any direct responsibility for the clinical care of trial volunteers. No representative of Celldex Therapeutics, 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
Phone: (585) 275-5871
Michael_Keefer@urmc.rochester.edu
Clinical expertise: infectious diseases, vaccines, HIV vaccines.

Karolina Palucka, MD
Professor of Medicine
Baylor Institute for Immunology Research

Phone:(214) 820-7451
karolinp@BaylorHealth.edu
Clinical expertise: immunotherapy, cancer vaccines

Eric Daar, MD
Chief, Division of HIV Medicine
Harbor-UCLA Medical Center
Professor of Medicine
David Geffen School of Medicine at UCLA
1124 W. Carson St., CDCRC 205
Torrance, CA 90502
(424) 201-3000 x7317
EDaar@LABioMed.org
Clinical expertise: clinical management of HIV infection

The SMC will be asked to review safety data as needed:

- Severe clinical adverse/reactogenicity events judged by the principal investigator or designee to be possibly, probably or definitely related to 3BNC117.
- Severe laboratory adverse events confirmed on retest and judged by the principal investigator or designee to be possibly, probably or definitely related to 3BNC117.
- 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 graded as severe and judged as possibly, probably or definitely related to the administration of 3BNC117 by the principal investigator or designee, no additional enrollment will take place pending a review by at least two members of the SMC. Following this review, the SMC member(s) will make a recommendation to the principal investigator regarding the continuation of the trial.

In addition, the SMC will review all available safety data up to day 21 (1 week after second infusion) of the first 3 subjects enrolled in group B. The SMC will then provide a recommendation regarding administration of a third dose. If the SMC determines it is safe to proceed, the third dose will be administered 2 weeks following the second dose (day 28) and the fourth dose will follow two weeks later (day 42). Two weeks after the third subject in group B receives the fourth dose, all available safety data will be reviewed by the SMC. If the SMC determines it is safe to proceed, additional subjects (n = 5) will be enrolled to receive 4 doses at 2-week intervals.

All updated versions of the protocol will be provided to the SMC members. The review of trial data by the SMC will take place at least annually. The study team will provide the SMC with updated records of all adverse events (AEs) of a grade 2 or higher at least annually.

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

15.2 Safety Review

Subjects will be closely monitored for 1.5 hours post infusion in the RUH inpatient unit. The Rockefeller University Hospital 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 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.

15.3 Monitoring

Safety monitoring will be conducted by the study investigators and by the IAVI. An external SMC will review SAE's and Unanticipated AEs and will be available to the study investigators for consultation. The RU IRB will conduct the initial review of the proposed study and will follow progress through annual reports and by immediate notification of SAEs and UAEs. External monitoring will occur at least quarterly.

15.4 Adverse Event Classification

- Scales to be used: the DAIDS AE Grading Table, 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 and to the sponsor at the Rockefeller University according to policy, within two working days of identification of the SAE. The RU sponsor will report SAEs directly to the FDA, 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 moderate severity must be reported to the local IRBs and to the sponsor at the Rockefeller University according to policy, within two working days of identification of the UAE. The RU sponsor will report UAEs to the FDA, per 21 CRF 312.

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

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

15.8 Toxicity Management and Stopping Rules

A dose limiting toxicity (DLT) will be defined as any adverse event of ≥ Grade 3 toxicity, if the study investigators recognize a probable or definite attribution to 3BNC117. In case of DLTs, further enrollment will not occur until investigators and SMC review the event. The investigators and SMC will mutually assess the information,

along with safety from other subjects, to determine whether a change in study conduct is warranted. Enrollment will stop but volunteers will continue to be monitored by the study investigators.

Volunteers will be withdrawn from the study if: a) the study team feels that continued participation in the study would be harmful to the health of a subject; b) if the study volunteer fails to comply with the study procedures and/or fails to keep study visit appointments; c) The RU IRB decided to stop or cancel the study for any reason.

16 Clinical Trial Registration

The proposed study involves testing of FDA regulated drugs or biologics and is registered at www.ClinicalTrials.gov, identifier NCT02446847.

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