Rockefeller University Institutional Review Board
IRB NUMBER: MCA-0994
IRB APPROVAL DATE: 08/03/2021
IRB EXPIRATION DATE: 05/27/2022

An open label, single arm study of the safety, pharmacokinetics and antiretroviral activity of the combination of 3BNC117-LS and 10-1074-LS in viremic HIV-infected individuals.

Clinical Trial Phase: 1

Local Protocol Number: MCA-0994

DAIDS-ES Number: 38670

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IND Sponsor: The Rockefeller University

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Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from The Rockefeller University, unless it is necessary to obtain informed consent from potential study participants.

Statement of Compliance

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

Signature Page 1

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

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

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

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LIST OF ABBREVIATIONS

10-1074	Anti-HIV-1 bNAb targeting the V3 loop of gp120
10-1074-LS	10-1074 with mutations in the Fc domain to extend half-life
3BNC117	Anti-HIV-1 bNAb targeting the CD4 binding site of gp120
3BNC117-LS	3BNC117 with mutations in the Fc domain to extend half-life
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
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
mAb	Monoclonal antibody
MTD	Maximum tolerated dose
N	Number (typically refers to participants)
NHP	Non-human primate

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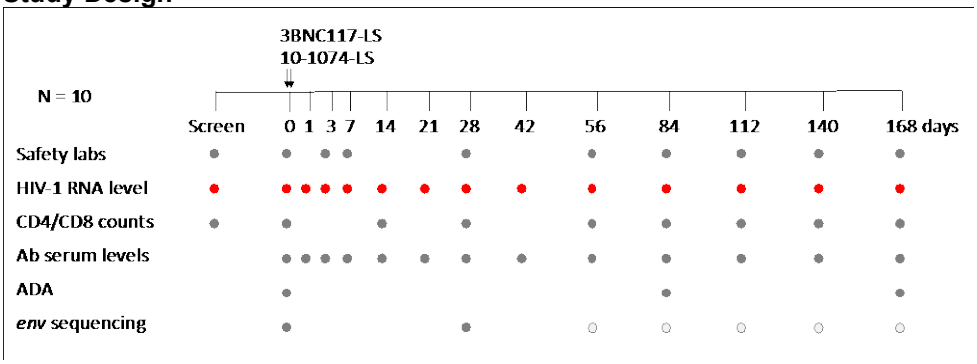
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
PBMC	Peripheral Blood Mononuclear Cell
PI	Principal Investigator
RU	The Rockefeller University
RUH	The Rockefeller University 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
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
T cell	T lymphocyte
V3 loop	Third Variable Loop of HIV-1 Envelope gp 120
WCMC	Weill Cornell Medical College
UPENN	University of Pennsylvania

PROTOCOL SUMMARY

Title	An open label, single arm study of the safety, pharmacokinetics and antiretroviral activity of the combination of 3BNC117-LS and 10-1074-LS in viremic HIV-infected individuals.
Short Title	3BNC117-LS and 10-1074-LS in Viremic HIV-infected Individuals
Protocol Number	MCA-0994
Phase	Phase 1
Study Design	The proposed study is a phase 1, open label, single arm study to evaluate the safety, pharmacokinetics and antiviral activity of single intravenous infusions of 3BNC117-LS and 10-1074-LS, each mAb dosed at 30 mg/kg in viremic HIV-infected individuals. Study participants will receive a single intravenous infusion of 3BNC117-LS and a single infusion of 10-1074-LS. The antibodies will be administered sequentially and dosed at 30 mg/kg. Following mAb administration, study participants will return for safety assessments on days 1 and 3, and weeks 1, 2, 3 and 4 following dosing, then bi-weekly or monthly until the end of study follow up as indicated in the Time of Events Schedule **(Appendix A).** All participants will be followed for 24 weeks after 3BNC117-LS and 10-1074-LS administration (see **Study design**). **Study Design**  Safety assessments will be performed at multiple time points following 3BNC117-LS and 10-1074-LS infusions. Serum samples for PK measurements will be collected before and at the end each mAb infusion administration and at multiple subsequent time points during study follow up, as indicated in the Time of Events Schedule **(Appendix A)**. Samples will also be collected for measurement of HIV-1 plasma RNA levels before 10-1074-LS and 3BNC117-LS infusions (screen and day 0) and at every follow up visit. T cell subsets will be monitored during study follow up. Assessments will also include measurement of anti-drug antibody (ADA) responses and sequencing of plasma envelope before infusions and after viral rebound, if it occurs prior to antiretroviral therapy (ART) initiation (first time point after viremia nadir is reached and viral load (VL) is > 1,000 copies/ml). Participants will be advised and encouraged to start ART within 4 weeks of receiving 3BNC117-LS and 10-1074-LS infusions, or sooner if: 1) VL fails to decrease by >0.5 $\log_{10}$ copies/ml within 2 weeks of antibody infusions, 2) VL increases > 0.5 $\log_{10}$ copies/ml between weekly measurements or 3) Significant T-cell decline (confirmed CD4+ T cell count < 200 cells/μl) is noted.

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Study Duration	24 months
Study Center(s)	RU site (The Rockefeller University) Cornell site (Weill Cornell Medicine Clinical Trials Unit) UPENN site (Perelman School of Medicine University of Pennsylvania)
Objectives	Primary objectives - To evaluate the safety and tolerability profile of single intravenous infusions of 3BNC117-LS in combination with 10-1074-LS at a single dose level (30 mg/kg, each mAb) in HIV-infected individuals off ART. - To determine the pharmacokinetic profile of single intravenous infusions of 3BNC117-LS in combination with 10-1074-LS at a single dose level (30 mg/kg, each mAb) in HIV-infected individuals off ART. - To determine the effect of single intravenous infusions of 3BNC117-LS in combination with 10-1074-LS at a single dose level (30 mg/kg, each mAb) on plasma HIV-1 RNA levels in viremic HIV-infected individuals. Secondary objective - To assess the frequency and magnitude of treatment-induced anti-drug antibody responses (anti-3BNC117-LS and anti-10-1074-LS antibodies) after a single intravenous infusion. Exploratory objectives - To evaluate the association between reduction in plasma viremia and predicted sensitivity to both 3BNC117-LS and 10-1074-LS by the Monogram PhenoSense assay (defined as IC_{50}s < 0.25 µg/ml) and other non-CLIA-certified assays. - To genotype viral escape variants that may arise after administration of 3BNC117-LS in combination with 10-1074-LS in viremic HIV-infected individuals. - To characterize the impact of treatment-induced anti-drug antibody (ADA) responses on the safety, pharmacokinetics and antiviral activity of 3BNC117-LS and 10-1074-LS. - To evaluate HIV-1 specific T and B cell immune responses following 3BNC117-LS and 10-1074-LS infusions. - To analyze gene expression profiles in HIV-1 infected CD4+ T cells.
Endpoints	Primary Outcomes - The occurrence of treatment-related solicited and unsolicited grade 3 and serious adverse events (including confirmed laboratory abnormalities). - The pharmacokinetic profile (including: peak concentrations, half-life, area under curve and clearance rate) of 3BNC117-LS and 10-1074-LS, when administered intravenously and in combination to viremic HIV-infected individuals. - The decline in plasma HIV-1 RNA levels after 3BNC117-LS plus 10-1074-LS intravenous infusions in viremic HIV-infected individuals through week 4 after infusions. Secondary Outcome - Proportion of individuals with treatment-induced ADA against each mAb and magnitude of the response. - The rate of adverse events and confirmed laboratory abnormalities that occur during the study follow up period after 3BNC117-LS and 10-1074-LS administration.

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	Exploratory Outcomes - Time until return of viremia to baseline levels in participants who elect to remain off ART after 4 weeks. - Decline in plasma viremia after antibody infusions across 3BNC117-LS and 10-1074-LS IC_{50} and IC_{80} cut points determined by PhenoSense assay or other assays (e.g. bulk PBMC cultures or Q2VOA followed by TZM/bl assay). - Phenotypic and genotypic analysis of baseline and escape viruses that might arise after single infusions of 3BNC117-LS and 10-1074-LS in viremic HIV-infected individuals. - Proportion of participants with reduction in half-life or antiviral activity concomitant with ADA. - Relationship of adverse events to ADA. - Frequency and magnitude of HIV-1 specific T cell responses and serum neutralizing activity against a multi-clade panel of HIV-1 pseudoviruses, following 3BNC117-LS and 10-1074-LS infusions. - Gene expression profiles by single RNA sequencing of HIV-1 infected CD4+ T cells.
Number of Participants	5 to 10
Study Population	HIV-infected individuals, off ART, and with plasma HIV-1 RNA levels between 500 and 125,000 copies/ml by standard assays.
Inclusion Criteria	**Inclusion Criteria:** - Males and females, >18 years of age. - Confirmed HIV-1 infection. - Off ART for at least 4 weeks with HIV-1 plasma RNA levels between 500 and 125,000 copies/mL (ART-naïve or off ART due to intolerance or by choice). - Current CD4+ T cell count > 300 cells/μl. - Participants who can become pregnant and are engaging in sexual activity that could lead to pregnancy agree to use two effective methods of contraception (i.e. condom with spermicide, diaphragm with spermicide, hormone-eluting IUD, hormone-based contraceptive with condom) from 10 days prior to and six months after 3BNC117-LS and 10-1074-LS administration. - Participants who can impregnate a partner and are engaging in sexual activity that could lead to pregnancy agree to use barrier protection from 10 days prior to and six months after 3BNC117-LS and 10-1074-LS administration to avoid impregnating a partner who can get pregnant. - Willingness to use barrier protection during sexual activity while not on ART to decrease the risk of HIV transmission to a partner at risk for HIV infection.

Exclusion Criteria	**Exclusion Criteria**
	- Have a history of AIDS-defining illness within 3 years prior to enrollment.
	- History of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the trial physician within the last 6 months.
	- Any clinically significant acute or chronic medical condition (such as autoimmune diseases), other than HIV infection, that in the opinion of the investigator would preclude participation.
	- Hepatitis B or C infection as indicated by the presence of Hepatitis B surface antigen (HBsAg) or hepatitis C virus RNA (HCV-RNA) in blood.
	- Laboratory abnormalities in the parameters listed below:
	  - Absolute neutrophil count ≤ 1,000 cells/μl;
	  - Hemoglobin ≤ 10 gm/dL;

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	- Platelet count ≤ 100,000 cells/µl; - ALT ≥ 1.5 x ULN; - AST ≥ 1.5 x ULN; - Alkaline phosphatase ≥ 1.5 x ULN; - Total bilirubin > 1.25 x ULN; - eGFR < 60 mL/min/1.73m2. - Pregnancy or lactation. - Any vaccination within 14 days prior to mAb infusions, except influenza vaccine. - Receipt of another investigational product currently or within the past 12 weeks, or expected concurrent participation in another study in which investigational products will be administered. - Receipt of any experimental HIV vaccine or anti-HIV monoclonal antibody therapy in the past. - History of severe reaction to a vaccine or drug infusion or history of severe allergic reactions. - Individuals with known hypersensitivity to any constituent of the investigational products.
Study Product, Dose, Route, Regimen	Study Products: - 3BNC117-LS is a recombinant, fully human monoclonal antibody (mAb) of the IgG1κ isotype that specifically binds to the CD4 binding site (CD4bs) within HIV-1 envelope gp-120. It contains two one-amino acid modifications in the Fc region to extend its biological half-life. - 10-1074-LS is a recombinant, fully human monoclonal antibody (mAb) of the IgG1λ isotype that specifically binds to the V3 loop within HIV-1 envelope gp-120. It contains two one-amino acid modifications in the Fc region to extend its biological half-life. Dose, Route Regimen: Single intravenous infusion of 3BNC117-LS and single intravenous infusion of 10-1074-LS, each dosed at 30 mg/kg.
Statistical Methodology	For safety, the number and percentage of participants experiencing one or more AEs will be summarized by relationship to study drug and severity. Pharmacokinetic parameters will be calculated using standard non-compartmental analysis methods. Plasma HIV-1 RNA levels will be evaluated at multiple time points following 3BNC117-LS and 10-1074-LS infusions and the log reduction in HIV-1 RNA levels from baseline (day 0) will be calculated. Continuous data will be summarized by descriptive statistics, including sample size, mean, standard deviation, median and range. Categorical data will be summarized by the number and percentage of participants with an outcome.

1 KEY ROLES

1.1 Study Sites and associated Institutions

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2 LAY SUMMARY

Broadly neutralizing antibodies against HIV arise in a small fraction of HIV-infected individuals. These antibodies might be able to play an important role in protection from acquisition of HIV infection, and also have the potential to alter the course of HIV infection. 3BNC117 and 10-1074 are anti-HIV neutralizing antibodies identified and cloned from two people living with HIV. They were chosen for clinical development for their neutralizing breadth and potency against diverse viral strains. Both antibodies have shown favorable safety, pharmacokinetics and antiviral activity in clinical trials. 3BNC117-LS and 10-1074-LS-LS are modified versions of the original antibodies and are expected to have extended duration of activity. The safety and pharmacokinetics profiles of 3BNC117-LS and 10-1074-LS are currently being evaluated in first-in-human studies in healthy volunteers and in people living with HIV. In this study, we aim to evaluate the safety, pharmacokinetics and the virologic effects of the combination of 3BNC117-LS and 10-1074-LS on HIV viral loads in people living with HIV who are not on antiretroviral therapy.

3 OBJECTIVES AND RATIONALE

3.1 Background

Despite the success of combination antiretroviral therapy (ART) in suppressing viral replication and preventing disease progression, HIV-1 persists in latent reservoirs (Chun, Carruth et al. 1997). In addition, worldwide HIV incidence rates have declined slowly, with 1.8 million new infections reported in 2017 (UNAIDS 2018). The use of antiretroviral agents by HIV-uninfected individuals before potential sexual exposure to HIV-infected partners, known as pre-exposure prophylaxis (PrEP), is a new effective preventive approach against HIV-1. However, an important challenge to the success of such strategy is that its efficacy is highly dependent on adherence to a daily oral drug regimen (Hanscom, Janes et al. 2016). Therefore, the search for novel preventive and therapeutic interventions is of high priority.

Passive administration of anti-HIV-1 bNAbs has been evaluated in humans. Earlier antibodies (such as 2G12, 4E10, 2F5) were administered intravenously at doses ranging from 0.5 to 2 gm and were generally found to be safe and well tolerated. However, these early studies showed that the selected HIV-1 bNAbs passively transferred to HIV-infected individuals had rather limited effects on delaying viral rebound during interruption of antiretroviral treatment (Trkola, Kuster et al. 2005, Mehandru, Vcelar et al. 2007).

A new generation of highly potent broadly neutralizing antibodies (bNAbs) may represent a novel strategy to combat HIV-1 infection. The advent of single-cell cloning techniques allowed the identification of potent bNAbs that target multiple epitopes on the HIV-1 envelope. Some of the new bNAbs demonstrate *in vitro* neutralizing activity against over 90% of HIV-1 pseudoviruses derived from diverse clades, even at low concentrations (Klein, Mouquet et al. 2013, West, Scharf et al. 2014). Broadly neutralizing antibodies are potential alternatives to standard antiretroviral drugs as they are likely to be safe and well tolerated, and to persist at neutralizing levels for longer periods of time.

Passive transfer of bNAbs can prevent simian-human immunodeficiency virus (SHIV) infection after high-dose intravenous challenge in non-human primates (Mascola, Lewis et al. 1999, Shibata, Igarashi et al. 1999, Shingai, Nishimura et al. 2013, Shingai, Donau et al. 2014). Neutralizing antibodies can also protect from multiple low dose mucosal challenges (Hessell,

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Poignard et al. 2009, Moldt, Rakasz et al. 2012, Gautam, Nishimura et al. 2016, Gautam, Nishimura et al. 2018).

3BNC117 and 10-1074 are two of the most potent broadly neutralizing antibodies available (Scheid, Mouquet et al. 2011, Mouquet, Scharf et al. 2012). They were chosen for clinical development for their neutralizing breadth and potency, and their antiretroviral activity when tested in humanized mice (hu-mice) and non-human primates (NHP) models (Klein, Halper-Stromberg et al. 2012, Pietzsch, Gruell et al. 2012, Horwitz, Halper-Stromberg et al. 2013, Shingai, Nishimura et al. 2013, Shingai, Donau et al. 2014, Gautam, Nishimura et al. 2016). Both antibodies have been evaluated in clinical studies, either alone or in combination. 3BNC117 and 10-1074 have shown favorable safety profiles in both HIV-infected and HIV-uninfected participants, and half-lives of approximately 2 and 3 weeks, respectively. A single infusion of 3BNC117 and 10-1074 at 30 mg/kg led to decline in plasma viremia of approximately 1.5 $\log_{10}$ copies/ml in viremic individuals (Caskey, Klein et al. 2015, Caskey, Schoofs et al. 2017). The modified LS versions of these two antibodies contain two one-amino acid substitutions of methionine to leucine at Fc position 428 (M428L), and asparagine to serine at Fc position 434 (N434S). These substitutions enhance the antibody binding affinity to the neonatal Fc receptor (FcRn), prolonging its half-life *in vivo.*

The safety and pharmacokinetics profiles of 3BNC117-LS and 10-1074-LS are currently being evaluated in two first-in-human studies in healthy volunteers and HIV-infected individuals (NCT03254277, NCT03554408).

In this proposed study, we aim to evaluate the safety, pharmacokinetics and the virologic effects of the combination of 3BNC117-LS and 10-1074-LS on plasma viremia in HIV-infected individual who are not on ART.

3.2 Preclinical Characterization of 3BNC117-LS and 10-1074-LS

3.2.1 Fc Modification to Extend Half-life

FcRn is an MHC class I like molecule associated with beta-2-microglobulin (β2m), known to play a role in IgG transport and homeostasis. It functions to protect IgG and albumin from catabolism, which explains the prolonged half-life of these two proteins compared with other classes of immunoglobulins and liver synthesized proteins. FcRn binds to the Fc portion of IgG with high affinity at an acidic pH (6.0 – 6.5) and protects the bound Ig from degradation in lysosomes. FcRn is a recycling receptor and it releases bound IgG into the extracellular space when it returns to the cell surface, thus prolonging the half-life of IgG (Roopenian and Akilesh 2007, Ward and Ober 2009).

Mutations in the CH2-CH3 domain of the IgG Fc region can enhance binding affinity to FcRn at low pH, and in turn extend antibody serum half-life. Two sets of mutations in the Fc domain, YTE (M252Y, S254T, T256E) and LS (M428L/N434S), are being evaluated in antibodies currently undergoing clinical testing (i.e. MEDI-557, VRC01-LS, VRC07-523LS).

The LS mutations were identified through rational design methods and high-throughput protein screening. The M428L/N434S variant of an anti-vascular endothelial growth factor IgG (Xtend-VEGF) provided 11-fold improvement in human and non-human primate FcRn binding affinity at pH 6.0 and prolonged antibody half-life by approximately 3-fold (Zalevsky, Chamberlain et al. 2010).

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Ko *et al.* evaluated if modulation of FcRn binding affinity can enhance the protective efficacy of the anti-HIV-1 antibody, VRC01. Similar to 3BNC117, VRC01 targets the CD4 binding site of HIV-1 gp-120. The VRC01LS-mutant bound to HIV-1 gp 120, similarly to the unmutated VRC01 antibody, and showed enhanced binding to FcRn at pH 6.0. VRC01LS exhibited a 12-fold higher human FcRn binding affinity than VRC01, whereas both displayed similar binding to human FcγRIIIa, FcγRIIa and FcγRIIb. These data suggest that VRC01LS does not differ from VRC01 with respect to ADCC effector function or immune suppression through FcγRIIa or FcγRIIb. Moreover, VRC01LS showed comparable ADCC activity to VRC01 in an *in vitro* ADCC assay using human PBMCs as effector cells and HIV-infected CEM-NKR cells (a NK-cell-resistant human T leukemia cell line) as targets. In addition, VRC01LS showed similar *in vitro* neutralization potency and breadth against HIV-1 strains than the unmutated antibody (Ko, Pegu et al. 2014).

In vivo, the VRC01LS mutant had a 2.5-fold longer half-life in rhesus macaques (VRC01, 4.65 days; VRC01LS, 11.80 days) and a slower clearance rate. Low dose VRC01LS (0.3 mg kg) protected rhesus macaques from intrarectal challenge with $SHIV_{BaLP4}$ (Ko, Pegu et al. 2014). Another study evaluated the protective efficacy of a single intravenous infusion of VRC01 or VRC01LS (20 mg/kg) against weekly low dose (10 $TCID_{50}$) $SHIV_{AD8\text{-}EO}$ intrarectal challenges (Gautam, Nishimura et al. 2016). VRC01LS showed median protection time of 14.5 weeks, while VRC01 protected animals for a median of 8 weeks. In HIV-uninfected individuals, VRC01-LS showed an elimination half-life of 71 +/- 18 days, which is more than 4-fold longer than VRC01's half-life (Gaudinski, Coates et al. 2018).

3.2.2 *In Vitro* Characterization of 10-1074-LS and 3BNC117-LS

Binding affinities of 10-1074-LS and 10-1074, 3BNC117-LS and 3BNC117 for all human FcγRs were analyzed by surface plasmon resonance (SPR) analysis. As expected, the presence of the LS mutations had no impact on FcγR binding when comparing the unmodified 10-1074 and 3BNC117 mAbs and their respective LS versions.

The *in vitro* neutralizing activities of the unmutated 3BNC117, 3BNC117-LS, 10-1074, and 10-1074-LS drug products were measured by a GLP TZM.bl luciferase-based neutralization assay performed in the laboratory of Dr. Michael Seaman (Beth Israel Deaconess Medical Center, Boston). In this assay, virus neutralization is detected as reduction in luciferase reporter gene expression after single round infection in TZM.bl cells. MuLV (murine leukemia virus) is used as a negative control.

The antibodies were tested at a primary concentration of 25 µg/ml and titrated 5-fold to a concentration of < 0.001 µg/ml. A panel of twelve tier 2 HIV-1 pseudoviruses from different HIV clades was used to compare 3BCN117 to 3BNC117-LS. The median and 80% inhibitory concentrations (IC_{50} and IC_{80}) were calculated and are displayed in **Table 1**. As expected, 3BNC117-LS titers were highly concordant with the unmutated 3BNC117 reference standard (< 2-fold difference for all IC_{50}/IC_{80} measurements).

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Table 1: 3BNC117 and 3BNC117-LS *In Vitro* Neutralizing Activity of Against Selected HIV-1 Pseudoviruses

		Titer in TZM.bl cells (µg/ml)					
		3BNC117 WT			3BNC117.LS		
Virus ID	Clade	IC_{50}	IC_{80}	MPI*	IC_{50}	IC_{80}	MPI
3301.v1.c24	AC	0.021	0.065	100	0.030	0.087	100
WITO4160.33	B	0.024	0.083	100	0.014	0.064	100
SC422661.8	B	0.028	0.083	100	0.018	0.074	100
Du156.12	C	0.053	0.129	100	0.047	0.143	100
X1193_c1	G	0.063	0.184	100	0.057	0.222	100
ZM135M.PL10a	C	0.076	0.201	100	0.075	0.260	100
235-47	CRF02_AG	0.078	0.796	94	0.065	0.747	93
CNE53	BC	0.125	1.101	94	0.125	0.829	93
CNE30	BC	0.284	0.997	100	0.423	1.527	100
CAAN5342.A2	B	0.421	1.522	100	0.336	1.338	100
Du172.17	C	0.434	3.873	93	0.812	5.178	90
CNE17	BC	4.327	>25	77	8.227	>25	69
MuLV (Neg. Control)		>50	>50	0	>50	>50	5

*Maximum Percent Inhibition

A panel of 10 tier HIV-1 pseudoviruses with known sensitivity to 10-1074 but resistant to 3BNC117 was used to compare the neutralizing activities of 10-1074 and 10-1074-LS. These pseudoviruses were selected to characterize the current clinical lot of 10-1074-LS, but also to allow measurement of 10-1074 neutralizing activity in future 10-1074-LS plus 3BNC117-LS co-formulated products. The median and 80% inhibitory concentrations (IC_{50} and IC_{80}) were calculated and are displayed in **Table 2**. As expected, 10-1074-LS titers were highly concordant with both the reference standard and the 10-1074 clinical lot (< 3-fold difference for all IC_{50} and IC_{80} measurements).

Table 2: 10-1074-LS and 10-1074 *In Vitro* Neutralization Activity Against a Selected Panel of Pseudoviruses

		Titer in TZM.bl cells (ug/ml)									Fold change			
		10-1074.LS Ref. Std. (Lot# 201707-REF)			10-1074.LS DP (Lot# 030-003-001)			10-1074 (Lot# 1-FIN-2149)			10-1074.LS Ref. Std. (Lot# 201707-REF) vs. 10-1074.LS Ref. Std. (Lot# 201707-REF)		10-1074.LS Ref. Std. (Lot# 201707-REF) vs. 10-1074 (Lot# 1-FIN-2149)	
Virus ID	Clade	IC50	IC80	MPI	IC50	IC80	MPI	IC50	IC80	MPI	Δ IC50	Δ IC80	Δ IC50	Δ IC80
1394C9_G1 (Rev-)	C(T/F)	0.029	0.109	100	0.024	0.088	100	0.037	0.139	100	0.83	0.81	0.65	0.63
ZM247v1 (Rev-)	C(T/F)	0.023	0.106	100	0.027	0.123	100	0.026	0.118	100	1.17	1.16	1.04	1.04
Du422.1	C	0.029	0.116	100	0.035	0.138	100	0.042	0.161	100	1.21	1.19	0.83	0.86
6631.v3.c10	C	0.167	0.808	99	0.174	0.640	99	0.221	1.019	99	1.04	0.79	0.79	0.63
377.v4.c9	C	0.299	1.442	100	0.325	1.171	100	0.372	1.329	100	1.09	0.81	0.87	0.88
20915593	C	0.978	4.462	100	0.663	3.121	100	1.146	5.356	99	0.68	0.70	0.58	0.58
0984.v2.c2	C	0.752	8.315	89	0.649	5.432	90	1.217	9.912	87	0.86	0.65	0.53	0.55
T278-50	CRF02_AG	1.287	11.043	87	0.924	11.449	88	1.886	17.308	84	0.72	1.04	0.49	0.66
21197826-V1	C	0.616	2.883	100	0.512	2.430	100	0.719	2.536	100	0.83	0.84	0.71	0.96
Du151.02	C	0.007	0.022	100	0.007	0.019	100	0.008	0.028	100	1.00	0.86	0.88	0.68
MuLV (Control)		>25	>25	18	>25	>25	22	>25	>25	13				

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3.2.3 3BNC117-LS and 10-1074-LS *In Vivo* Activity in Non-human Primates

The *in vivo* activity of 10-1074-LS and 10-1074-LS in combination with 3BNC117-LS was evaluated in a non-GLP study in rhesus macaques conducted at NIH/NCI. Animals were administered a single intravenous infusion of 10-1074-LS (20 mg/kg) or 3BNC117-LS (20 mg/kg); or a single subcutaneous injection containing both 3BNC117-LS and 10-1074-LS in combination (7.5 mg/kg, each mAb) (**Figure 1**). In addition, animals that received no mAbs served as controls. All animals were challenged weekly with low doses of $SHIV_{AD8-EO}$ (10 $TCID_{50}$ intrarectally, starting 1 week after mAb administration. The median time to infection after 10-1074-LS was 27 weeks (range 18-37 weeks), as compared to the previously reported 12.5 weeks with the unmodified 10-1074; and the median time to infection after 3BNC117-LS was 16.5 weeks (range 11-23 weeks), as compared to the previously reported 13 weeks with the unmodified 3BNC117. Control animals were infected after a median of 3 weeks. The combination of 3BNC117-LS plus 10-1074-LS, at a lower dose (7.5 mg/kg of each mAb), protected animals for a median of 20 weeks (Gautam, Nishimura et al. 2018). These results demonstrate that the introduction of the LS mutations significantly extends the antiviral effects of bNAbs.

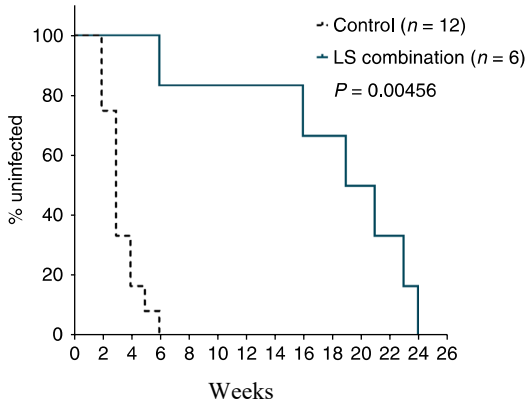

Figure 1: Protective effects of 3BNC117-LS and 10-1074-LS monoclonal antibodies against virus acquisition in rhesus macaques.

Kaplan–Meier showing the infection rates for controls (no mAb), recipients of 3BNC117-LS plus 10-1074-LS in combination (7.5 mg/kg ea. mAb, s.c., once).

The estimated average half-life of 10-1074-LS was approximately 29 days, as compared to 9 days for 10-1074, and the estimated average half-life of 3BNC117-LS was 18 days as compared to 9 days for 3BNC117. The median mAb serum concentrations at breakthrough of infection were calculated to be 0.13 and 1.07 µg/ml for the unmodified 10-1074 and 10-1074-LS, respectively; 0.20 and 0.28 µg/ml for the unmodified 3BNC117 and 3BNC117-LS, respectively; and 0.67 µg/ml for the mAb combination group. The slightly higher breakthrough plasma bNAb concentration observed for the 10-1074-LS mAb (1.07 µg/ml) compared to the other three individual mAbs analyzed cannot be presently explained despite their similar potencies when measured *in vitro* (Gautam, Nishimura et al. 2018).

Of note, one of the six recipients of 3BNC117-LS and 10-1074-LS s.c. (DFM6) experienced rapid decay of serum antibody levels, which fell to background levels between weeks 4 and 6 after administration. This rapid clearance of 10-1074-LS correlated with the emergence of anti-10-1074-LS antibody responses and infection following 6 weekly viral challenges.

Non-GLP safety assessments were performed during this study. No clinical adverse events were observed in these rhesus macaques following intravenous administration of 10-1074-LS alone or subcutaneous administration of 3BNC117-LS plus 10-1074-LS over a 40-week observation period. In addition, no clear changes in hematologies were observed during follow up after administration.

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3.2.4 10-1074-LS Tissue Cross Reactivity Study

A tissue cross-reactivity study was performed on a full panel of human tissues. The objective of this study was to determine the potential cross reactivity of 10-1074 and 10-1074-LS with cryosections of human tissues. In order to detect binding, the test articles were applied to cryosections of normal human tissues (at least 3 donors per tissue) at two concentrations (25 and 5 µg/mL).

10-1074 and 10-1074-LS moderately to strongly stained cytoplasmic granules/globules of rare or rare to occasional epithelium in the pituitary adenohypophysis at the higher concentration of both test articles. Similar staining was observed at the lower concentration except in one donor where staining was reduced in intensity and frequency with 10-1074 only.

In the thyroid, 10-1074 and 10-1074-LS stained the cytoplasm and cytoplasmic granules of follicular epithelium in the thyroid. This staining was weak or weak to moderate and rare or occasional to frequent at the higher concentration of 10-1074 with a reduction or absence of staining at the lower concentration, while this staining was weak to moderate or moderate to strong and occasional to frequent at the higher concentration of 10-1074-LS with variably present staining at the lower concentration.

As the HIV-1 envelope glycoprotein is a viral protein not expected to be expressed in any normal human tissues, the epithelial staining observed in the pituitary and thyroid with 10-1074 and 10-1074-LS in the current study represented unexpected tissue cross-reactivity. However, this staining was cytoplasmic in nature, and monoclonal antibody binding to cytoplasmic sites generally is considered of little to no toxicologic significance due to the inability of antibody therapeutics to access the cytoplasmic compartment *in vivo*. No plasma membrane staining was observed with 10-1074 and 10-1074-LS in the human tissues.

3.2.5 3BNC117-LS Tissue Cross Reactivity Study

A tissue cross-reactivity study was performed on a full panel of human tissues. The objective of this study was to determine the potential cross reactivity of 3BNC117 and 3BNC117-LS with cryosections of human tissues. In order to detect binding, the test articles were applied to cryosections of normal human tissues (3 donors per tissue) at two concentrations (10 and 2 µg/mL). Staining with 3BNC117 and 3BNC117-LS was observed in the human tissue panel as summarized below:

• Plasma membrane only:
- squamous epithelium in the esophageal mucosa

• Plasma membrane and cytoplasm:
- Kupffer cells (specialized macrophages) in the liver
- macrophages in the lymph node

• Cytoplasm only:
- acinar epithelium of the pancreas, endocrine epithelium in the pituitary, squamous epithelium in the epidermis of the skin, germinal epithelium in the testis, and glandular epithelium in the uterus (endometrium)
- extracellular material in the placenta and spinal cord.

As the HIV-1 envelope glycoprotein is a viral protein not expressed in any normal human tissue, all staining observed with 3BNC117 and 3BNC117-LS represented unexpected tissue cross reactivity. Membrane staining with 3BNC117 and 3BNC117-LS was present in Kupffer cells of the liver, macrophages of the lymph node, and mucosal epithelium of the esophagus. All other cellular

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staining with 3BNC117 and 3BNC117-LS in the current study was cytoplasmic in nature and was considered of little to no toxicologic significance, as it is unlikely that the cytoplasm and cytoplasmic structures would be accessible to the test articles *in vivo*. The toxicologic relevance of the binding of 3BNC117 and 3BNC117-LS to extracellular material in the placenta and spinal cord is unknown.

In general, the observed staining was more intense and/or frequent with 3BNC117-LS compared to 3BNC117, however the staining pattern was similar between the two test articles.

3.2.6 10-1074 *In Vivo* Toxicology Study in Rats

Since 10-1074-LS has the same antigen binding characteristics and showed comparable binding as 10-1074 in the GLP-compliant human tissue crossreactivity study (Section 3.2.5), the previously performed toxicology study of 10-1074, supports the proposed phase 1 clinical study.

10-1074 was evaluated for safety in a multidose study in rats. Twice weekly intravenous administration of 10-1074 at doses of 4, 15, and 60 mg/kg/injection, as well as the combination intravenous dose of 10-1074 and 3BNC117 (each 60 mg/kg once weekly), and twice weekly doses of 10-1074 at 60 mg/kg/injection via the subcutaneous route, for a 25-day dosing period were considered well-tolerated in male and female Sprague Dawley rats. Main animals were euthanized on Day 27; following the end of the 45-day recovery period, recovery animals (control and high dose groups) were euthanized on Day 71.

Test item-related findings were consistent with an immune response to repeated administration of a foreign protein primarily in subcutaneously-dosed animals, as would be expected when evaluating a human protein in rats. These consisted of slight increases in white blood cells counts (primarily neutrophils), slight decrease in platelets, mononuclear cell infiltrate, sinusoid histiocytosis, and/or sinusoid dilatation in the liver, and lymphoid hypercellularity, sinusoid histiocytosis, and/or extramedullary hematopoiesis in the spleen. The changes reversed completely following a 45-day Recovery period in the Recovery rats receiving 60 mg/kg intravenously.

Based on the results of this study, and absence of apparent direct toxicity of 10-1074 in the presence of apparent immunogenicity, the No-Observed-Adverse-Effect-Level (NOAEL) of 10-1074 in the rat was considered to be 60 mg/kg/injection when administered either by the intravenous or subcutaneous route twice weekly and the combination intravenous dose of 10-1074 and 3BNC117 (each 60 mg/kg/injection once weekly), for up to 25 days.

3.2.7 3BNC117 *In Vivo* Toxicology Study in Rats

Since 3BNC117-LS has the same antigen binding characteristics and showed comparable binding as 3BNC117 in the GLP-compliant human tissue crossreactivity study (Section 3.2.5), the previously performed toxicology study of 3BNC117, supports the proposed phase 1 clinical study.

3BNC117 was evaluated for safety in a multidose study in rats to determine its toxicity and toxicokinetic profiles, following twice weekly intravenous/subcutaneous administrations to Sprague-Dawley rats over 25 days and to assess the reversibility of any changes following a 47-day recovery period. Main animals were euthanized on Day 27; following the end of the 47-day recovery period, recovery animals were euthanized on Day 72.

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

3.3 Clinical Safety of Monoclonal Antibodies to Treat or Prevent Infection

Several monoclonal antibodies that target HIV-1 gp120 have been evaluated in clinical studies. 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 gp41. These neutralizing antibodies were evaluated in combination in HIV-infected individuals. The first two studies included ART-naïve individuals. The antibodies were administered intravenously at 0.5 to 1 gm doses; 4 to 8 weekly infusions were given (Armbruster, Stiegler et al. 2004). Two other studies with 2F5, 4E10 and 2G12 included HIV-infected individuals on suppressive ART. 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 (Trkola, Kuster et al. 2005, Mehandru, Vcelar et al. 2007). Antibody infusions were well tolerated in most participants; mild and transient adverse events were reported only occasionally. No serious adverse events (SAEs) were recorded. Adverse events included body aches, fatigue, flushed sensation, joint soreness and redness at infusion site. A low-level antibody response against 2G12 was found in two participants. Anti-4E10 and anti-2F5 IgM and IgG immune responses were not detected, even after repeated infusions of high doses of the mAbs. This antibody combination did not significantly delay viral rebound or decreased plasma viremia.

VRC01 is another human anti-HIV-1 broadly neutralizing antibody, targeting the CD4 biding site of HIV-1 gp120. It has been evaluated in both HIV-infected and HIV-uninfected individuals at doses ranging from 5 to 40 mg/kg. (Ledgerwood, Coates et al. 2015, Lynch, Boritz et al. 2015, Bar, Sneller et al. 2016). Reported adverse events assessed as possibly related to VRC01 were mild in severity and resolved with no residual effects. No related serious adverse events or dose-limiting toxicities have been reported. The half-life of VRC01 in HIV-uninfected individuals was 15 days and no anti-VRC01 antibody responses were detected (Ledgerwood, Coates et al. 2015). The half-life of VRC01 in HIV-infected individuals was 12 days for intravenous infusion and 11 days for subcutaneous injection. No anti-VRC01 antibodies were detected. In viremic individuals with virus sensitive to VRC01, a reduction in viremia of 1.1 to 1.8 $\log_{10}$ copies/ml was observed.

VRC01 is currently being tested in two multi-center phase 2b studies to evaluate its safety and efficacy to reduce acquisition of HIV-1 infection in women (NCT02568215), MSM or transgender persons who have sex with men (NCT02716675). Participants are administered up to 10 intravenous VRC01 infusions of 10 or 30 mg/kg every 8 weeks. Over 4,000 participants enrolled in the study in the Americas and in several African countries.

3.4 Clinical Experience with Fc-modified Antibodies to Enhance Binding to the FcRN Receptor

VRC01LS is another human anti-HIV-1 CD4 binding site antibody that has been modified in the Fc region to include the LS substitutions (M428L/N434S). Like 3BNC117-LS, it is being evaluated for HIV-1 therapy and prevention. VRC01LS is being evaluated in four ongoing clinical studies in HIV-infected (NCT02840474) and HIV-uninfected adults (NCT02599896, NCT02797171), and in

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infants (NCT02256631). VRC01LS showed good safety profile in a first-in-human study in HIV-uninfected participants. A total of 37 participants were administered VRC01LS, and received one or three intravenous infusions or subcutaneous injections at 5, 20 or 40 mk/kg dose levels. There were no SAEs or DLTs. Mild malaise and myalgia were the most common adverse events (AEs). There were six AEs assessed as possibly related to VRC01LS administration, and all were mild in severity and resolved during the study. The mean (±SD) serum concentration 12 weeks after one IV administration of 20 mg/kg or 40 mg/kg were 180 ± 43 µg/mL (n = 7) and 326 ± 35 µg/mL (n = 5), respectively. The mean (±SD) serum concentration 12 weeks after one IV and SC administration of 5 mg/kg were 40 ± 3 µg/mL (n = 2) and 25 ± 5 µg/mL (n = 9), respectively. VRC01LS clearance rate was 36 ± 8 mL/d with an elimination half-life of 71 ± 18 days. VRC01LS retained its expected neutralizing activity in serum, and anti-VRC01 antibody responses were not detected (Gaudinski, Coates et al. 2018).

3.5 Clinical Experience with 10-1074 (IND 123713)

10-1074 was evaluated in a phase 1 study in both HIV-uninfected and HIV-infected individuals (NCT02511990). Study participants were administered one intravenous infusion of 10-1074 at increasing dose levels (3 mg/kg, 10 mg/kg or 30 mg/kg), and were followed for 24 weeks after infusion. A total of 33 study participants enrolled in the study (14 HIV-uninfected, 16 viremic HIV-infected, and 3 ART-HIV-infected individuals received 10-1074 was generally safe and well tolerated. A total of 57 adverse events were reported during a follow-up period of 6 months, 88% of these were of grade 1 severity. The most commonly reported adverse event deemed possibly related to the study drug was transient, mild headache. There were no serious adverse events, or grade 3 related adverse events. A safety data summary is included in the 10-1074 Investigator's Brochure (IB).

10-1074 was eliminated more rapidly in HIV-1-infected individuals than in uninfected participants, resulting in a $t_{1/2}$ of 24 and 12.8 days in uninfected and HIV-1-infected individuals, respectively. Thirteen viremic participants received 10-1074 at 30 mg/kg. Eleven of these participants were 10-1074-sensitive and showed a rapid decline in viremia by a mean of 1.52 $\log_{10}$ copies/ml (range, 0.9–2.06 $\log_{10}$ copies/ml). The nadir was reached after an average of 10 days (range 7–25 days). Virologic analysis revealed the emergence of 10-1074-resistant viruses within 28 days after infusion. Emerging escape variants carried mutations in known contact sites (N332, N334 and D/N425), were generally resistant to the related V3-specific antibody PGT121, but remained sensitive to antibodies targeting non-overlapping epitopes, such as the anti-CD4-binding-site antibodies 3BNC117 and VRC01 (Caskey, Schoofs et al. 2017).

3.6 Clinical Experience with 3BNC117 (IND 118225)

A phase 1 study tested a single infusion of **3BNC117** at increasing dose levels in both HIV-infected and HIV-uninfected individuals (n= 55, 22 HIV-uninfected and 33 HIV-infected). 3BNC117 was generally safe and well-tolerated, and mild transient myalgia, fatigue and headache were the most commonly reported AEs. There were no serious adverse events, or grade 3 related adverse events. A safety data summary is included in the 3BNC117 Investigator's Brochure (IB).

3BNC117's half-life was found to be approximately 17.6 days in HIV-uninfected and 9.6 days in viremic HIV-infected individuals. When administered at 30 mg/kg, 3BNC117 induced rapid decreases in plasma HIV-1 RNA levels that varied between individuals from 0.8 to 2.5 $\log_{10}$ copies/ml, and the mean drop in viral load (VL) was 1.48 $\log_{10}$ at nadir. The median time to reach

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the lowest level in viremia was 7 days (range 7-21 days). Viral strains carrying different env mutations emerged after treatment, and some of them were associated with different levels of 3BNC117 resistance (Caskey, Klein et al. 2015, Schoofs, Klein et al. 2016). A mathematical model of HIV-1 dynamics suggested that 3BNC117 effects were not simply limited to free viral clearance and blocking new infection, but also included potentially significant acceleration of infected cell clearance (Lu, Murakowski et al. 2016). Experiments using infected human cells in mice confirmed the idea that 3BNC117 infusion clears infected cells *in vivo* (Lu, Murakowski et al. 2016). In addition to lowering plasma viremia, 3BNC117 enhanced serum neutralizing activity against autologous and heterologous viruses in HIV-infected individuals (Schoofs, Klein et al. 2016).

3BNC117 has also been studied in the setting of analytical treatment interruption (ATI, (NCT02446847)). Thirteen ART-treated participants with 3BNC117-sensitive viruses isolated from PBMC cultures underwent ATI and received two to four 3BNC117 infusions at 30 mg/kg. The infusions delayed viral rebound for an average of 8.4 weeks, in contrast to an average of 2-3 weeks in studies that simply stopped ART. In 4 of 13 treated individuals, viral suppression was maintained until antibody levels fell below 20 µg/ml. In contrast to non-interventional ATI studies where rebound viremia is typically polyclonal, rebound viremia arose predominantly from a single provirus and emerging viruses showed decreased sensitivity to 3BNC117 compared to pre-treatment viruses isolated from PBMC cultures, indicating that 3BNC117 restricted viral emergence from the reservoir and selected resistant strains. Re-initiation of ART rapidly suppressed viremia (Scheid, Horwitz et al. 2016). An additional study (NCT02588586) in which individuals that remained on ART were given 2 infusions of 3BNC117 3 months apart showed no measurable reduction in the number of latently-infected cells in viral outgrowth assays (Cohen, Lorenzi et al. 2018).

Overall, 3BNC117 was given to 88 individuals in these 3 studies and was found to be generally safe and well-tolerated. The most common related AEs reported were headache (18%), malaise/fatigue (16%) and upper respiratory infection (12.5%).

3.7 Clinical Experience with 3BNC117 and 10-1074 in Combination

The **combination of 3BNC117 plus 10-1074**, administered intravenously, was tested in two phase 1 studies. In one study (NCT02824536) HIV-uninfected individuals received 1-3 doses of the antibody combination at 3 or 10 mg/kg or placebo. A total 24 of participants enrolled in the study, and 18 received the 3BNC117 and 10-1074 combination. In the second study (NCT02825797), HIV-infected individuals on or off ART received 1 to 3 doses of 3BNC117 at 10 or 30 mg/kg each or placebo. Fifteen study participants discontinued ART and received up to 3 infusions of the mAbs at weeks 0, 3 and 6. A total of 34 individuals enrolled (30 received the antibody combination and 4 received placebo). Of those, 12 received 3 infusions of 30 mg/kg, administered 3 weeks apart, and 3 received 3 infusions of 30 mg/kg, 2 weeks apart.

There were no SAEs in these two studies of the combined parental antibodies, and the safety profile of the 3BNC117 plus 10-1074 combination was similar to what was observed with either antibody alone. Most reported AE's were graded as mild (77%), and the most commonly reported AEs were upper respiratory infection, headache and malaise/fatigue. The estimated half-lives of 3BNC117 and 10-1074 in HIV-uninfected individuals when given in combination were similar to what was observed when the antibodies were administered alone: 3BNC117's half-life when in combination with 10-1074 was 18.4 ± 2.5 days versus 17.6 ± 5.7 days when administered alone;

10-1074's half-life when in combination with 3BNC117 was 22.3 ± 1.5 days versus 24 ± 6.6 days when administered alone.

The combination of 3BNC117 and 10-1074 significantly delayed viral rebound in the absence of ART. In this study group, participants with baseline sensitivity to 3BNC117 and 10-1074, defined as IC_{50} < 2 µg/ml against viruses outgrown from PBMC, discontinued ART two days after the first infusions of 3BNC117 and 10-1074 (week 0) and received two additional combination antibody infusions at weeks 3 and 6. Of the 15 participants enrolled, 6 participants experienced viral rebound (VL > 200 copies/ml) prior to or at week 12 (or 6 weeks after last mAb infusions). Four of these participants had viral blips (VL < 100 copies/ml) prior to first mAb infusions and decreased baseline sensitivity to at least one of the antibodies, and the two other participants had pre-existing resistance to either 3BNC117 or 10-1074. The median time to rebound for 7 of the 9 antibody-sensitive participants who experienced viral rebound during the study period was 21 weeks, or 15 weeks after last mAb infusions. The average 3BNC117 serum concentration at the time of rebound in these sensitive participants was 1.9 µg/ml. In contrast, the average serum concentration of 10-1074 at rebound was 14.8 µg/ml. The difference in the antibody concentrations at the time of rebound is consistent with the longer half-life of 10-1074 which resulted in a period of 10-1074 monotherapy and selection or development of resistance. Remarkably, 2 of the 9 individuals have now maintained viral control for 10 to 11 months. These results show that the combination of 3BNC117 and 10-1074 successfully maintained viral suppression in participants harboring sensitive viruses until serum levels of at least one of the antibodies declined below 10 µg/ml. Moreover, development of resistance to both antibodies did not occur (Mendoza P 2018).

Seven HIV-1 infected participants, who were pre-screened for baseline sensitivity to 3BNC117 and 10-1074 (defined as IC_{50} < 2 µg/ml against viruses outgrown from PBMC) enrolled in two additional study groups and were administered one or three doses of 3BNC117 plus 10-1074 at 30 mg/kg of each mAb, at week 0 or weeks 0, 2 and 4. The average decline in viral load for all 7 viremic participants was 1.65 log_{10} copies/ml and viremia remained significantly reduced until day 86. The median time to reach the lowest viremia level was 24 days (range 7-56 days), whereas a decline in viremia of > 1.0 log_{10} copies/ml was reached within 14 days after the first antibody infusions. Analysis of circulating plasma viruses by single genome amplification (SGA) showed that 3 of the 7 enrolled participants carried pre-existing resistance to one or both antibodies. These participants showed either no response or short-lived decline in viremia after antibody infusions. The 4 individuals with sensitive viruses showed a more pronounced drop in viremia compared with the other individuals (average of 2.05 log_{10} copies/ml) and viremia was significantly reduced until day 94. The participant with the highest initial viral load (97,800 copies/ml; 9343) was the first to rebound at 8 weeks (**Figure 2**). The 2 individuals with the lowest initial viral loads, 91C22 and 9342 (750 and 2,550 copies/ml, respectively), demonstrated suppression to near or below the limit of detection for 12 and 16 weeks, respectively. Finally, viremia in participant 91C34 was reduced for a period of 12 weeks but never dropped below 810 copies/ml. Despite persistent viremia, resistance against both antibodies did not develop in this participant for as long as bNAb serum levels were above 10 µg/ml.

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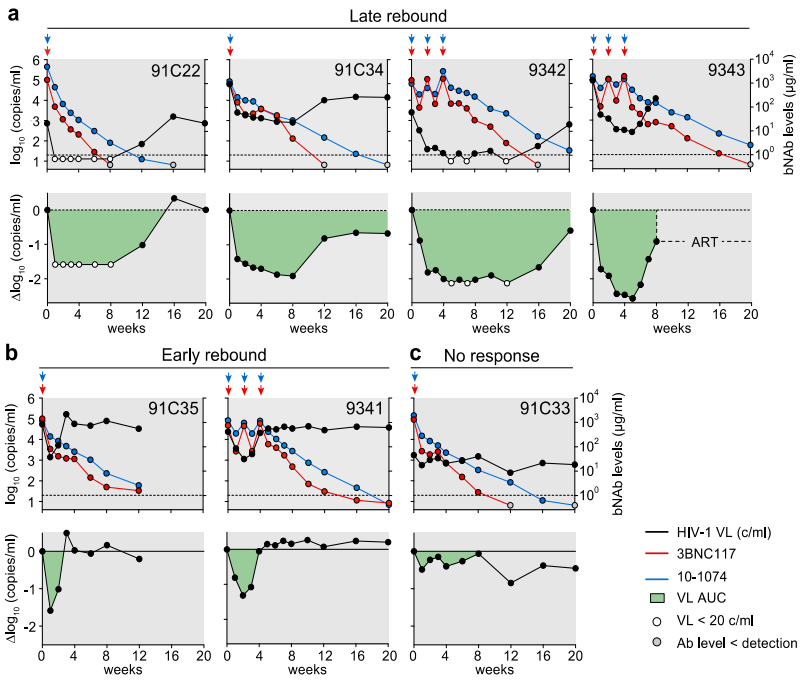

Figure 2: Viral load after 3BNC17/10-1074 infusions in viremic HIV-1-infected participants.

(a-c) Changes in viremia and bNAb serum concentrations in HIV-1-infected participants showing (a) late rebound, (b) early rebound or (c) no response after 3BNC117 and 10-1074 combination therapy. Upper graphs show HIV-1 RNA in copies/ml (black, left y-axis), and 3BNC117 (red) and 10-1074 (blue) serum levels (right y-axis, as determined by TZM-bl). X-axis shows weeks after the first antibody infusion. Dashed line indicates the lower limit of detection of HIV-1 RNA (20 copies/ml). Arrows indicate antibody infusions. Lower graphs show $\log_{10}$ changes of HIV-1 RNA copies compared to day 0. Green shading depicts viral suppression compared to day 0.

In comparison to a single infusion of either 3BNC117 or 10-1074, viremic individuals receiving one or three infusions of the combination of both antibodies showed significantly prolonged viral suppression. Rebound viremia was associated with the appearance of viruses that were resistant to 10-1074 in 3 of the 4 antibody-sensitive participants, but remained sensitive to 3BNC117. This is again consistent with the relatively shorter half-life of 3BNC117, which led to a period of 10-1074 monotherapy at the end of the observation period. The participant with the lowest initial viral load only returned to baseline viremia after both antibodies were below the limit of detection, and rebound viruses remained sensitive to both antibodies. Overall none of the 4 participants that were initially sensitive to the two antibodies developed *de novo* resistance to 3BNC117, despite the residual viremia observed in three of these participants and frequent recombination events between circulating viruses (Bar-On, Gruell et al. 2018).

These results highlight some of the limitations of immunotherapy with the combination of 3BNC117 and 10-1074 in viremic individuals. Whereas 2 antibodies may be sufficient to achieve and/or maintain suppression in individuals harboring sensitive viruses with very low levels of viremia or ART-suppressed individuals undergoing ATI, additional antibodies or combinations of small molecule drugs and antibodies would be required if this type of therapy is to be considered for viremic individuals. In this protocol, we will evaluate the safety, pharmacokinetics and *in vivo* antiviral activity of the long-acting variants of 3BNC117 and 10-1074 in viremic individuals. Participants will be encouraged and advised to initiate ART within 4 weeks after antibody infusions to achieve sustained viral suppression.

3.8 Clinical Data with 3BNC117-LS and 10-1074-LS

Safety summary:

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3BNC117-LS and 10-1074-LS are being evaluated in two ongoing first-in-human (FIH) phase 1 studies (NCT03254277, NCT03554408). Twenty-seven participants (6 HIV-infected individuals on suppressive ART) received 10-1074-LS at doses ranging from 150 mg or 300 mg SC up to 30 mg/kg IV, and 39 (15 HIV-infected individuals on suppressive ART) received 3BNC117-LS at the same dose levels. The admixture of the two antibodies has also been administered subcutaneously to 18 HIV-uninfected participants so far. Both intravenous infusions and subcutaneous injections have been well tolerated without Grade 3 adverse events or serious adverse events deemed possibly related to the antibodies reported to date. The safety profiles of the LS-variants so far are similar to the parental antibodies.

10-1074-LS: Twenty-seven participants received a single dose of 10-1074-LS at doses ranging from 3 to 30 mg/kg (IV) or 140 or 280 mg (SC). Sixteen additional participants received a single SC injection of the combination of 10-1074-LS and 3BNC117-LS. Of the enrolled participants, 37 were HIV-uninfected. Study follow up is ongoing. As of June 2019, 8 solicited AEs were reported, all of Grade 1 severity: erythema/skin discoloration (n=2) and pain at administration site (n=1), headache (n=2), feverishness (n=2), malaise/fatigue (n=2), and myalgia (n=1). In addition, 43 non-solicited AEs were reported. Of these, 8 were graded as moderate: localized musculoskeletal pain (n=3), rash (n=1), elevated systolic blood pressure (n=1), abdominal pain (n=1), upper respiratory infection (URI) (n=1) and sciatica (n=1). Two reported events were of Grade 3 severity: nephrolithiasis and elevated diastolic blood pressure. Two participants experienced a Grade 3 decline in hemoglobin from baseline. All other adverse events (n=32) were of Grade 1 severity, and of these, 5 were considered possibly, probably or definitely related to IP administration. The most common adverse events were those related to upper respiratory infections, localized musculoskeletal pain and symptoms of gastroenteritis.

3BNC117-LS: Thirty-nine participants received a single dose of 3BNC117-LS at doses ranging from 3 to 30 mg/kg (IV) or 150 or 300 mg (SC). Of the enrolled participants, twenty-seven were HIV-uninfected. As of June 2019, 5 solicited AEs were reported, all of Grade 1 severity. These included tenderness at administration site (n=1), headache (n=1), malaise/fatigue (n=1), and nausea (n=2). In addition, 39 non-solicited AEs reported by 23 enrolled participants. Of these, 6 were of Grade 2 severity: worsening hypertension (n=2), hyperbilirubinemia (n=1), URI symptoms (n=1), excessive alcohol intake (n=1), and elevated creatinine (n=1). One reported event was of Grade 3 hyperalbuminuria measured prior to 3BNC117-LS administration, which did not recur. An instance of Grade 4 hypokalemia was also reported in a participant without associated complaints, which resolved upon repeat testing.

Pharmacokinetics:

The parental 3BNC117 showed an average half-life of 17 days in HIV-uninfected individuals, and 10-1074 showed an average half-life of 24 days in the same study population. Preliminary analysis of pharmacokinetics in the ongoing first-in-human study of 3BNC117-LS suggests that its half-life is > 60 days in HIV-uninfected individuals, or 3.9-fold longer than 3BNC117 (**Figure 3a-b**). Whereas the half-life of 10-1074-LS appears to be > 90 days (**Figure 3c-d**). Additional safety and pharmacokinetics data continues to be generated under the two ongoing FIH studies of 3BNC117-LS and 10-1074-LS.

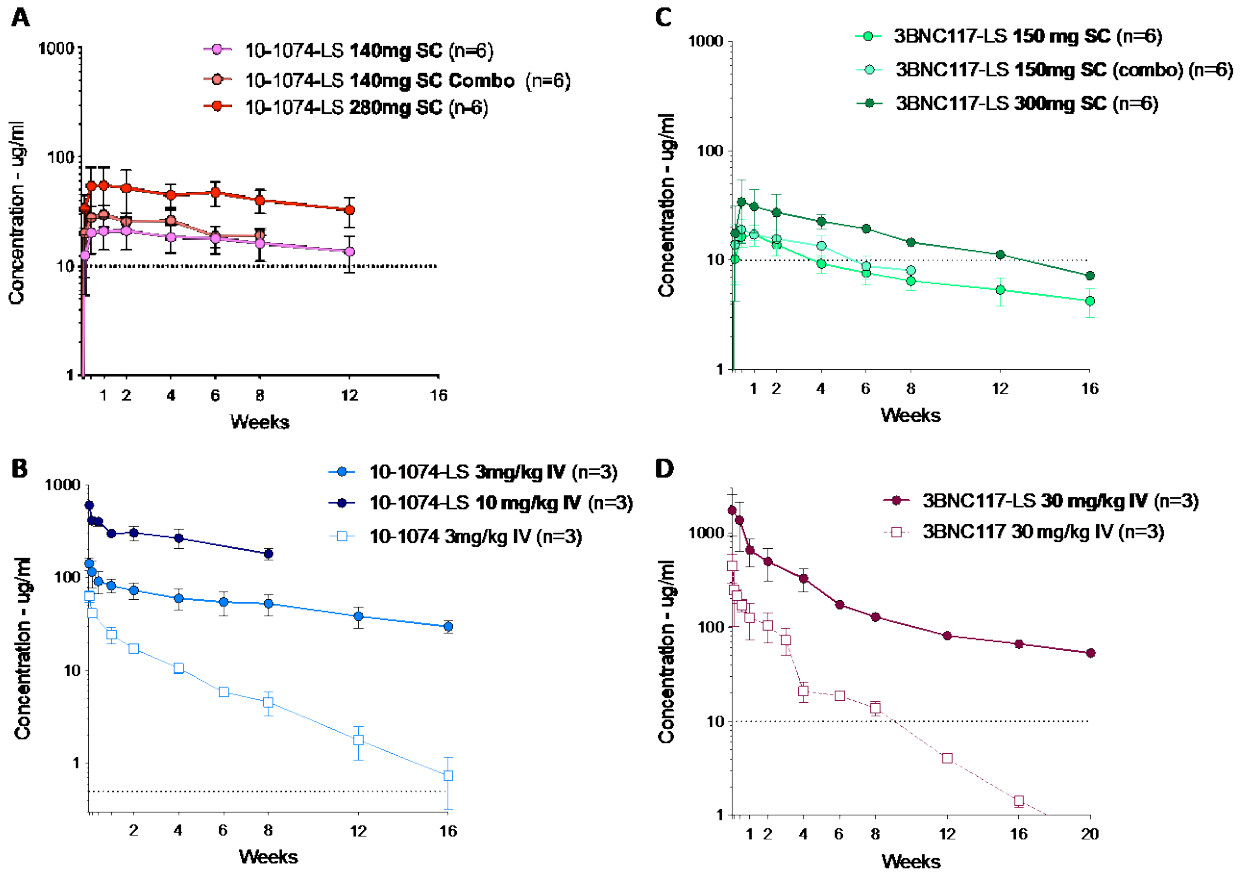

Figure 3: Serum levels of 3BNC117 and 10-1074 parental and LS variants.

Graphs show mean and s.e.m serum concentrations (y-axis) following a single administration of 3BNC117, 3BNC117-LS, 10-1074 or 10-1074-LS. (**A**) 10-1074-LS, administered SC alone (140 mg, n=6; 280 mg, n=6), or admixed with 3BNC117-LS (140 mg combo, n=6). (**B**) 10-1074 or 10-1074-LS, administered SC alone (each group, n=3). (**C**) 3BNC117-LS, administered IV alone (150 mg, n=6; 300 mg, n=6), or admixed with 10-1074-LS (150 mg combo, n=6). (**D**) 3BNC117 or 3BNC117-LS, administered IV alone (each group, n=3).

3.9 10-1074-LS and 3BNC117-LS Drug Product Manufacture

The manufacture of the recombinant human monoclonal antibodies 10-1074-LS and 3BNC117-LS were carried out by in vitro serum-free CHO cell culture. 10-1074-LS and 3BNC117-LS were manufactured by Celldex therapeutics as sterile solutions 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. In addition, two chromatography column steps contribute to viral clearance: MabSelect SuRe (Protein A Chromatography) and Sartobind Q (Anion Exchange Chromatography). 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). The clinical trial products were formulated as a single-use sterile solution intended for parenteral use. Drug product stability-testing programs are established to

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monitor the quality of 10-1074-LS and 3BNC117-LS over the duration of the clinical dosing period as well as to gain predictive information regarding the product's stability characteristics, and are based on 21 CFR 211.166 and ICH Q1A (R2) and ICH Q5C.

- 10-1074-LS stability will be 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.
- 3BNC117-LS stability will be evaluated in real time at the recommended storage conditions of 5 ± 3°C as well as at accelerated temperature conditions of 25 ± 2°C / 60 ± 5% RH.

3.10 Hypotheses

The administration of single infusions of the combination of 3BNC117-LS and 10-1074-LS to viremic HIV-infected participants (30 mg/kg of each mAb) will be generally safe and well tolerated and will lead to significant decline in plasma viremia. Both LS-variant antibodies will demonstrate longer half-lives and lower clearance rates when compared to data available from the two parental antibodies.

3.11 Aims

Primary objectives

- To evaluate the safety and tolerability profile of single intravenous infusions of 3BNC117-LS in combination with 10-1074-LS at a single dose level (30 mg/kg, each mAb) in HIV-infected individuals off ART.
- To determine the pharmacokinetic profile of single intravenous infusions of 3BNC117-LS in combination with 10-1074-LS at a single dose level (30 mg/kg, each mAb) in HIV-infected individuals off ART.
- To determine the effect of single intravenous infusions of 3BNC117-LS in combination with 10-1074-LS at a single dose level (30 mg/kg, each mAb) on plasma HIV-1 RNA levels in viremic HIV-infected individuals.

Secondary objective

- To assess the frequency and magnitude of treatment-induced anti-drug antibody responses (anti-3BNC117-LS and anti-10-1074-LS antibodies) after a single intravenous infusion.

Exploratory objectives

- To evaluate the association between reduction in plasma viremia and predicted sensitivity to both 3BNC117-LS and 10-1074-LS by the Monogram PhenoSense assay (defined as IC_{50}s < 0.25 µg/ml) and other non-CLIA-certified assays.
- To genotype viral escape variants that may arise after administration of 3BNC117-LS in combination with 10-1074-LS in viremic HIV-infected individuals.
- To characterize the impact of treatment-induced anti-drug antibody (ADA) responses on the safety, pharmacokinetics and antiviral activity of 3BNC117-LS and 10-1074-LS.
- To evaluate HIV-1 specific T and B cell immune responses following 3BNC117-LS and 10-1074-LS infusions.

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- To analyze gene expression profiles in HIV-1 infected CD4+ T cells.

3.12 Outcomes

Primary Outcomes:

- The occurrence of treatment-related solicited and unsolicited grade 3 and serious adverse events (including confirmed laboratory abnormalities).

- The pharmacokinetic profile (including: peak concentrations, half-life, area under curve and clearance rate) of 3BNC117-LS and 10-1074-LS, when administered intravenously and in combination to viremic HIV-infected individuals.
- The decline in plasma HIV-1 RNA level after 3BNC117-LS plus 10-1074-LS intravenous infusions in viremic HIV-infected individuals through week 4 after infusions.

Secondary Outcomes:

- Proportion of individuals with treatment-induced ADA against each mAb and magnitude of the response.

- The rate of adverse events and confirmed laboratory abnormalities that occur during the study follow up period after 3BNC117-LS and 10-1074-LS administration.

Exploratory Outcomes:

- Time until return of viremia to baseline levels in participants, who elect to remain off ART after 4 weeks.

- Decline in plasma viremia after antibody infusions across 3BNC117-LS and 10-1074-LS IC_{50} and IC_{80} cut points determined by PhenoSense assay or other assays (e.g. bulk PBMC cultures or Q2VOA followed by TZM/bl assay).

- Phenotypic and genotypic analysis of baseline and escape viruses that might arise after single infusions of 3BNC117-LS and 10-1074-LS in viremic HIV-infected individuals.

- Proportion of participants with reduction in half-life or antiviral activity concomitant with ADA.

- Relationship of adverse events to ADA.

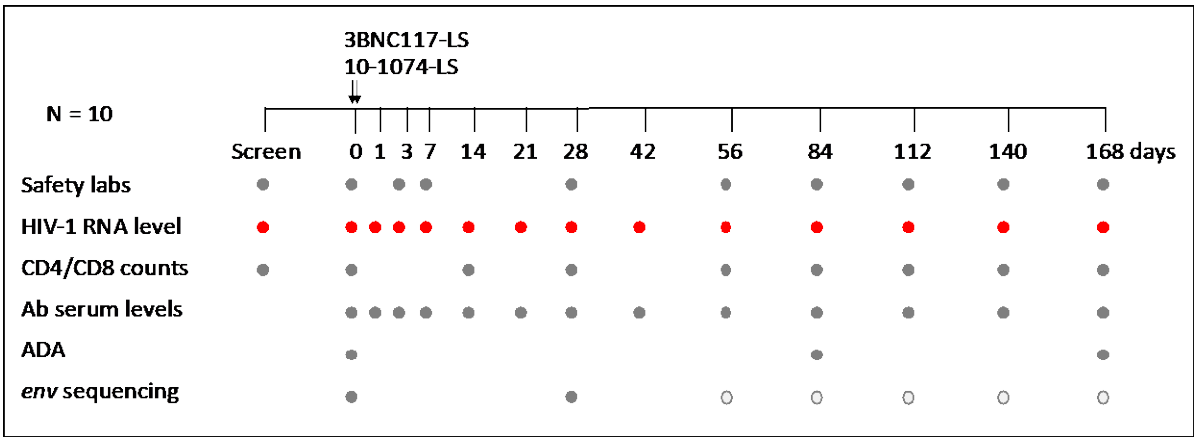
- Frequency and magnitude of HIV-1 specific T cell responses and serum neutralizing activity against a multi-clade panel of HIV-1 pseudoviruses, following 3BNC117-LS and 10-1074-LS infusions.

- Gene expression profiles by single RNA sequencing of HIV-1 infected CD4+ T cells.

4 STUDY DESIGN

The proposed study is a phase 1, open label, single arm study to evaluate the safety, pharmacokinetics and antiviral activity of single intravenous infusions of 3BNC117-LS and 10-1074-LS in viremic HIV-infected individuals. (**Figure 4**, Study Design).

Figure 4: Study Design



Ten eligible participants will be enrolled sequentially in the study and will receive each mAb, dosed at 30 mg/kg intravenously and in sequence on study day 0. Following mAb administration, study participants will return for safety assessments on days 1 and 3, and weeks 1, 2, 3 and 4 following dosing, then bi-weekly or monthly until the end of study follow up as indicated in the Time of Events Schedule **(Appendix A).** All participants will be followed for 24 weeks after 3BNC117-LS and 10-1074-LS administration.

Safety assessments will be performed at multiple time points following 3BNC117-LS and 10-1074-LS infusions. Serum samples for PK measurements will be collected before and at the end each mAb infusion administration and at multiple subsequent time points during study follow up, as indicated in the Time of Events Schedule **(Appendix A)**. Samples will also be collected for measurement of HIV-1 plasma RNA levels before 3BNC117-LS and 10-1074-LS infusions (screen and day 0) and at every follow up visit. T cell subsets will also be monitored during study follow up. Assessments will also include measurement of ADA responses and sequencing of plasma envelope before infusions and after viral rebound (first time point after viremia nadir is reached and VL is > 1,000 copies/ml).

Participants will be advised and encouraged to start ART within 4 weeks of receiving 3BNC117-LS and 10-1074-LS infusions or sooner if: VL fails to decrease by >0.5 $\log_{10}$ copies/ml within 2 weeks of antibody infusions, VL increases > 0.5 $\log_{10}$ copies/ml between weekly measurements or significant T-cell decline (confirmed CD4+ T cells < 200 cells/µl) is noted. Participants with current CD4 counts > 300 cells/µl will be eligible to enroll in the study. Studies with the unmodified 3BNC117 and 10-1074 in the same study population used the same criterion for entry and showed that CD4 counts remained stable during follow up prior to ART initiation (Caskey, Klein et al. 2015, Caskey, Schoofs et al. 2017) (Bar-On et al. 2018). We have maintained the same criterion in this study to facilitate enrollment, given the overall favorable safety profile seen in the previous studies using similar cutoff. To account for the possibility of transient CD4 count fluctuations in participants who have starting CD4 counts of about 300 cells/mm^3, we selected 200 cells/mm^3 as the cutoff to re-initiate ART sooner than 4 weeks. The selected CD4 count levels might delay initiation of ART by 1 or 2 weeks, compared to using a slightly higher cutoff. It is also unlikely that participants will experience an accelerated decline in CD4 counts in the course of 4 weeks from antibody infusions that would pose significant additional risk of poor outcomes, such as

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development of opportunistic infections. However participants will be closely monitored during this period.

5 STUDY POPULATION

5.1 Inclusion Criteria

1. Males and females, >18 years of age.
2. Confirmed HIV-1 infection.
3. Off ART for at least 4 weeks with a HIV-1 plasma RNA level between 500 and 125,000 copies/mL (ART-naïve or off ART due to intolerance or by choice).
4. Current CD4+ T cell count > 300 cells/µl.
5. Participants who can become pregnant and are engaging in sexual activity that could lead to pregnancy agree to use two effective methods of contraception (i.e. condom with spermicide, diaphragm with spermicide, hormone-eluting IUD, hormone-based contraceptive with condom) from 10 days prior to and six months after 3BNC117-LS and 10-1074-LS administration.
6. Participants who can impregnate a partner and are engaging in sexual activity that could lead to pregnancy agree to use barrier protection from 10 days prior to and six months after 3BNC117-LS and 10-1074-LS administration to avoid impregnating a partner who can get pregnant.
7. Willingness to use barrier protection during sexual activity while not on ART to decrease the risk of HIV transmission to a partner at risk for HIV infection.

5.2 Exclusion Criteria

1. Have a history of AIDS-defining illness within 3 years prior to enrollment.
2. History of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the trial physician within the last 6 months.
3. Any clinically significant acute or chronic medical condition (such as autoimmune diseases), other than HIV infection, that in the opinion of the investigator would preclude participation.
4. Hepatitis B or C infection as indicated by the presence of Hepatitis B surface antigen (HBsAg) or hepatitis C virus RNA (HCV-RNA) in blood.
5. Laboratory abnormalities in the parameters listed below:
   - Absolute neutrophil count ≤ 1,000 cells/µl;
   - Hemoglobin ≤ 10 gm/dL;
   - Platelet count ≤ 100,000 cells/µl;
   - ALT ≥ 1.5 x ULN;
   - AST ≥ 1.5 x ULN;
   - Alkaline phosphatase ≥ 1.5 x ULN;
   - Total bilirubin > 1.25 x ULN;
   - eGFR < 60 mL/min/1.73m^2.
6. Pregnancy or lactation.
7. Any vaccination within 14 days prior to mAb infusions, except for influenza vaccine.

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8. Receipt of another investigational product currently or within the past 12 weeks, or expected concurrent participation in another study in which investigational products will be administered.
9. Receipt of any experimental HIV vaccine or anti-HIV monoclonal antibody therapy in the past.
10. History of severe reaction to a vaccine or drug infusion or history of severe allergic reactions.
11. Individuals with known hypersensitivity to any constituent of the investigational products.

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**. At the Cornell site, recruitment, screening, and follow up visits during the study period will be performed either at the Weill Cornell Medical Center (WCMC), and antibody infusions will occur at the Rockefeller University Hospital (RUH). At the RU and UPENN sites, all study procedures will occur at the RUH or at the Center for Human Phenomic Science (CHPS) at the Perelman Center for Advanced Medicine (PCAM) of the Perelman School of Medicine University, respectively.

6.1.1 Pre-Screening Questionnaire

Potential participants will first undergo pre-screening by telephone to assess medical history and qualification for the study. Potential participants 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 participation will attend a screening visit at the RUH, WCMC, or UPENN McGregor Outpatient Clinics.

6.1.2 Screening Visit

Initial Screening Visit:

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

1. Risk-reduction counseling including safer sex (including discussion of sexual activity that could lead to HIV transmission) and pregnancy avoidance counseling;
2. One must assume that no improvement in control of HIV infection will occur given the experimental nature of the monoclonal antibodies;
3. That sexually active males and females, participating in sexual activity that could lead to pregnancy, should use two reliable forms of contraception for 10 days prior to and six months following 3BNC117-LS and 10-1074-LS administration.

If the potential participant consents to participate, site personnel will:

- Perform complete medical history (including review of concomitant medications);

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- 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;
- Collect blood and urine specimens for all tests as indicated in the Time of Events Schedule (**Appendix A**);
- Perform a pregnancy test for all female volunteers of child-bearing potential.

If the initial screening visit occurs more than 49 days prior to the date of 3BNC117-LS and 10-1074-LS administration, only laboratory tests (blood and urine specimens) will be repeated and a review of the medical history will be performed.

HIV-1 infected participants that do not meet eligibility criteria due to HIV viral load levels outside of the range specified in the protocol will be independently counseled regarding their HIV care. Participants will be counseled and encouraged to initiate therapy and referrals to HIV providers will be provided, if needed.

6.1.3 Study Drug Administration Visit

Prior to administration of the investigational product(s), site personnel will:

- Review the informed consent form administered at the screening visit with the participant;
- Answer any questions about the study;
- Review interim medical history (including concomitant medications);
- Review safety laboratory data;
- Perform a directed 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 safer sex counseling;
- Perform a serum pregnancy test for all female volunteers of child-bearing potential and obtain results prior to drug infusion.
- Perform baseline assessment and record any systemic symptoms;
- 3BNC117-LS and 10-1074-LS will be prepared for administration according to **Appendix C**;

<u>Antibody Administration:</u>

- 3BNC117-LS will be administered via a peripheral vein over 30 minutes. The IV line will be flushed with normal saline after all the contents of the infusion bag are administered.
- 10-1074-LS will be administered after 3BNC117-LS infusion is completed and the line is flushed with normal saline. It will also be administered via a peripheral vein over 30 minutes. The IV line will be flushed with normal saline after all the contents of the infusion bag are administered.
- If participants develop grade 3 acute infusion reaction, an immediate hypersensitivity reaction or a life-threatening event during study drug administration, the infusion will be

discontinued and will not be reinitiated (see Section 6.1.7.1). If the acute infusion reaction occurs during 3BNC117-LS infusion, 10-1074-LS infusion will not be infused.

- Participants will be observed for adverse reactions at the study site for 1 hour after the end of the 10-1074-LS infusion. Presence or absence of adverse events will be recorded at 1 hour post infusion.
- Vital signs (pulse, respiratory rate, blood pressure and temperature) will be monitored before administration, at the end of each infusion, 30 minutes (+/- 10min) post final infusion, and at 1 hour (+/- 10 min) post final infusion;
- Rescue medications, including acetaminophen, diphenhydramine (or an alternative antihistaminic) and glucocorticoids will be available in the RUH or at the Center for Human Phenomic Science (CHPS) at the Perelman center for advanced Medicine (PCAM) of the Perelman School of Medicine University for use if clinically indicated.

6.1.4 Post-Study Drug Administration Visit

Participants will be followed through study week 24.

At these follow up visits the following will be conducted:

- Review of interim medical history and use of concomitant medications;
- Perform a symptom-directed physical examination if symptoms are present;
- Local and systemic solicited and unsolicited adverse events will be assessed;
- Pregnancy and safer sex counseling;
- Vital Signs;
- Collect blood and urine specimens for all tests as indicated in the Time of Events Schedule (**Appendix A**);
- In case of adverse event(s), the participant 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 for all study groups are illustrated in the Time of Events Schedules (**Appendix A**).

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

6.1.5 Final Visit/Early Termination Visit

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

6.1.6 Discontinuation of Study Drug Infusions and/or Participant Withdrawal from Study

6.1.6.1 Discontinuation of Study Drug Infusion

Antibody intravenous infusion will be discontinued for any of the following reasons:

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1. Grade 3 acute infusion reactions that occur during infusion.
2. Any immediate hypersensitivity reaction (such as urticarial rash; bronchospasm; laryngeal edema; anaphylaxis; syncope).
3. Life threatening medical event during 3BNC117-LS or 10-1074-LS infusion.

6.1.6.2 Withdrawal from the Study (Early Termination)

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

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

6.1.6.3 Follow Up after Withdrawal from Study (Early Termination)

Any adverse event resulting in withdrawal of a participant 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 participant 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 (early termination) from the study should be collected and reported to the Sponsor at the RU, the SMC, and the local IRBs.

A pregnant participant will not receive the study drugs. If pregnancy occurs after 3BNC117-LS and 10-1074-LS administration, the participant will be followed until the end of the study and until delivery, if delivery occurs after the study has ended. Approximately 2-4 weeks after delivery, the baby will be examined by a pediatrician to assess his/her health status. The outcome of the pregnancy and the health status of the baby will be reported to the Sponsor at the RU, the SMC, and the local IRBs.

6.2 Study Procedures

6.2.1 Consent Procedure

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

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

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

The "Teach Back" method will be used to ask research participants to repeat or “Teach Back” the information, concepts and directions that the staff member has attempted to convey to the participant. This method is used to assess comprehension and retention of protocol requirements, adverse event information, risks and benefits, and the participant's rights described in the Informed Consent process.

6.2.2 Study Assignment and Randomization

Enrollment will be open-label, and participants will be enrolled sequentially as they meet enrollment criteria. Study ID numbers will be assigned by the Emmes Corporation, to prevent over-enrollment. Over-enrollment will only be permitted to replace participants lost to follow up prior to week 4, as discussed in Section 8.2 Sample Size Considerations.

6.2.3 Study Drug Administration Procedure

3BNC117-LS will be provided in single-use vials containing 1 mL of the product at a concentration of 150 mg/mL. 10-1074-LS will be provided in single-use vials containing 1 mL of the product at a concentration of 140 mg/mL.

The volume of 3BNC117-LS to be administered will be calculated by the site research pharmacist. Weight measurements collected at the day 0 visit will be used to calculate the dose of 3BNC117-LS. The appropriate volume of 3BNC117-LS will be diluted in sterile normal saline to a total volume of 100 mL, and will be administered as an intravenous infusion over 30 minutes.

The volume of 10-1074-LS to be administered will be calculated by the site research pharmacist. Weight measurements collected at the day 0 visits will be used to calculate the dose of 10-1074-LS. The appropriate volume of 10-1074-LS will be diluted in sterile normal saline to a total volume of 100 mL, and will be administered as an intravenous infusion over 30 minutes, after the infusion of 3BNC117-LS is completed.

The study drugs will be administered via a peripheral vein in one of the upper extremities. The administration site should be free of potentially complicating dermatologic conditions. The entire contents of the infusion bags must be administered. At the end of each infusion, the IV line will be flushed with Normal Saline to ensure all the study drug has been delivered.

6.2.4 Medical History and Physical Examination

At the time of screening, participant’s past medical history will be collected and 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**).

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A general physical examination will be conducted at screen including weight, height, vital signs, and examination of skin, respiratory, cardiovascular and abdominal systems. At the study drug administration and follow up visits, directed physical examinations will be performed according to the Time of Events Schedule (**Appendix A**). A directed physical examination will include vital signs, examination of infusion site, and any further examination indicated by history or observation.

6.2.5 Ophthalmologic Evaluations

In the tissue cross-reactivity study (TCR) in human tissues, 3BNC117 stained rare cells in the conjunctival recesses, and 10-1074 stained the cytoplasm of nerve cells in the optic nerve of the eye. *In vivo* GLP toxicology studies performed in rats with 3BNC117 and 10-1074, alone and in combination, did not show toxicity in ocular tissues. Moreover, these tissue binding findings were not reproduced in repeat TCR studies comparing the unmodified with the LS variants.

In humans, approximately 6% of participants enrolled in 3BNC117 trials reported mild ocular complaints (such as pruritus, conjunctival erythema, increased lacrimation, blurry vision) during study follow up of 6 to 12 months. In all instances, symptoms resolved without specific treatment, and evaluations by an ophthalmologist at 1 or 5 months after 3BNC117 administration did not reveal changes from baseline. It remains unclear if these symptoms were related to 3BNC117 infusions. Two ocular symptoms were reported during 10-1074 studies (grade 1, dry eyes and diplopia), and follow up ophthalmologic exams did not reveal abnormalities or changes from the baseline exams. A temporal relationship between time of 3BNC117 and/or 10-1074 administrations and the occurrence of ocular complaints is not clear at this time To date, only 1 out of 39 participants reported an ocular AE in the studies of 3BNC117-LS alone or in combination with 10-1074-LS. This was grade 1 ocular pruritus, which occurred 3 days post-infusion and resolved 1 day later.

The occurrence of ocular AEs will be monitored as solicited AEs. Participants will be evaluated by an ophthalmologist (including slit lamp exam) prior to 3BNC117-LS and 10-1074-LS administration. In addition, participants will be monitored for the occurrence of ocular symptoms. If symptoms of ocular disease develop after study infusions and persist for > 48 hrs, participants will be promptly referred to an ophthalmologist for diagnosis and management.

6.2.6 Diagnostic Work Up in the Event of Grade 3 or 4 Elevations in Total Bilirubin

Transient elevations in total bilirubin have been observed following 3BNC117 dosing and in 1 participant who received 3BNC117-LS. Typically, these are isolated laboratory abnormalities of grade 1 severity that resolve within a few weeks without need for specific treatment. A causal relationship has not been determined but bilirubin levels will be followed during study follow up.

Any participant with a grade 3 or 4 elevation in total bilirubin will undergo a diagnostic work up that includes right upper quadrant ultrasound, testing for gamma glutamyl transferase (GGT) HAV (IgM and IgG), HBV (hepatitis B surface antigen and IgM anti-hepatitis B core antigen), HCV (anti-hepatitis C antibody and HCV PCR), EBV (IgM and IgG VCA and EBNA antibodies), CMV (IgM and IgG), VZV (IgM and IgG) and HSV (IgM and IgG), and any other relevant laboratory tests as determined by the investigators. These evaluations will be of no cost to the participant.

6.2.7 Monitoring for Cytokine Release Associated Adverse Events and Treatment of Cytokine Release Syndrome, Immediate Hypersensitivity Reactions or Other

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Life-Threatening Adverse Events

Based on previous clinical experience with similar monoclonal antibodies, it is unlikely that administration of 3BNC117-LS and 10-1074-LS would lead to cytokine release syndrome. However, a potential side effect of a monoclonal antibody can be the stimulation of a massive release of cellular cytokines, which can have profound effects on blood pressure, vascular integrity, and myocardial, lung, liver, and kidney functions. If cytokine release syndrome occurs, the participant may need to be treated with intravenous fluids, vasopressors, and high-dose corticosteroids and may require ventilator support.

Study participants will be observed at the site infusion unit on the day of study drug administration. 3BNC117-LS and 10-1074-LS will each be administered over 30 minutes. Participants will remain in the unit for at least 60 minutes after last infusion. Access to a twenty-four hour on-call physician is available at all sites. The study sites are equipped with crash carts for immediate medical care, should the need arise. In case of an emergency, after stabilization of the volunteer, he/she will be transferred to a tertiary care center for specialized medical care.

6.2.8 Family Planning Counseling

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

Female study participants of reproductive potential are defined as pre-menopausal women who have not had a sterilization procedure (e.g. hysterectomy, bilateral oophorectomy, tubal ligation or salpingectomy). Women are considered menopausal if they have not had a menses for at least 12 months and have a FSH of greater than 40 IU/L or if FSH testing is not available, they have had amenorrhea for 24 consecutive months.

Should pregnancy occur, a pregnant participant will not receive the study drug(s). If pregnancy occurs after study drug administration, the participant will be followed until the end of the study and until delivery, if it occurs after the study has ended. Approximately 2-4 weeks after delivery, a pediatrician will examine and assess the health status of the baby. The baby's health status will be reported to the Sponsor at the RU, the local IRBs, and the SMC.

6.2.9 Safety Assessments

6.2.9.1 Solicited Adverse Events

Solicited adverse events in this study include presence of feverishness, chills, headache, nausea, vomiting, malaise, myalgia and arthralgia occurring in the two weeks following 3BNC117-LS and 10-1074-LS administration, as well as infusion site reaction or extravasation changes.

Solicited adverse events will be collected prospectively by structured interviews on infusion and post-infusion follow up visits; recorded and graded according to pre-established criteria (see **Appendix B**). The DAIDS AE Grading Table, corrected v2.1 (July 2017) will be used to grade adverse events in HIV-infected participants. In addition, the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (27Nov2017) grading scale will be used for reporting and grading adverse events in all groups occurring within 24 hours of the start of 3BNC117-LS and 10-1074-LS infusions that are considered infusion reactions or cytokine release syndromes. Symptoms that may constitute an infusion reaction or cytokine release syndrome include: fever and/or shaking chills, flushing and/or pruritus, alterations in heart rate and blood pressure,

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dyspnea or chest discomfort, back or abdominal pain, nausea, vomiting, and/or diarrhea, skin rash.

Vital signs (pulse, respiratory rate, blood pressure and temperature) will be measured prior to each antibody infusion, at the end, and 1-hour post-infusion, and will be graded according to the CTCAE v5.0 toxicity table and recorded. All medications required for treatment of adverse events will be recorded.

6.2.9.2 Unsolicited Adverse Events

During all follow up visits, the occurrence of unsolicited adverse events will be assessed following an open question to participants, with the dates of commencement and resolution and any medication required. Adverse events will be followed to resolution or stabilization. They will be graded as indicated in the appropriate toxicity table **(Appendix B)**.

Laboratory abnormalities that are considered clinically significant and are grade 3 or higher will be reported as adverse events.

6.2.10 Blood Collection, Storage and Shipment

Venous blood will be collected at every study visit according to the Time of Events Schedule (**Appendix A**). Up to 120 mL will be collected at day 0. Up to 100 mL will be collected at other visits. At no time will the total volume of blood collected exceed 550 ml over an 8-week period. All specimens will be handled according to Processing Laboratory SOPs. Frozen PBMCs, plasma, and serum will be processed and stored at the study sites.

6.2.11 Routine Laboratory Parameters

Laboratory parameters will routinely include hematology (WBC and differential, hemoglobin/hematocrit, platelets), clinical chemistry (creatinine, total and direct bilirubin, AST and ALT, alkaline phosphatase), and urinalysis (dipstick). TSH, T3, and free T4 will be measured at week 0 and week 4. Female participants will have serum beta-HCG measured on the day of study drug administration, and urine beta-HCG checked at screening and follow up visits. 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, participants may be asked to have additional sample(s) collected at the discretion of the principal investigator or designee.

HIV-1 viral load and CD4+ T cell counts will be closely monitored as outlined in the Time of Events Schedule (**Appendix A**).

Participants will be screened for syphilis (RPR), gonorrhea and chlamydia (urine GC/Chlamydia nucleic acid amplification test), and viral hepatitis (HBsAg and HCV viral load) at the Screening Visit.

6.2.12 Antiretroviral and Immunogenicity Assessments

1. Standard HIV-1 viral load assay (CLIA-certified). 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-LS and 10-1074-LS administration.

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2. Levels of circulating CD4+ and CD8+ T cell counts will be determined by a CLIA-certified assay.
3. Measurement of 3BNC117-LS and 10-1074-LS levels by sandwich ELISA will be performed in the laboratory of Dr. Georgia Tomaras at Duke University by qualified assays. mAb levels will be measured in serum at multiple time points during the study, according to the Time of Events Schedule (**Appendix A**).
4. Anti-drug (3BNC117-LS or 10-1074-LS) antibody responses in serum. Assays will be performed in the Laboratory of Dr. Margaret Ackerman at Dartmouth College by qualified assays, according to the Time of Events Schedule (**Appendix A**).
5. 3BNC117-LS and 10-1074-LS sensitivity (CLIA-certified). Baseline (day 0) sensitivity to 3BNC117-LS and 10-1074-LS will be evaluated by a PhenoSense assay developed by Monogram. In this assay, a library of pseudoviruses expressing envelope sequences isolated from PBMC proviral DNA is tested for neutralization sensitivity to a given bNAb in TZM.bl cells. Sensitivity will be defined as IC_{50}s < 0.25 µg/ml. This assay will be performed at Monogram.
6. Genotyping – Sequencing of HIV-1 env viral isolates will be performed in plasma samples collected before and after 3BNC117-LS and 10-1074-LS infusions. Genotyping will be performed in the RU Laboratory of Molecular Immunology.
7. Phenotyping of viral escape variants in viremic participants - HIV-1 pseudoviruses expressing selected envelope sequences will be generated for subsequent characterization by *in vitro* neutralization assays. Representative sequences, including sequences with substitutions not known to confer reduced susceptibility to 3BNC117 or 10-1074, will be selected for phenotypic analysis. Pseudoviruses will be generated in the RU Laboratory of Molecular Immunology and neutralization assays will be performed in the Laboratory of Dr. Michael Seaman at Beth Israel Deaconess Medical Center.
8. HLA-typing will be performed on PBMC samples at a contract laboratory.
9. Functional properties of cytotoxic T cells analysed by flow cytometry at baseline and following 3BNC117-LS and 10-1074-LS infusions. These assays will be performed in the RU Laboratory of Molecular Immunology.
10. TZM-bl neutralization assay will be performed in the laboratory of Dr. Michael Seaman of the Beth Israel Deaconess Hospital in Boston. This assay will be performed to determine serum neutralizing activity against a panel of pseudoviruses representative of multiple clades at baseline and following 3BNC117-LS and 10-1074-LS infusions.
11. Gene expression profile of isolated HIV-1 infected cells by single cell RNA sequencing will be performed in the RU 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.

6.2.13 Pharmacokinetic Evaluations

3BNC117-LS and 10-1074-LS serum levels will be measured by validated sandwich ELISA methods performed at Duke University. Serum samples will be collected before 3BNC117-LS and 10-1074-LS administration, at the end of the 3BNC117-LS and 10-1074-LS intravenous infusions and at all follow up visits.

Pharmacokinetic parameters, including AUC, Cmax, $T_{1/2}$, Tmax, clearance rate and others will be estimated by performing a non-compartmental analysis (NCA). Pharmacokinetic parameters will be examined to correlate exposure with safety and pharmacodynamic parameters (decline in plasma HIV-1 RNA), and variance, based on population intrinsic factors such as weight and gender, will be explored.

6.2.14 Specimen Shipment Preparation, Handling and Storage

- Safety labs:

Specimens collected for safety labs at RUH will be transported to Memorial Sloan Kettering Cancer Center laboratory (MSKCC) via a courier. Specimens for LabCorp will be picked up by LabCorp staff at RUH.

Safety labs will be collected and tested at the WCMC and the UPENN sites.

- Research labs:

Specimens collected at RUH will be transported to the Clinical Processing lab in the Laboratory of Molecular Immunology by laboratory staff. The buildings are adjacent to each other and are connected by an underground tunnel.

Specimens collected at WCMC will be transported to the Processing Lab on site at the local Clinical Trials Unit.

Specimens collected at UPENN will be transported to the Processing Lab on site at the local Clinical Trials Unit.

1. Peripheral Blood Mononucleated Cells (PBMC) (isolated from ACD tubes or from leukapheresis): PBMCs are isolated using density gradient centrifugation with Histopaque.

PBMC sample aliquots will be stored in liquid nitrogen freezers located at the local sites. PBMCs will also be used for future phenotypic and functional assays to characterize B, T and NK cells, as well future assessments to proviral HIV-1 DNA.

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

Plasma samples will be stored at the local sites. Plasma samples will be used to isolate circulating viral sequences.

3. Serum: Samples will be collected in Serum Separation Tubes (SST). Following centrifugation, serum from multiple tubes, from the same participant, will be pooled, divided in 200 or 500 µl aliquots and stored at -80 degrees Celsius.

Serum samples will be shipped to the laboratory of Drs. Georgia Tomaras and Margaret Ackerman. Serum samples will be used for measurement of 3BNC117-LS and 10-1074-LS levels, anti-3BNC117-LS and anti-10-107-LS antibodies and for *in vitro* neutralization assays. The remaining aliquots will be stored at the local sites.

All infectious specimens will be transported using packaging mandated in the Code of Federal

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

6.2.15 Biohazard Containment

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

6.2.16 Compensation

Participants will be compensated according to standards at each study site.

7 INVESTIGATIONAL PRODUCTS

Investigational Drug Name:	10-1074-LS
Manufacturer Name of Drug:	Celldex Therapeutics, Inc.
IND Number:	136387
IND Sponsor:	Rockefeller University

Investigational Drug Name:	3BNC117-LS
Manufacturer Name of Drug:	Celldex Therapeutics, Inc.
IND Number:	131872
IND Sponsor:	Rockefeller University

7.1 Regimen

- 3BNC117-LS and 10-1074-LS will be administered intravenously, in sequence, at 30 mg/kg (each mAb) once.

7.2 Study Product Formulation and Preparation

Study Drugs Formulation:

- 3BNC117-LS will be provided by Celldex Therapeutics in single-use vials containing 1 mL of 3BNC117-LS protein at a concentration of 150 mg/mL in a 1.0 mL buffered solution composed of 10 mM Histidine, 245 mM Trehalose, 10 mM Methionine, 0.05% Polysorbate 20, pH 5.2. The drug product is brownish yellow in appearance and slightly opalescent at storage conditions.
- 10-1074-LS will be provided by Celldex Therapeutics in single-use vials containing 1 mL of 10-1074-LS protein at a concentration of 140 mg/mL in buffered solution composed of 5 mM Histidine, 250 mM Trehalose, 10 mM Methionine, 5 mM Sodium Acetate, 0.05% Polysorbate 20, pH 5.5. The drug product is brownish yellow in appearance and slightly opalescent at storage conditions.

Preparation:

- Each mAb will be diluted in normal saline (NaCl 0.9%) to a volume of 100 mL for intravenous infusion. Normal saline will be obtained by the local site pharmacies.
- 3BNC117-LS and 10-1074-LS are stored at 5 ± 3°C. The appropriate dose of each mAb should be drawn soon after vials are removed from the refrigerator. Vials should be checked for particulates before drawing doses, but no other swirling or inversion are needed.
- The appropriate dose will be calculated by the site research pharmacist according to participant's weight (measured at the day 0 visit). 3BNC117-LS and 10-1074-LS will be dispensed in a small volume parenteral infusion, diluted in normal saline (NaCl 0.9%) ready for administration by the study investigators. Standard 18G needles are recommended to draw the required dose of each mAb to decrease the preparation time. Prior to injection of the mAb solution into the IV bag, remove air from the syringe and inject slowly, to avoid foaming. After preparation, infusion bags should be handled gently to avoid foaming (do not shake). Infusion bags should also be checked for particulates.

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- 3BNC117-LS and 10-1074-LS should be administered through a 0.2 or 0.22 micron in-line filter.
- Finished infusion preparations with IV lines attached and primed may be stored at either room temperature or refrigerated. Infusion beyond use dating depends upon the IV product preparation method and local pharmacy SOPs. A recommendation is to begin the infusion within 4 hours of preparation, if stored at room temperature, and 6 hours, if stored refrigerated (2-8 C).

Dispensing and Handling of Investigational Product:
3BNC117-LS and 10-1074-LS will be shipped from Celldex Therapeutics and will be stored in the site research Pharmacy at 5 ± 3°C.

Trial personnel will ensure that the study ID number on the infusion bag matches the study ID assigned to the participant prior to administration.

7.3 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, transferred to the Laboratory of Molecular Immunology at RU for research purposes only, or destroyed.

7.4 Assessment of Participant Adherence with Study Product

Not applicable. Participants will be administered 3BNC117-LS and 10-1074-LS at the study sites on study day 0.

7.5 Concomitant Medications and Procedures

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

Participants will be advised and encouraged to initiated ART 12 weeks after 3BNC117-LS and 10-1074-LS infusions. The initiated ART regimen will be recorded.

7.6 Permitted Medications and Procedures

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

7.7 Prohibited Medications and Procedures

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

Use of systemic corticosteroids (long term use), immunosuppressive anti-cancer, interleukins, systemic interferons, systemic chemotherapy within 6 months of study enrollment is not permitted. Short term use of systemic steroids (e.g. steroid taper for allergic or infusion reactions or asthma exacerbation) is permitted.

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7.8 Precautionary Medications and Procedures

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

7.9 Required Medications

Not applicable. Participants will be advised and encouraged to initiated ART within 4 weeks after 3BNC117-LS and 10-1074-LS infusions within 4 weeks of receiving 3BNC117-LS and 10-1074-LS infusions, or sooner if: VL fails to decrease by >0.5 $\log_{10}$ copies/ml within 2 weeks of antibody infusions, VL increases > 0.5 log10 copies/ml between weekly measurements or significant T-cell decline (confirmed CD4+ T cell count < 200 cells/µl) is noted.

7.10 Rescue Medications

If volunteers develop grade 3 acute infusion reaction, an immediate hypersensitivity reaction or a life-threatening event during study drug administration, the infusion will be discontinued and will not be reinitiated (see Section 6.1.7.1). Rescue medications, including acetaminophen, diphenhydramine and glucocorticoids will be available at the clinical sites for use if clinically indicated.

8 DATA ANALYSIS

8.1 Analysis of Safety, PK and Antiretroviral Effects

Primary Outcomes

- Safety: The safety population will include all participants who receive a dose of 3BNC117-LS and 10-1074-LS. A baseline measurement and at least one laboratory, vital sign, or other safety-related measurement obtained after 3BNC117-LS and 10-1074-LS dosing may be required for inclusion in the analysis of a specific safety parameter.

  The number and percentage of participants experiencing one or more AEs will be summarized by relationship to study drug, and severity. AEs will be summarized by the number and percentage of participants who experienced the event, according to system organ class (SOC) and preferred term. AEs will also be summarized by severity grade and by relationship to study drug according to the DAIDS AE Grading Table, corrected v2.1 (July 2017). The CTCAE v5.0 grading scale will be used for reporting and grading adverse events occurring within 24 hours of the start of 3BNC117-LS and/or 10-1074-LS infusions that are considered infusion reactions or cytokine release syndromes. Changes in hematology, chemistry, and other laboratory values will be summarized descriptively. Changes will be calculated relative to the values collected at baseline.

- Pharmacokinetic parameters: will be calculated using standard non-compartmental analysis methods. Pharmacokinetic parameters, including AUC, Cmax, $T_{1/2}$, Tmax, clearance and others will be summarized. Pharmacokinetic parameters will be examined to correlate exposure with safety and pharmacokinetics parameters, and variance based on population intrinsic factors such as weight and gender will be explored.

- Antiretroviral activity: The magnitude of change in plasma HIV-1 RNA levels from baseline will be evaluated. Plasma HIV-1 RNA levels will be evaluated prior to and at multiple time points following 3BNC117-LS and 10-1074-LS infusions and the log copies/ml reduction in HIV-1 RNA level from baseline will be calculated.

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Secondary Outcomes

- Anti-3BNC117-LS and anti-10-1074-LS antibodies: The frequency of induced anti-3BNC117-LS or anti-10-1074-LS antibodies will be reported. Occurrence of ADA will be evaluated by a three-tiered approach using validated screening and confirmatory assays, followed by tittering of responses to determine if responses were treatment-induced or treatment-boosted.

Other Exploratory Measurements

- Genotyping and phenotyping of HIV isolates will be performed to analyze the induction of escape mutations following 3BNC117-LS and 10-1074-LS infusions in viremic individuals enrolled in the study. Specifically, we will perform single genome amplification (SGA) of plasma viruses to define the relationship between individual responses to antibody therapy and circulating virus sensitivity to the antibodies. CMV-promoter-based pseudoviruses will be constructed from selected SGA sequences and tested for bNAb sensitivity in a TZM-bl 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 participants.

The analysis of study data will be primarily descriptive, with emphasis on tabular and graphical displays. Summary statistics will be calculated, along with point and interval estimates of solicited and unsolicited adverse events. The pharmacokinetic profiles of a single administration of 3BNC117-LS in combination with 10-1074-LS will also be determined. This study is exploratory, and any statistical inferences will be hypothesis generating and not confirmatory.

8.2 Sample Size Considerations

Five to 10 evaluable participants are sought. The total number of screened participants to achieve 5 to 10 evaluable participants is estimated to be 15 to 30. Replacement for 2 participants lost to follow up prior to week 4 will be allowed.

Safety:
We expect that the administration of a single infusion of 3BNC117-LS in combination with 10-1074-LS will be generally safe and well tolerated.

The sample size of 5 to 10 participants receiving 3BNC117-LS and 10-1074-LS in combination will provide 95% probability of observing a treatment-related AE that would occur in 26% to 45% or more of treated participants. If none of the participants experiences a grade 3 AE related to 3BNC117-LS and/or 10-1074-LS, the one-sided 95% upper confidence bound for the rate of AEs in the population is 25.9% to 45.1%.

Pharmacokinetics:
Based on the pharmacokinetic profile of VRC01LS in humans, another anti-HIV-1 antibody targeting the same gp120 site as 3BNC117-LS, 3BNC117-LS and 10-1074-LS data in NHP, and preliminary 3BNC117-LS and 10-1074-LS data in humans, it is expected that the half-lives of 3BNC117-LS and 10-1074-LS will be approximately 3-fold higher than the unmodified antibodies. Therefore, we expect that 3BNC117-LS will have a $t_{1/2}$ in humans of approximately 70 days. Similarly, we expect that 10-1074-LS will have a $t_{1/2}$ in humans of approximately 90 days.

In a previous study with 10-1074, the mean elimination half-life of approximately 24 days (SD 6.6 days) in HIV-uninfected and 12.8 days (SD 4.9 days) in viremic HIV-infected individuals (Caskey et al 2017). 3BNC117 has a mean elimination half-life of approximately 17.6 days (SD 5.7 days) in HIV-uninfected and 9.6 days in viremic HIV-infected individuals (SD 2.9 days) (Caskey et al., 2015). PK parameters were maintained when the two antibodies were administered in combination.

The margins of error at 95% confidence level for estimating the mean elimination half-life of either mAb, based on standard deviations in the range of 4.5 to 6.5 days using the available pharmacokinetics data of 3BNC117 and 10-1074, and 5 or 10 participants are included in **Table 3**.

Table 3. Margin of Error at 95% Confidence Level for Estimating the Mean Elimination Half-life of 3BNC117-LS and 10-1074-LS

Standard Deviation (days)	95% margin of error (+/- days) n = 5	95% margin of error (+/- days) for n = 10
4.5	3.9	2.8
5	4.4	3.1
5.5	4.8	3.4
6	5.3	3.7
6.5	5.7	4.0

Antiviral activity:

Single infusions of 3BNC117 and 10-1074, dosed at 30 mg/kg, led to an average decline in viremia of 1.48 $\log_{10}$ copies/ml (range = 0.8-2.5 and SD = 0.6 $\log_{10}$ copies/ml) (Caskey, Klein et al. 2015) and 1.52 $\log_{10}$ copies/ml (range = 0.9-2.06 and SD = 0.4 $\log_{10}$ copies/ml) (Caskey, Schoofs et al. 2017). The average decline in viral load for 4 viremic participants who received one or three infusions of the 3BNC117 and 10-1074 combination was 2.05 $\log_{10}$ copies/ml (range = 1.58-2.57 and SD = 0.7 $\log_{10}$ copies/ml) (Bar-On et al. 2018).

A recent study, ACTG NWCS 413, utilized the Monogram PhenoSense assay to estimate baseline 3BNC117 and 10-1074 sensitivity of HIV pseudovirions that express envelope proteins representative of the quasispecies of proviral HIV-1 DNA in PBMCs. For 3BNC117, the median IC_{50} was 0.087 µg/mL (Q1, Q3 of 0.061, 0.183) and median IC_{80} was 0.301 µg/mL (Q1, Q3 of 0.206, 0.680); whereas for 10-1074, the median IC_{50} was 0.044 µg/mL (Q1, Q3 of 0.020, 0.222) and median IC_{80} was 0.184 µg/mL (Q1, Q3 of 0.066, 1.578). 61% (37/61) of the participants' virus swarms fell under the predicted sensitivity threshold of IC_{80} < 1 µg/mL to both 3BNC117 and 10-1074, with 77% and 74% falling under this level for 3BNC117 only and 10-1074 only, respectively, and 89% for either antibody.

Table 4 shows the minimum average decline in plasma HIV-1 RNA levels ($\log_{10}$ copies/ml) that can be detected with 80% power and a two-sided 0.05 test, assuming a standard deviation of 0.7 ($\log_{10}$ copies/ml) from the 3BNC117 plus 10-1074 data. *If 4 out of 10 participants harbor viruses sensitive to both antibodies, the minimum average decline in plasma HIV-1 RNA levels that can be detected with 80% power and a two-sided 0.05 test is 1.49 $\log_{10}$ copies/ml*. If we assume 60% of the participants will be sensitive to either antibody, the probability of observing at least 4 responders (HIV-1 RNA ≥ 0.5 $\log_{10}$ copies/ml) out of up to 10 enrolled participants who receive 3BNC117-LS and 10-1074-LS is 0.95.

Table 4. Minimum average decline in plasma viremia that can be detected for varying sample sizes

N	SD (log_{10} copies/ml)	two-sided test alpha =0.05	
		Minimum average decline in plasma HIV-1 RNA (log_{10} copies/ml)	Effect size
3	0.7	2.29	3.26
4	**0.7**	**1.49**	**2.13**
5	0.7	1.18	1.68
6	0.7	1.00	1.43
7	0.7	0.89	1.27
8	0.7	0.81	1.16
9	0.7	0.75	1.07
10	0.7	0.70	1.00

8.3 Enrollment/Stratification/Randomization/Blinded Procedures

This will be an open-label, single arm study. Participants will be enrolled sequentially, as they meet enrollment criteria for study participation. Enrollment will be competitive between the RU, WCMC and UPENN sites. Study ID numbers will be assigned by the Emmes Corporation.

8.4 Participant Enrollment and Follow-Up

The total number of evaluable participants in the study will be 5 to 10.

An over-enrollment of 2 participants will be allowed if participants drop-out prior to week 4. Participants who are discontinued from the study due to AEs will not be replaced. Additional participants will be enrolled after study withdrawal is confirmed. If a participant drops out after receiving 1 or both study drugs, he/she will be invited to return every 4 weeks, for at least 3 months after antibody infusion, for safety monitoring only.

9 DATA AND SAMPLE STORAGE

9.1 Data Collection

The Principal Investigator(s) will oversee how the data are collected, entered, and protected. All study data will be collected by the clinical study staff using designated source documents and entered onto the appropriate electronic case report forms (eCRFs). All study data must be verifiable to the source documentation. All source documents will be kept in a locked facility at the clinical sites and remain separate from participant identification information (name, address, etc.) to ensure confidentiality. All data with participant identifiers will be kept in a locked facility and/or encrypted files. Source documentation will be available for review to ensure that the collected data are consistent with the eCRFs.

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

All research samples will have a unique identifier. The PIs 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-LS and 10-1074-LS administration
- Documentation of any existing conditions or past conditions relevant to eligibility
- Reported laboratory results
- All adverse events
- Concomitant medications
- Reported unsolicited and solicited adverse events

9.2 Quality Control and Quality Assurance

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

10 RECRUITMENT AND ADVERTISING

Both men and women, > 18 years of age 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.

- **RU Site:**

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

The CRSO will conduct telephone screenings of selected Volunteer Repository members, and of volunteers who call 1-800-RUCARES, to facilitate screening efficiently. Based on IRB approved eligibility criteria, potentially eligible candidates pre-screened by CRSO staff will be referred to the study coordinator/investigator for further evaluation.

In addition, referrals are expected through existing collaboration between Rockefeller and the Montefiore Medical Center AIDS Center and the Clinical Core of the Einstein-Rockefeller-CUNY CFAR.

- **Cornell (WCMC) Site:**

Recruitment fliers will be placed in the Weill Cornell Clinical Trials Unit, and interested participants will contact study investigators. Approximately 2,500 patients are followed at the two clinic sites. Providers will refer newly diagnosed individuals who choose not to initiate ART or people who have fallen out of care or have had lapses in ART coverage. The site will also engage with a large network of providers who refer patients for clinical trials, and pursue direct to advertising to potential participants through social media, online and print media.

- **UPENN Site:**

At the University of Pennsylvania Health system approximately 2,000 patients receive HIV care, and 150 new HIV-infected patients are seen each year. The site has an extensive network of referrals from the community (Philadelphia FIGTH, the Partnership and the Health Centers of the city) as well as a dedicated group that does outreach for research projects in collaboration with the Penn CFAR.

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10.1 Participant Retention

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

11 POTENTIAL BENEFITS TO PARTICIPANTS

There is no direct benefit to participants participating in this study.

12 POTENTIAL RISKS TO THE PARTICIPANT INCLUDING TO THE FETUS

This study entails moderate risk to study participants since 3BNC117-LS and 10-1074-LS are investigational new drugs with limited human safety data.

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-LS and 10-1074-LS. Passive administration of anti-HIV-1 antibodies has been evaluated in humans in the past, including the parental 3BNC117 and 10-1074 antibodies. Both 3BNC117-LS and 10-1074-LS are undergoing first-in-human testing. As observed with other monoclonal antibodies, anti-HIV-1 antibodies were generally safe and well-tolerated and most adverse events observed were transient malaise/fatigue and headache.

- Immunologic symptoms such as listed below are possible with administration of a mAb and will be considered adverse events of interest. Potential allergic-type reactions during and immediately following the administration of 3BNC117-LS and 10-1074-LS will be carefully monitored.
    - Constitutional symptoms, such as fever, rigors/chills;
    - Infusion site reaction/extravasation changes, pruritus, urticaria, erythema, desquamation, ulceration;
    - Serum sickness like syndromes as evidenced by fever, rash, arthralgia, arthritis, nephritis;
    - Deposition of immune complexes in the kidneys leading to renal insufficiency;
    - Anaphylaxis; Adult Respiratory Distress Syndrome, bronchospasm/wheezing;
    - Cytokine release syndrome/ acute infusion reaction.
- 3BNC117-LS and/or 10-1074-LS-resistant viral strains might be selected following administration of 3BNC117-LS with 10-1074-LS. Development of antibody resistance might limit the future use of these mAbs and other mAbs targeting the same HIV-1 envelope epitopes by the study participant, if they are licensed for clinical use.
- In a tissue cross-reactivity (TCR) study performed in human tissues, 3BNC117 stained rare cells in the conjunctival recesses, and 10-1074 stained the cytoplasm of nerve cells in the optic nerve of the eye. In vivo GLP toxicology studies performed in rats with 3BNC117 and

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10-1074, alone and in combination, did not show toxicity in ocular tissues. Moreover, these tissue binding findings were not reproduced in repeat TCR studies comparing the unmodified with the LS variants.

In humans, approximately 6% of participants enrolled in 3BNC117 trials reported mild ocular complaints (such as pruritus, conjunctival erythema, increased lacrimation, blurry vision) during study follow up of 6 to 12 months. In all instances, symptoms resolved without specific treatment, and evaluations by an ophthalmologist at 1 or 5 months after 3BNC117 administration did not reveal changes from baseline. It remains unclear if these symptoms were related to 3BNC117 infusions. Two ocular symptoms were reported during 10-1074 studies (grade 1, dry eyes and diplopia), and follow up ophthalmologic exams did not reveal abnormalities or changes from the baseline exams. A temporal relationship between time of 3BNC117 and/or 10-1074 administrations and the occurrence of ocular complaints is not clear at this time To date, only 1 out of 39 participants reported an ocular AE in the studies of 3BNC117-LS alone or in combination with 10-1074-LS. This was grade 1 ocular pruritus, which occurred 3 days post-infusion and resolved 1 day later.

Although binding to ocular tissues was not observed in TCR studies with the LS variants of 3BNC117 and 10-1074, participants will undergo a baseline ophthalmologic evaluation and will be monitored closely and evaluated by an ophthalmologist after mAb administration if ocular complaints occur.

- Transient elevations in total bilirubin have been observed following 3BNC117 dosing. Typically, these are isolated laboratory abnormalities of grade 1 severity that resolve within a few weeks without need for specific treatment. A causal relationship has not been determined but bilirubin levels will be followed closely during study follow up.

- In the cross-reactivity study in human tissues with 10-1074 and 10-1074- LS staining in the epithelium of the pituitary adenohypophysis and follicular epithelium in the thyroid were observed. Staining was cytoplasmic in nature, and therefore considered of low toxicologic concern. However, TSH, T3, and free T4 will be measured at study week 0 and week 4, and additional work up pursed if indicated.

- 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 the administration of 3BNC117-LS with 10-1074-LS would have in a fetus or unborn child are unknown.

- Participants may engage in increased risk taking after receiving anti-HIV-1 mAbs. One to one counseling will be routinely performed.

13 PROCEDURES TO MINIMIZE RISK

- With any new investigational drug, there is a possibility of totally unexpected side effects. On the day of 3BNC117-LS and 10-1074-LS administration, participants will be observed for one hour after administration. The clinical sites are equipped for providing emergency medical interventions in the unlikely event of acute allergic or other reactions. In case of an emergency, after stabilization of the participant, he/she will be transferred to a tertiary care center for specialized medical care.

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- Participants will have regularly scheduled visits to the outpatient clinic and routine safety laboratories.

- Participants will be closely monitored for the development of symptoms of ocular disease (such as blurry vision, increased lacrimation, redness, dryness, pain) and the study investigators will perform a directed exam of the eyes. If participants develop symptoms or signs of ocular disease, they will be referred to an ophthalmologist for diagnosis and management. These evaluations will be performed at no cost to the participant.

- HIV-1 RNA levels and CD4+ T cell counts will be monitored during the study. Participants will be advised and encouraged to start ART within 4 weeks of receiving 3BNC117-LS and 10-1074-LS infusions. ART may be initiated sooner if: VL fails to decrease by >0.5 $\log_{10}$ copies/ml within 2 weeks of antibody infusions, VL increases > 0.5 log10 copies/ml between weekly measurements or significant T-cell decline (confirmed CD4+ T cell count < 200 cells/μl) is noted. ART will be initiated in collaboration with the participant's HIV primary care physician. ART will not be provided by the study.

- Females of childbearing potential and who participate in sexual activity that might lead to pregnancy will be advised to use two reliable forms of contraception from 10 days prior to and six months after 3BNC117-LS and 10-1074-LS administration. In addition, a pregnancy test will be performed at screening, on the day of mAb administration, 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 10 days prior to and six months after 3BNC117-LS and 10-1074-LS administration. Condoms will be provided. Safer sex counseling will be provided for the entire duration of the study.

- To minimize risks associated with phlebotomy, blood drawing will be performed by experienced phlebotomists under aseptic conditions. Subjects will be closely monitored for signs and symptoms of anemia.

- Participants will have regularly scheduled visits to the site outpatient clinics and routine safety laboratories will be checked according to the Time of Events Schedule (**Appendix A**).

- Adverse events will be monitored and graded using the DAIDS AE Grading Table, corrected v2.1. The CTCAE v5.0 grading scale will be used for reporting and grading adverse events related to infusion reactions and cytokine release syndromes in all groups. All toxicity tables are included in **Appendix B**.

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

- Safety monitoring at each site will be conducted by the study investigators, by an external Study Monitoring Committee (SMC), and by the International AIDS Vaccine Initiative (IAVI). The proposed study will be reviewed by a centralized IRB. The Rockefeller University will perform the initial review and will follow progress through annual reports and by immediate notification of serious adverse events. The local IRBs at WCMC and UPENN will follow progress through annual reports and by immediate notification of serious adverse events. Any serious and unanticipated adverse events will be immediately reviewed by the study investigators. Site investigators will notify the local IRB and the sponsor at the RU within 2 working days from the investigators being made aware of the event. The RU sponsor will notify the FDA, per 21 CFR 312, for serious adverse events deemed at least possibly related

to the study products. The SMC will be available to the investigators for consultation and review of severe adverse events if needed.

14 ALTERNATIVE METHODS OR TREATMENTS

HIV-infected individuals who are off ART at the time of screening may choose to start ART immediately, instead of participating in the study.

15 DATA AND SAFETY MONITORING PLAN

This is a phase 1 study of two investigational products, which exposes study participants to "moderate risk". A Study Monitoring Committee (SMC) will be established to monitor the study.

15.1 Safety Monitoring Committee

The purpose of the Safety Monitoring Committee (SMC) is to provide an ongoing assessment of participant safety during the conduct of the study. The SMC will consist of three independent individuals who have no relationship to the Principal Investigator and Co-Investigators involved in the trial, and one non-voting member from DAIDS. No member of the SMC will have any direct responsibility for the clinical care of study participants. 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 investigator (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. Dr. Pat Fast, from the International AIDS Vaccine Initiative (IAVI) can be invited to participate in SMC meetings and to comment on study occurrences, as the medical monitor for the study.

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

Magdalena Sobieszczyk, MD, MPH
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Areas of expertise: clinical evaluation of antiretrovirals

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

The SMC will be asked to review study safety data on an interim basis and in the following scenarios:

1. Grade 3 solicited and unsolicited adverse events judged by the principal investigator or designee to be possibly, probably or definitely related to 3BNC117-LS and/or 10-1074-LS.

2. Grade 3 laboratory adverse events confirmed on retest and judged by the principal investigator or designee to be possibly, probably or definitely related to 3BNC117-LS and/or 10-1074-LS.

3. The investigator will report any “late occurring” DLT (i.e., a DLT occurring after 12 weeks of dosing) to the SMC. The investigators and SMC will mutually assess this information, along with safety from other participants, to determine whether a change to study conduct is warranted.

4. If two or more grade 3 adverse events, deemed probably or definitely related to the study drugs occur, no additional administration of the investigational products will take place pending a Safety Monitoring Committee (SMC) review. The SMC will provide a recommendation regarding subsequent enrollment in the study.

5. If a grade 2 ophthalmic AE, judged to be at least possibly related to 3BNC117-LS and/or 10-1074-LS occurs, or any grade 3 or 4 ophthalmic AE occur, regardless of causality assessment, no additional administration of the investigational product will take place pending a Safety Monitoring Committee (SMC) review. The SMC will provide a recommendation regarding subsequent enrollment in the study.

6. SAEs, which are deemed possibly, probably or definitely related to 3BNC117-LS and/or 10-1074-LS. by the principal investigator or designee, 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, grade 3 or higher, and judged as possibly, probably or definitely related to the administration of 3BNC117-LS and/or 10-1074-LS by the principal investigator or designee, no additional administration of the investigational product(s) will take place pending a review by at least two members of the SMC. Following this review, the SMC will make a

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recommendation to the principal investigator regarding the continuation of investigational product administration.

The occurrence of such adverse events will not result in a study pause, unless it is judged by the principal investigator or designee that the risk/benefit ratio of the study has changed such that risk of currently enrolled or future participants has increased; or unless recommended by the IRB, SMC, or FDA.

7. If, at any time, a fatal, life-threatening or permanently disabling SAE with a suspected causal relationship to 3BNC117-LS and/or 10-1074-LS occurs, no further administration of the investigational product(s) will occur until a consensus plan forward has been approved by investigators, SMC, the IRB and the FDA.

All updated versions of the protocol, investigator's brochure, and related documents will be provided to the SMC members and the DAIDS Medical Officer (MO) and DAIDS Program Officer (PO). The review of trial data by the SMC will take place at least annually. Prior to data review, the study team will provide the SMC with updated records of all adverse events (AEs) of a grade 2 or higher.

The SMC will acknowledge receipt of annual reports and will indicate if there are concerns with the continuation of the study. The SMC will provide a written report to the sponsor at the RU and the site PIs after each evaluation. The PIs in turn will distribute these reports to the study team and the local IRBs and the DAIDS MO and DAIDS PO.

15.2 Safety Review

Participants will be closely monitored for 1 hour after the 10-1074-LS infusion at the study sites. The study sites are equipped for providing emergency medical interventions in the unlikely event of acute allergic or other reactions. The clinical trial units at all sites are equipped with crash carts for immediate medical care, should the need arise.

In case of an emergency at RUH, after stabilization of the volunteer, he/she will be transferred to the neighboring tertiary care center, New York Presbyterian Hospital (Cornell) for specialized medical care.

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

15.3 Clinical Site Monitoring

Safety monitoring will be conducted by the study investigators, by the external Study Monitoring Committee (SMC) and by the International AIDS Vaccine Initiative (IAVI).

The proposed study will be reviewed by a centralized IRB. The Rockefeller University will perform the initial review and will follow progress through annual reports and by immediate notification of serious adverse events. The local IRBs at WCMC and UPENN will follow progress through annual reports and by immediate notification of serious adverse events. External monitoring will occur at least quarterly and will be conducted by IAVI.

15.4 Adverse Event Classification

The DAIDS AE Grading Table, corrected v2.1 (July 2017) will be used for reporting and grading adverse events. The CTCAE v5.0grading scale will be used for reporting and grading adverse events related to infusion reactions and cytokine release syndromes. All toxicity tables are included in **Appendix B**.

15.5 Reporting Adverse Events

All adverse events will be reported to the local IRBs at and the SMC at least annually. Serious Adverse Events, (SAEs) will be reported to the local IRBs, SMC, and to the sponsor at The Rockefeller University within two working days of identification of the SAE. The RU sponsor will report SAEs considered at least possibly related to the study products will be reported directly to the FDA, per 21 CFR 312.

15.6 Reporting Unanticipated AEs

Unanticipated Adverse Events (UAEs) will be reported to the local IRBs and SMC. UAEs that are related and greater than moderate severity must be reported to the local IRBs, SMC, and to the sponsor at The Rockefeller University within two working days of identification of the UAE. UAEs considered at least possibly related to the study products will be reported by the RU sponsor to the FDA, per 21 CRF 312.

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

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

15.8 Toxicity Management and Stopping Rules

A dose limiting toxicity (DLT) will be defined as any adverse event of Grade 3 or greater toxicity, if the study investigators recognize a probable or definite attribution to 3BNC117-LS and/or 10-1074-LS mAb. Clinically significant grade 3 laboratory abnormalities must be confirmed by a repeat test, obtained as soon as possible following the initial result.

Investigators will promptly notify the PI and Sponsor at The Rockefeller University in the event of any DLT.

In the case of two or more DLTs, further enrollment or infusions of 3BNC117-LS and/or 10-1074-LS will not occur until investigators and SMC review the events and all available safety data. Enrollment will stop but participants will continue to be monitored by the study investigators. The SMC members will make a recommendation to the principal investigators regarding the continuation of the trial.

15.9 Other Disease Events

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

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stable.

15.10 Critical Event Reporting

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

16 CLINICAL TRIAL REGISTRATION

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

17 STUDY DISCONTINUATION

The study may be discontinued at any time by the local IRBs, NIAID, the FDA or other government entities as part of their duties to ensure that research participants are protected. In the event that the study is discontinued, 3BNC117-LS and 10-1074-LS infusions will be halted and participants will be followed to ensure resolution of all adverse events. It is not applicable in this study to have participants continue therapy elsewhere as the investigational products do not provide the participants any direct benefit. In addition, the study does not have placebo recipients.

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