CLINICAL TRIAL PROTOCOL: CP-MGD014-01 PROTOCOL AMENDMENT 6

Study Title:	A Phase 1 Study to Evaluate the Safety, Immunologic and Virologic Responses of MGD014 Therapy in HIV-Infected Individuals on Suppressive Antiretroviral Therapy
Study Number:	CP-MGD014-01
Study Phase:	Phase 1
Product Name:	MGD014
Product Number:	MGD014
IND Number:	
UNC IRB Number:	18-0608
Contract Site Principal Investigator:	
Protocol Principal Investigator:	
Sponsor:	MacroGenics, Inc. 9704 Medical Center Drive Rockville, MD 20850 301.251.5172
Sponsor's Medical Monitor:	9704 Medical Center Drive Rockville, MD 20850 301.251.5172

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

SIGNATURES

Study Title: A Phase 1 Study to Evaluate the Safety, Immunologic and Virologic Responses of MGD014 Therapy in HIV-Infected Individuals on Suppressive Antiretroviral Therapy

Study Number: CP-MGD014-01

This clinical study protocol has been approved by:

Signed: ***See Appended Electronic Signature Page*** Date: _____

Medical Monitor
Executive Clinical Research Director
MacroGenics, Inc.
9704 Medical Center Drive
Rockville, MD 20850

Signed: ***See Appended Electronic Signature Page*** Date: _____

Executive Director, Biostatistics
MacroGenics, Inc.
9704 Medical Center Drive
Rockville, MD 20850

Signed: ***See Appended Electronic Signature Page*** Date: _____

University of North Carolina at Chapel Hill
Division of Infectious Diseases
120 Mason Farm Rd
2049G Genetic Medicine Bldg.
Chapel Hill, NC 27599

Signed: ***See Appended Electronic Signature Page*** Date: _____

Associate Professor of Medicine
Division of Infectious Diseases

Medical Director, UNC HIV Cure Center
University of North Carolina at Chapel Hill

Signed: ***See Appended Electronic Signature Page*** Date: _____

Professor
Department of Biostatistics
University of North Carolina at Chapel Hill
3107c McGavran-Greenberg Hall
Chapel Hill, NC 27599

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACTG	AIDS Clinical Trials Group
ADA	anti-drug antibody
ADCC	antibody dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral drug
AST	aspartate aminotransferase
AUC	area under the curve
BBB	blood-brain-barrier
BLT mice	bone marrow, liver, and thymus mice
BP	blood pressure
CD3	cluster of differentiation 3
CFAR	Center for Aids Research
CHSLC	CFAR HIV/STD Laboratory Core
CI	confidence interval
CKD	chronic kidney disease
CL	clearance
CLIA	clinical laboratory improvement amendments
Cmax	maximum serum concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRS	cytokine release syndrome
CSF	cerebral spinal fluid
CSR	clinical study report
CTL	cytotoxic T lymphocytes
CTRC	Clinical and Translational Research Center
DAIDS	Division of AIDS
DLT	dose limiting toxicity
EAE	expedited adverse event reporting
EC_{50}	half maximal effective concentration
E/CIA	enzyme or chemiluminescence immunoassay
E:T	effector to target (cell ratio)
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay

env	envelope; envelope in this document, denotes specifically the HIV-1 env glycoprotein
FcγRs	Fc-gamma receptors
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
gp 41	glycoprotein 41
gp 120	glycoprotein 120
gp 160	glycoprotein 160
HCV	hepatitis C virus
HIV	human immunodeficiency virus, in this document the virus denotes specifically HIV-1
HIV-1 env	human immunodeficiency virus 1 envelope
HLA	human leukocyte antigen
IB	investigational brochure
IC	informed consent
ICFs	informed consent forms
ICH	International Conference on Harmonization
IDS	Investigational Drug Services
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
IgG	immunoglobulin G
IL-2	interleukin-2
IL-4	interleukin-4
IL-5	interleukin-5
IL-6	interleukin-6
IL-10	interleukin-10
IMC	infectious molecular clones
INR	international normalized ratio
IRB	Institutional Review Board
IRE	immediately reportable event
IRR	infusion related reaction
IUPM	infectious units per million
IV	Intravenous(ly)
kDa	kilodalton

K+	potassium
Kg	kilogram
LDH	lactate dehydrogenase
LRA	latency reversing agent
LTFU	lost to follow up
LUM	luminescence
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MFI	mean fluorescence intensity
MHC	major histocompatibility complex
µg	microgram
µl	microliter
mL	milliliter
MRT	mean residence time
MTD	maximum tolerated dose
NCA	noncompartmental analysis
NCI	National Cancer Institute
ng	nanogram
nM	nanomolar
NNRTI	non-nucleoside reverse transcriptase inhibitors
NSAID	non-steroidal anti-inflammatory drug
NIH	National Institutes of Health
NOAEL	no-observed-adverse-effect level
OBD	optimal biologic dose
PBMC	peripheral blood mononuclear cell
pg	picogram
PHI	personal health information
PID	participant identifier
PD	pharmacodynamics
PI	principal investigator
PK	pharmacokinetics
PLWH	people living with HIV

PO	oral administration
POCT	point of care testing
PQC	product quality complaint
PT	preferred term
Q2W	once every 2 weeks
QVOA	quantitative viral outgrowth assay
RBC	red blood cell
RNA	ribonucleic acid
RPR	rapid plasma reagin
RO	receptor occupancy
RSV	respiratory syncytial virus
SAE	serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCA	single copy assay
SHIV	simian human immunodeficiency virus
SID	study-specific identifier
SOC	system organ class
SOP	standard operating procedure
SPR	surface plasmon resonance
SUSAR	suspected, unexpected serious adverse reactions
T_{max}	time to maximal concentration
TCR	T-cell receptor
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
UNC-CH	University of North Carolina at Chapel Hill
US	United States
VOR	vorinostat
V_{ss}	steady-state volume of distribution
VS	vital signs
WOCBP	women of child-bearing potential

1 SYNOPSIS

Sponsor: MacroGenics, Inc.	**IND Number:**
Name of Product: MGD014	
Study Title: A Phase 1 Study to Evaluate the Safety, Immunologic and Virologic Responses of MGD014 Therapy in HIV-Infected Individuals on Suppressive Antiretroviral Therapy	
Study Number: CP-MGD014-01	
UNC IRB Number: 18-0608	**NCT:** 03570918
Study Phase: Phase 1	
Investigator(s)/Centers: The study will be carried out at a single institution in the United States (US) experienced in the conduct of Phase 1, first-in-human (FIH) studies in participants with human immunodeficiency virus (HIV) infection on suppressive antiretroviral therapy (ART).	
Primary Objective(s): Characterize the safety and tolerability of MGD014 administered intravenously (IV) to persons living with HIV (PLWH) maintained on suppressive ART.	
Secondary Objective(s): • Assessment of pharmacokinetics (PK) and immunogenicity (anti-drug antibody [ADA]) of MGD014. • Assessment of serum cytokine levels following MGD014 administration.	
Exploratory Objective(s): • Explore the impact of MGD014 administration on the immunologic response to HIV. • Explore correlations between virologic and immunologic responses to MGD014. • Assess the ability of MGD014 to alter markers of persistent HIV-1 infection.	
Rationale: DART® molecules are bispecific, antibody-based molecules that can bind 2 distinct antigens simultaneously. T cell redirecting DART® molecules, which have binding arms for a selected target antigen and for CD3, are designed to target the antigen-expressing cells for recognition and elimination by CD3-expressing T lymphocytes as effector cells. MGD014, a T cell redirecting DART® molecule developed for the HIV setting, targets HIV-1 infected, envelope (env) glycoprotein-expressing cells for recognition and elimination by T lymphocytes. MGD014 is thus being studied to determine if it could be used as an immunotherapeutic agent to mediate the clearance of HIV-infected CD4 T cells that express env on their surface. In this FIH study, MGD014 will be evaluated as a single agent in PLWH maintained on suppressive ART.	

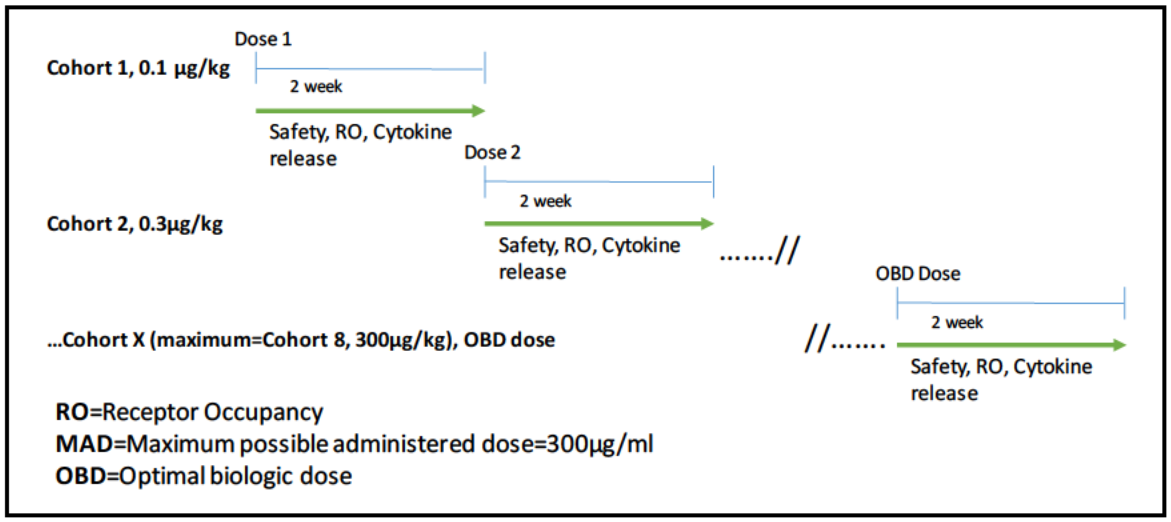
Study Population:

Number of Participants: approximately 26 are anticipated (at least 20 in Dose Escalation Phase (Part 1), and up to 6 in Multi-Dose Cohort Expansion Phase (Part 2). The maximum number of participants to be enrolled in this study is dependent upon the potential need for replacement of participants in Part 1 and/or Part 2.

Study Design:

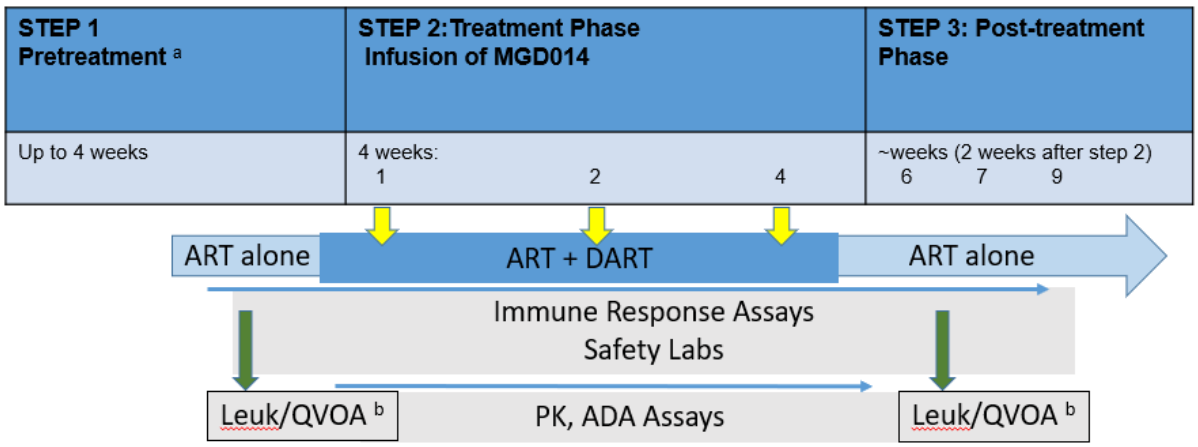
This is a Phase 1, open-label single-center study of MGD014 in PLWH on ART. Eligible participants will be maintained on ART and receive either one infusion (Part 1) or an IV infusion once every 2 weeks (Q2W) for a total of three infusions of MGD014 for 4 weeks (Part 2).

Part 1: Single Ascending Dose. Part 1 is a single ascending dose study with a 1+3 design for the first 2 dose cohorts, and a 3+3 design with staggered accrual for the 6 higher dose cohorts, with an aim of determining the safety, PK, and pharmacodynamics (PD) of ascending doses up to either the Optimal Biologic Dose (OBD) or the maximum administered dose (MAD).



Note: Cohort X represents any cohort number

Part 2: Multi-dose Expansion Cohort. Part 2 is a multi-dose expansion cohort with MGD014 300 mcg/kg administered IV once every 2 weeks (Q2W) for a total of three doses, as determined in Part 1 (which is equal to the MAD).



(a) Screening, eligibility and optional baseline leukapheresis (b) optional leukapheresis post-treatment for frequency of persistent infection of resting CD4 T cells.

Abbreviations: ADA = anti-drug antibody; ART = antiretroviral therapy; Leuk = leukapheresis; PK = pharmacokinetics; QVOA = quantitative viral outgrowth assay.

Main Criteria for Inclusion/Exclusion:

PLWH (18 to 65 years old) on ART with plasma HIV RNA < 50 copies/mL for 24 months prior to enrollment.

Test Product and Mode of Administration:

MGD014 will be supplied by MacroGenics, and administered via 2-hour infusions, a single IV infusion in Part 1, or IV infusion once every 2 weeks for 3 infusions over 4 weeks in Part 2.

Duration of Treatment and Study Duration:

The overall study duration will be approximately 24 months. For each individual participant, study duration will be approximately 10 weeks (Part 1) or 20 weeks (Part 2).

Treatment Schedule and Procedures:

See **Appendix 1**.

Criteria for Evaluation:

Safety Assessments

Safety assessments will be based on medical review of adverse event (AE) reports, the results of vital sign (VS) measurements, electrocardiograms (ECGs), physical examinations, and clinical laboratory tests. The incidence of AEs will be tabulated and regularly reviewed for potential significance and clinical importance.

PK Assessments

- Single-dose and multiple-dose PK parameters for MGD014 may be derived from MGD014 serum concentration versus time data using non-compartmental analysis.

Immunogenicity (ADA) Assessments

- Immunogenicity determination will be based on the determination of titers of ADA in serum over time.

PD Assessments

- Examination of RO (and/or T-cell binding).
- Examination of the ability of MGD014 to impact T cell phenotype (activation and/or exhaustion).
- Characterization of alterations in serum cytokine levels, including but not limited to IL-2, IL-5, IL-6, IL-10, IFN-γ, and TNF-α.

Markers of Persistent HIV-1 Infection (Part 2)

- The frequency of latent infection in resting CD4 T cells by QVOA, as a direct measure of persistent HIV infection.
- Residual low-level HIV-1 viremia by SCA, as evidence suggests that such HIV-1 viremia originates in persistently infected cells, and low-level HIV-1 viremia might be reduced by an augmented antiviral immune response.

2 INTRODUCTION

2.1 Rationale for Study

Despite successful antiretroviral therapy (ART), human immunodeficiency virus (HIV) persists in a latent, transcriptionally quiescent state in rare but persistently infected cells – the latent reservoir. This reservoir is the major obstacle to the eradication of infection and a cure for HIV **[1, 2, 3]**. Following reactivation of HIV-1 with a latency reversing agent (LRA), viral antigens such as envelope (env) may be presented on the surface of the cell, allowing for recognition and clearance of HIV-1. CD8 T cells are the principal effector population responsible for detection and clearance of virus-infected cells **[4, 5]**. However, CD8 T cells in successfully treated (ART suppressed) HIV-infected individuals fail to clear persistent infection; the vast majority of HIV-infected individuals experience rebound of HIV-1 with interruption of ART therapy within a matter of days to weeks **[6]**.

There are several identified challenges to immune-mediated clearance of the latent HIV-1 reservoir, including: 1) the likely low levels of env antigen produced on rare latently HIV-1 infected cells, even following reactivation of HIV-1 with LRAs; 2) the presence of T-cell escape variants in the latent reservoir HIV-1; 3) the low frequency of HIV-specific CD8 T cells and 4) the dysfunctional HIV-specific CD8 T cell response.

There is a strong rationale for use of the MGD014 DART® molecule to co-engage HIV-infected env-expressing cells and CD3 T cells to induce cytolysis of the infected target cells. In brief, MGD014 binds infected target cells through engagement of the cell surface env protein and binds effector cells through the T-cell receptor (TCR)/CD3 complex, independently of the TCR/major histocompatibility complex (MHC) interaction. The close engagement of the env-expressing target cells with the effector T cells promotes T-cell activation and potentiates T-cell mediated cytolytic killing of target cells. DART® molecules have inter-chain disulfide bonds that provide stability and structural compactness; the close positioning of the two binding arms facilitates the formation of stable cell-to-cell contacts between target and effector cells, contributing to a high level of target cell killing [**7**, **8**, **9**]. MGD014 has the potential to overcome the challenges described above for immune-mediated clearance of the latent HIV-1 reservoir, because it is capable of recognizing low levels of env antigen on target cells and can recruit all types of CD3 T cells to serve as effector cells, and thus is not limited by the deficiencies and dysfunction associated with HIV-specific CD8 T cells.

2.1.1 Co-targeting human immunodeficiency virus 1 envelope (HIV-1 env) and CD3

The envelope (env) protein is the only virally-encoded protein expressed on the surface of HIV-1 infected cells and therefore is the primary target for antibodies or antibody-derived molecules capable of redirecting effector cells that mediate cytolytic activity. The env glycoprotein (gp) is produced as a gp160 precursor, which is cleaved by furin to form gp120 and gp41 subunits. The gp120 and gp41 subunits remain in association with each other and assemble into mature 'functional' trimers, although alternate 'nonfunctional' forms of env have also been characterized **[10]**. All env proteins are highly glycosylated. On the cell surface, gp41 subunits are anchored in the membrane, while gp120 subunits are noncovalently bound to the gp41 extracellular domains.

Mature trimers in 'closed' conformations undergo extensive structural rearrangements to form 'open' conformations in response to binding to CD4 [**11**], one of the receptors for virions. Major challenges for utilizing cell surface env antigen as a target are the large diversity of env sequence variants among HIV-1 isolates worldwide and the frequent emergence of escape mutants due to env sequence changes resulting from error-prone reverse transcription of viral RNA genomes.

The anti-HIV env component of MGD014 is based on non-neutralizing monoclonal antibody (mAb) A32, isolated from an individual with HIV-1, that binds to a discontinuous set of gp120 residues located in conserved regions C1-C2, which are extremely highly conserved **[8**, **9**, **12]**. Accordingly, the A32 mAb is broadly reactive with env proteins from diverse HIV-1 isolates, and there are no known resistant escape variants; the implication is that viruses lose fitness when mutations occur in A32 binding residues **[13]**. A32 mAb binding is enhanced by the CD4-inducible conformational changes in the env protein **[14**, **15**, **16**, **17]**. A32 mAb binds inefficiently to env on HIV-1 virions **[18]**, which are comprised of mature env trimers in 'closed' conformation, but binds to env on surfaces of infected cells and is one of the most potent and broadly reactive antibodies to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) against env-expressing target cells [**12**]. The cell surface targets for A32 may consist of env trimers in the CD4-induced 'open' conformation or nonfunctional forms of env, which may be the predominant ones on infected cells [**10**, **19**, **20**, **21**, **22**, **23**, **24**]. The A32 mAb epitope is the earliest epitope known to be expressed on the surface of infected cells during the process of syncytia formation [**23**] or following tier 2 HIV-1 infection [**24**]. The anti-HIV env arm of MGD014 retains the binding properties of the parental A32 mAb.

CD3 is an invariant complex of proteins required for expression of and signaling through the antigen-specific TCR on T cells. CD3 consists of a protein complex and is composed of four distinct chains: a CD3γ chain, a CD3δ chain, and two CD3ε chains. These chains associate with the TCR and the ζ-chain (zeta-chain). The TCR, ζ-chain, and CD3 molecules together constitute the TCR complex, which is responsible for signal transduction in T cells, including activation during immune response [**25**, **26**]. CD3 is expressed almost exclusively by T cells and is present in all stages of T-cell development [**27**]. The CD3 arm of MGD014 is derived from hXR32, a humanized anti-CD3ε mAb.

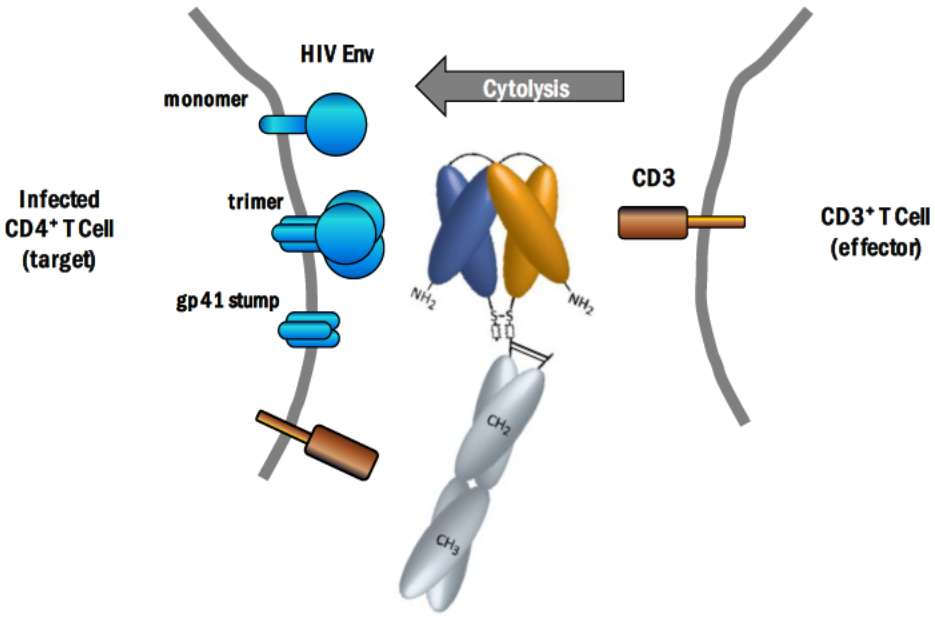
Through co-targeting CD3 and A32, the cytolytic activity of polyclonal CD3 T cells can be redirected, in an MHC-independent manner, against the env-expressing infected cells. MGD014 may thus be able to circumvent or overcome the aforementioned obstacles to clearance of the latent reservoir. Studies conducted with the predecessor of MGD014 (HIV_{A32} x CD3 [basic format], a DART® molecule identical to MGD014, except it lacks the Fc region for extended serum half-life], demonstrated the ability to mediate potent redirected killing activity (nanomolar EC_{50} values) in vitro against CD4 cells infected by diverse infectious molecular clones (IMC) of HIV [**8**, **9**]. The HIV_{A32} x CD3 molecule targets a highly conserved region of the env antigen and does not rely on pre-existing HIV-specificity in the effector cells, but rather recruits from all CD3 effector cells. In support of this, in vitro studies demonstrated that HIV_{A32} x CD3 (basic format) was capable of redirecting T cells against both autologous targets infected with diverse autologous reservoir HIV-1 as well as against latently infected resting CD4 T cells obtained from ART-suppressed PLWH following exposure to the LRA vorinostat (VOR) [**8**]. As summarized in the following sections, MGD014 retains these activities.

2.2 Background on MGD014

MGD014 (also referred to as HIV$_{A32}$ x CD3) is a human immunodeficiency virus-1 envelope (HIV-1 env) x CD3 DART molecule. DART® molecules are bispecific, antibody-based molecules that can bind 2 distinct antigens simultaneously. MGD014 is designed to target HIV-1 infected, env-expressing cells for recognition and elimination by CD3-expressing T lymphocytes as effector cells. The anti-HIV-1 env component of MGD014 is derived from A32, a nonneutralizing mAb that recognizes conserved regions (C1-C2) of the gp120 subunit of HIV-1 env and is broadly reactive with env from diverse isolates of HIV-1. The anti-human CD3 component of MGD014 is derived from mAb hXR32, which is cross-reactive with similar affinity to cynomolgus monkey CD3. To prolong circulating half-life, MGD014 contains a human IgG1 Fc domain that has been mutated to greatly reduce or eliminate effector function via binding to Fc-gamma receptors (FcγRs) and complement, while retaining binding to the neonatal Fc receptor to take advantage of the immunoglobulin G (IgG) salvage pathway mediated by this receptor.

A schematic depicting MGD014 structure and mechanism of action is shown in **Figure 1**.

Figure 1 **MGD014 Structure and Mechanism for Redirected T-cell Killing of HIV-1 env-expressing Target Cells**



The anti-CD3 arm (orange) of MGD014 binds to CD3 at the surface of T cells and the anti-HIV env arm (blue) binds to env antigen at the surface of HIV-infected CD4 T cells. Cell surface env antigen may be in the form of functional mature trimers or nonfunctional variant forms such as cleaved or uncleaved gp160 monomers or gp41 stumps [28]. MGD014-mediated co-engagement of target and effector cells results in activation of effector cell cytolytic responses and target cell killing.

2.2.1 MGD014 Nonclinical Pharmacology

A brief summary of MGD014 nonclinical pharmacology data is provided below; please reference the **MGD014 Investigator's Brochure (IB)** for a more detailed description.

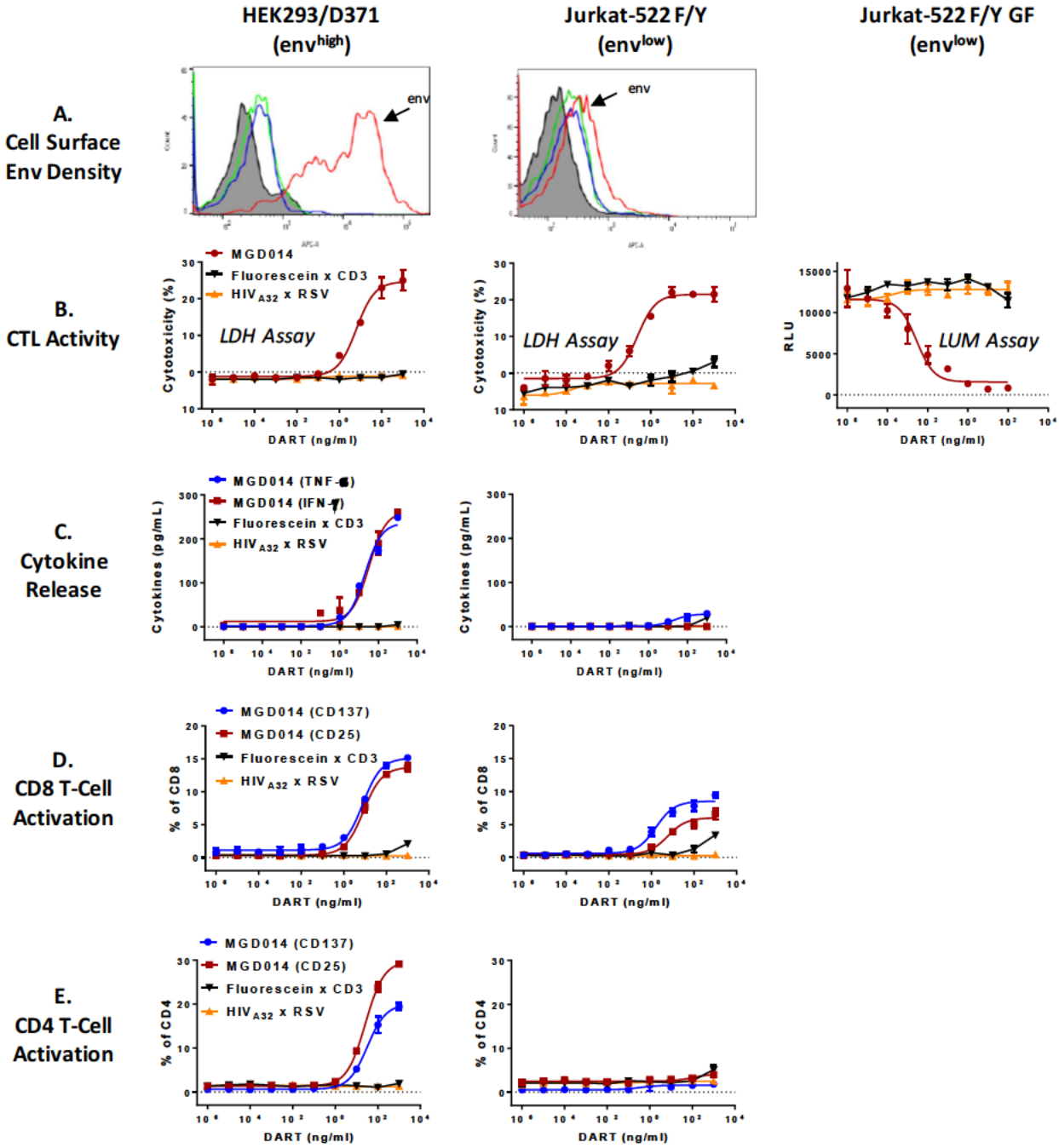
Binding of MGD014 to its target antigens, HIV-1 env and human CD3, was characterized in vitro by both surface plasmon resonance (SPR) analysis and flow cytometry. SPR analysis using recombinant soluble human antigens revealed MGD014 binds with K_D values of approximately 6.9 nM to CD3 and with subnanomolar (<1 naM) K_D values to HIV-1 env. Like the parent A32 antibody, MGD014 binding to HIV-1 env was enhanced in the presence of soluble CD4 protein, which is known to trigger conformational changes in HIV-1 env proteins. Flow cytometry analyses confirmed the ability of MGD014 to bind natively expressed cell surface CD3 on human T cells, as well as to cell surface HIV-1 env on human cell lines engineered to express HIV-1 gp140 or gp160 or on human CD4 cells infected by HIV-1 isolates. However, like the parental A32 antibody, MGD014 was inefficient at binding HIV-1 virions, indicating that MGD014 selectively recognizes the env antigen structures expressed on the surface of HIV-1 infected cells.

Consistent with its bispecific binding properties and intended mechanism of action, MGD014 efficiently mediated the cytolysis of the env-expressing target cell lines in the presence of CD8 T cells as effector cells. MGD014 redirected T-cells to mediate the killing of human cell lines expressing env antigen at high level (HEK293/D371) or low level (Jurkat-522 F/Y or Jurkat-522 F/Y GF), respectively (**Figure 2 A, B**). While maximal cytolysis (E_{max}) was 22-25% for env^{high} and env^{low} target cells by lactate dehydrogenase (LDH) release assay, E_{max} was >90% for env^{low} target cells by luminescence (LUM) assay. The LDH assay tends to yield low maximal percent cytolysis values, because LDH may be released from effector cells as well as target cells and lead to higher assay background. By contrast, the LUM assay yields high maximal % cytolysis because it is a more sensitive and specific assay but can only be applied when target cells are engineered for reporter gene expression (Jurkat-522 F/Y GF cells were engineered to express a luciferase reporter gene). The control DART® molecules lacking one of the specificities (fluorescein x CD3 or HIV_{A32} x respiratory syncytial virus (RSV) did not mediate cytolysis, confirming that co-engagement of cells expressing the different antigen targets is required for cytotoxic T lymphocyte (CTL) activity. When effector cells were from the same donor, the EC_{50} values for MGD014-mediated CTL activity against the env^{high} and env^{low} target cell lines were 6.4-6.6 and 0.7-1.0 ng/mL, respectively. Thus, low levels of cell surface env protein expression are sufficient for potent MGD014-mediated killing activity.

MGD014-dependent killing of the env^{+} cell lines was associated with concomitant dose-dependent activation of T cells, as evidenced by upregulation of the activation markers CD25 and CD137 in both CD4 and CD8 T-cell subsets, and with concomitant induction of cytokine production, as evidenced by induction of the release of interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) (**Figure 2 C, D, E**). However, only low levels of CD8 T-cell activation, no CD4 T-cell activation and just trace levels of cytokines and were observed in the presence of the Jurkat-522 F/Y (env^{low}) target cells. The data indicate that MGD014-dependent T-cell activation and cytokine release, but not MGD014-dependent cytolytic activity, was highly dependent upon on the density of env antigen on the target cells. Moreover, data obtained with a fluorescein x CD3 control DART® molecule (which lacks the anti-HIV env specificity) confirm

that monovalent DART® molecule binding to CD3 triggered minimal T-cell activation or cytokine release. These in vitro findings suggest a low probability for T-cell activation and cytokine release when MGD014 is to be administered to HIV participants on ART, because the levels of env antigen expressed by CD4 cells infected by a transmitted/founder HIV-1 isolate are comparable to those expressed by the env^{low} cells (**Figure 3**).

Figure 2 **Impact of Target Cell HIV-1 env Antigen Density on MGD014-dependent Cytolytic Activity, Cytokine Release and T-cell Activation**

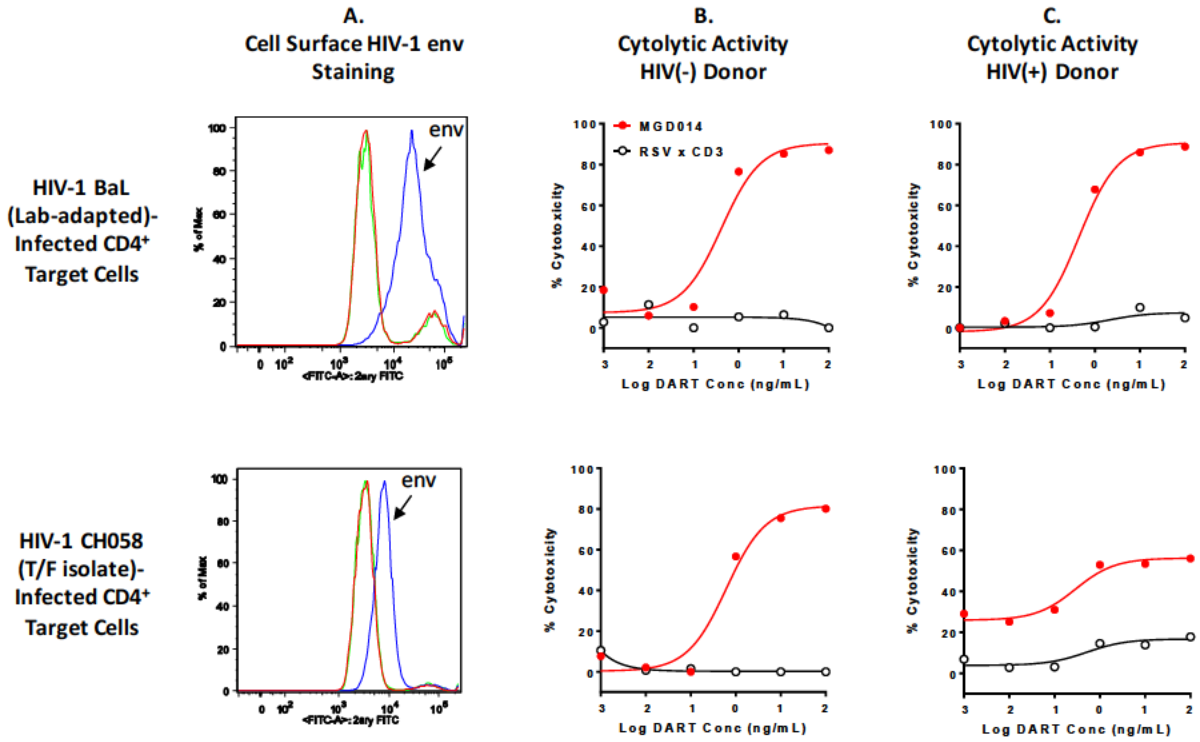


(A) Levels of HIV-1 env antigen expression on HEK293/D371 (env^{high}) and Jurkat−522 F/Y (env^{low}) cell lines measured by flow cytometry with A32 mAb (red). Comparison of baseline-corrected mean fluorescent intensity (MFI) values reveals an ~90-fold difference in env antigen density. Other traces are for negative control mAb (blue), secondary labeled antibody alone (green) and unstained cells (filled). (B) MGD014-mediated killing of HEK293/D371 and Jurkat−522 F/Y cells measured by LDH (lactate dehydrogenase) assay. The target cells were incubated with human CD8 T cells at an E:T ratio of 10:1 (10% target cell frequency).

Control DART® molecules were fluorescein x CD3 and HIV_{A32} x RSV. MGD014 EC_{50} values were 6.4 ng/mL and 0.23 ng/mL with the HEK293/D371 and Jurkat−522 F/Y target cells, respectively. Also shown is MGD014-mediated killing of Jurkat-522 F/Y GF cells (Jurkat-522 F/Y cells engineered to express a luciferase reporter gene), thus allowing the viable env-expressing target cells to be specifically and more sensitively quantitated by luminescence (LUM) assay. Maximal cytolysis levels measured by the LUM assay are substantially higher than those measured by the LDH assay, but the EC_{50} values from both assay methods are comparable. (C) MGD014-mediated release of IFN−γ and TNF−α under the same conditions as in panel B. (D, E) MGD014-mediated induction of activation markers CD25 and CD137, measured by flow cytometry, on CD8 T cells (D) or CD4 T cells (E) under the same conditions as in panel B. All experiments, except the one conducted with Jurkat-522 F/Y GF cells, were conducted with effector cells from the same HIV-uninfected, healthy donor.

Importantly, MGD014 mediated the redirected killing of CD4 target cells infected by subtype B HIV-1 IMCs, including ones derived from transmitted/founder HIV-1 isolates, in the presence of autologous CD8 cells as effector cells (**Figure 3**). Resting CD8 effector cells from both uninfected (seronegative) donors and from HIV-1 infected (seropositive) donors on ART were similarly effective in mediating MGD014-dependent redirected killing of the autologous HIV-1 IMC-infected CD4 target cells. With cells from uninfected donors, E_{max} (maximum cytolysis) and EC_{50} values (mean ± standard deviation) were 72 ± 14% and 1.4 ± 1.7 ng/mL, respectively. Similarly, with cells from HIV-infected donors on ART, E_{max} and EC_{50} values were 67 ± 24% and 2.1 ± 4.5 ng/mL, respectively. There were no statistically significant differences in MGD014-mediated cytolytic activity with cells obtained from uninfected or HIV-infected donors.

Figure 3 **HIV-1 env Antigen Expression on Virus-infected CD4 Target Cells and MGD014-dependent Cytolytic Activity**



(A) Levels of HIV-1 env antigen expression on surface of human CD4 cells infected by HIV-1 infectious molecular clones (IMCs) for BaL (subtype B, laboratory-adapted isolate) and CH058 (subtype B, transmitted/founder isolate) were measured by flow cytometry with A32 mAb (blue lines) compared to controls, negative control mAb (green) and 2nd antibody alone (red). Mean fluorescence intensity (MFI) values for A32 staining were 24850 for BaL and 7967 for CH058 and 3235-3415 for controls. Comparison of baseline-corrected MFI values revealed an ~5-fold difference in env antigen density. (B, C) Representative data for MGD014-dependent cytolytic activity against HIV-infected target cells. Titrated concentrations of MGD014 or RSV x CD3 control DART molecule incubated with CD8 cells (effector cells) and autologous CD4 cells infected by HIV-1 IMCs for BaL or CH058 (target cells) at E:T ratios of 33:1 for 24h and the cytolysis of the HIV-1 infected target cells was measured by declines in luciferase luminescence. The CD8 effector cells and the autologous in vitro infected CD4 target cells were prepared from cryopreserved PBMCs obtained from (B) normal (seronegative) donors or (C) HIV-infected (seropositive) donors maintained on ART.

The in vivo activity of MGD014 was evaluated in humanized bone marrow-liver-thymus (BLT) mice infected by HIV-1 (JR-CSF isolate) and treated with ART for 3-4 weeks to suppress plasma HIV-1 viremia. In the first experiment, MGD014 (IV administration, 2 doses, 1-week apart) reduced the levels of residual HIV-1 RNA in the tissues (spleen, lung, liver, lymph nodes, thymic remnant, blood) of HIV-infected animals suppressed with ART. When compared to the RSV x CD3 control molecule, animals treated with MGD014 exhibited an average decrease of approximately 3-fold in the levels of cell-associated viral RNA in blood and tissues after only two DART® molecule doses. In the second experiment, MGD014 delayed and transiently inhibited viral rebound in HIV-infected animals suppressed with ART and then withdrawn from ART. In this study, MGD014 was co-administered with ART for 4 weeks, then administered for 3 additional weeks in the absence of ART. At 7-days post ART interruption, mean HIV-1 viral load

levels were decreased by more than 27-fold in animals treated with MGD014 compared to those treated with the RSV x CD3 control molecule. By 14-days post ART interruption, however, the mean viral loads in the MGD014- and RSV x CD3-treated groups were not distinguishable. Thus, while treatment with MGD014 inhibited and delayed HIV-1 rebound following ART interruption, the effect was transient and did not reduce the eventual magnitude of the HIV-1 viral load response. The data suggest that the administered MGD014 doses were not sufficient to fully clear the HIV-1 infected cells, especially after HIV-1 replication began to increase exponentially. It is important to note, however, that the abundance and characteristics of the residual infected cell populations harboring active or latent HIV-1 in the HIV-infected humanized mouse model following short-term (8-week) ART therapy are likely to be very different from those present in HIV-infected individuals maintained on ART for many years.

The human IgG1 Fc region incorporated into MGD014 has been mutated to greatly reduce or eliminate FcγR and complement binding and hence Fc-mediated effector functions. SPR analysis demonstrated that MGD014 binding to FcγRs, including CD16A (FcγRIIIa), CD32A (FcγRIIa), CD32B (FcγRIIb), and CD64 (FcγRI), was greatly reduced compared with a control DART protein with a wild-type human IgG Fc. MGD014 binding to complement (C1q) was not detected. Importantly, no ADCC or CDC activity was observed for MGD014. These data demonstrate that the mutated human IgG1 Fc domain incorporated into MGD014 functionally eliminates undesired binding to FcγRs and complement. Furthermore, no hemolysis was observed following treatment of either purified red blood cells (RBCs) or whole blood from healthy human donors with MGD014 in vitro.

The potential for MGD014 to mediate the production of cytokines (IFN-γ, IL-2, IL-4, IL-6, IL-10, and TNF-α) was evaluated in vitro with peripheral blood mononuclear cells (PBMCs) obtained from seronegative donors or PLWH under a variety of conditions, ranging from ones that approximate the physiological conditions of PLWH on ART to supra-physiological ones that employ target cells at highly elevated frequencies and, in some cases, target cells with highly elevated env antigen density, exaggerated to maximize the potential for cytokine induction.

MGD014 concentrations of 1000 ng/mL or greater did not induce notable cytokine release when incubated with PBMCs from HIV-uninfected donors, which lack env^+ target cells. When presented in immobilized form to PBMCs from HIV-uninfected donors, MGD014 at concentrations of 400 ng/mL or greater induced detectable levels of some cytokines (IFN-γ, TNF-α, IL-6), as expected, as immobilization of MGD014 results in high localized concentrations of the molecule which have an increased potential to interact multivalently with CD3 on T cells and induce their activation. This latter condition, however, is not physiologic and does not mimic the environment of aviremic PLWH on suppressive ART.

HEK293/D371 (env^{high}) is a cell line that expresses an HIV-1 env protein at levels that ***greatly*** exceed those observed with HIV-1 infected CD4 cells. When PBMCs from 6 HIV-uninfected donors were supplemented with HEK293/D371 (env^{high}) target cells at an effector cell to target cell (E:T) ratio of 20:1 [which provide a target cell frequency of 5%, which is at least 500-fold higher than that (0.0001 – 0.01%) anticipated for PLWH on ART] [**29**, **30**], incubation with MGD014 resulted in the induction of IFN-γ, TNF-α, IL-10 and IL-6 at moderate levels (mean E_{max}: 205, 186, 55 and 359 pg/mL, respectively). Under these exaggerated conditions, the mean EC_{50} for MGD014-mediated production of the 4 cytokines was 26.2 ng/mL. In parallel assays to

assess MGD014-mediated cytolytic activity against the HEK293/D371 (env^{high}) cells, the mean EC_{50} was 1.4 ng/mL. Thus, the potency of MGD014 for redirected T-cell cytolytic activity was ~20-fold higher than for cytokine release.

The potential for MGD014-dependent cytokine release was also evaluated with PBMCs obtained from aviremic, PLWH maintained on ART or viremic, PLWH naïve to ART. These PBMC samples contain physiologically relevant, albeit low, frequencies of env-expressing, HIV-infected target cells. The in-vitro incubations with PBMC samples from PLWH on ART represent the best approximations of the physiological conditions anticipated to be encountered clinically with PLWH maintained on ART, whereas those with PBMC samples from PLWH naïve to ART represent more exaggerated conditions. MGD014-dependent cytokine release was absent when PBMCs from PLWH on ART or PBMCs from PLWH naïve to ART were incubated with MGD014 at concentrations up to 1000 ng/mL. MGD014-dependent cytokine release was also absent when PBMCs from both types of PLWH were supplemented with autologous activated, HIV-infected CD4 cells at an E:T (PBMC:CD4) ratio of 100:1. Because ~20% of the CD4 cells were HIV-infected, the co-mixtures had an overall infected target cell frequency of ~0.2%, which exceeds, by 20-fold or more, the target cell frequencies of 0.0001 to 0.01%, or fewer, anticipated for PLWH maintained on suppressive ART **[29, 30]**.

MGD014-dependent cytokine release was observed when the PBMC samples from the aviremic HIV^+ donors on ART or viremic HIV^+ naïve to ART were supplemented with higher amounts of autologous activated, HIV-infected CD4 target cells (E:T ratios of 30:1 or 10:1, which resulted in co-mixtures with infected target cell frequencies of ~0.7% or ~2%, exceeding those anticipated for PLWH on ART by 70 or 200-fold, respectively). With the co-mixtures derived from PLWH HIV^+ donors on ART, release of IFN-γ, TNF-α or IL-10 at moderate levels (E_{max}: 431, 290 and 187-297 pg/mL, respectively) was observed for 1 of the 4 donors, and the mean EC_{50} for MGD014-mediated release of these cytokines was 24.6 ng/mL. With the co-mixtures derived from HIV^+ donors naïve to ART, release of IFN-γ or TNF-α at moderate levels (E_{max}: 285-628 and 111-210 pg/mL, respectively) was observed for 2 of the 3 donors, and the mean EC_{50} for MGD014-mediated release of these cytokines was 0.42 ng/mL.

In summary, the most physiologically relevant conditions for assessing the potential for MGD014-dependent cytokine release were those conducted with PBMCs from aviremic, HIV^+ donors on ART, either incubated with MGD014 by themselves or supplemented with autologous HIV-infected CD4 cells to achieve a target cell frequency to ~0.2%. Even under the latter condition, in which env-expressing HIV-infected target cells were present at frequencies at least 20-fold higher than anticipated for PLWH on ART, there was no notable cytokine release at MGD014 concentrations as high as 1000 ng/mL. Similarly, no cytokine release occurred when PBMCs from viremic, PLWH naïve to ART (expected to have higher frequencies of HIV-infected env-expressing target cells and more highly activated effector T-cell populations due to the unsuppressed viral infection) were incubated alone or supplemented with autologous HIV-infected CD4 cells to achieve a target cell frequency of ~0.2%. Thus, the risk of inducing substantial cytokine release following MGD014 administration to PLWH maintained on ART is very low.

However, under the more exaggerated conditions in which PBMCs were supplemented with more highly elevated frequencies of target cells, moderate levels of IFN-γ, TNF-α and IL-10

were released in response to MGD014 with mean EC_{50} values of 24.6 ng/mL (PBMCs from normal HIV^- donors), 26.2 ng/mL (PBMCs from aviremic HIV^+ donors on ART) and 0.42 ng/mL (PBMCs from viremic HIV^+ donors naïve to ART). By comparison, the MGD014-mediated cytolytic activity of CD8 T cells directed against autologous HIV-infected CD4 target cells under comparably exaggerated conditions yielded EC_{50} values of 1.4 ng/mL (normal HIV^- donors) and 2.1 ng/mL (aviremic HIV^+ donors on ART). Based on these results, minimum anticipated biological effect level (MABEL) values of 1.4-2.1 ng/mL were used to guide selection of the FIH starting dose. This represents a highly conservative approach, because MABEL values based on assays conducted under the exaggerated, non-physiologic conditions must be considered artificially low, and because no cytokine release was detected under the most physiological representative conditions with MGD014 concentrations as high as 1000 ng/mL. This conservative approach ensures a wide safety margin and acknowledges MGD014 as the first T-cell redirecting DART molecule to be administered to PLWH (see **Section 2.4**).

2.2.2 MGD014 Pharmacokinetics and Toxicology

A brief summary of nonclinical PK and toxicology data with MGD014 are provided below, please reference the **MGD014 IB** for a more detailed description.

The nonclinical toxicology program for MGD014 was performed exclusively in the cynomolgus monkey as MGD014 does not bind to CD3 in rodents or dogs. The cynomolgus monkey was selected as the most appropriate animal model for nonclinical safety evaluation of MGD014 given the homology of cynomolgus monkey and human CD3, the ability of MGD014 to bind with similar affinity to monkey and human CD3 and to efficiently mediate redirected T-cell killing with effector cells from both species.

The cynomolgus monkey is a relevant species with regard to the anti-CD3 component of MGD014, but not for the anti-HIV env component. The anti-HIV arm of MGD014 does not bind to any antigens in humans in the absence of HIV-1 infection and is not known to bind to any monkey antigens. Due to the lack of targets for the anti-HIV arm, toxicity assessments related to this component of MGD014 are limited to off-target effects in naïve cynomolgus monkeys (i.e., ones not infected by an HIV-related virus). However, in PLWH on suppressive ART, env antigen-expressing infected CD4 target cells are rare – exact frequencies have not been measurable, but estimates range from 1 per 10^4 (0.01 %) to 1 per 10^6 (0.0001 %) CD4 T cells [**29**], or even less frequent [**30**]. Due to the extremely low frequencies of target cells in PLWH on ART, the primary on-target toxicities of concern would be those related to MGD014 binding to CD3 on T cells, which are plentiful. Based on these considerations, the naïve cynomolgus monkey model represents an approximation, albeit imperfect, of the conditions anticipated in PLWH on ART.

The alternative strategy of conducting a toxicology study of MGD014 in monkeys infected by virus (simian-human immunodeficiency virus [SHIV]) was not pursued because proof of anti-HIV activity in animal models is not required per the Food and Drug Administration (FDA) Guidance entitled Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment (November 2015), and because toxicology evaluation in this model would be technically challenging and difficult to interpret. In SHIV-infected monkeys, the analysis for toxicological endpoints would be complex because toxicities potentially related to MGD014 would need to be clearly distinguished from ones related to the SHIV infection. Further, the

administration of MGD014 to animals with elevated levels of circulating SHIV and infected CD4 T cells would model an unrepresentative physiological condition and potentially reveal toxicological findings that are unlikely (or much less likely) to be evident when infected target cells are only present at low levels, as is with PLWH on suppressive ART. If a suppressive ART regimen were incorporated into the infected animal model to better mimic the status of the intended participant population, the analysis would be even more complex, because toxicities related to the addition of ARVs (typically comprised of a mixture of 3 drugs administered on a daily schedule) would need to be considered. Finally, SHIV infected monkey studies are not readily amenable to Good Laboratory Practice (GLP) compliance. Thus, while suitable for assessing efficacy and some limited safety parameters associated with MGD014 administration, the SHIV infected animal models are not well suited to assess toxicology.

In the repeat-dose GLP study conducted in cynomolgus monkeys (Study 20093423), 40 animals, consisting of 4 groups of 10 animals (5 males, 5 females), received 6 repeated administrations of MGD014 at weekly intervals at dose levels of 0 (saline), 0.1, 1 or 10 mg/kg. MGD014, administered as a 2-hour IV infusion on a weekly schedule for 6 consecutive weeks, was well-tolerated and all animals survived to their scheduled euthanasia. There were no MGD014-related effects on any of the following study parameters or end points: clinical signs, body weights, food consumption, ophthalmology, electrocardiology, body temperature, blood pressure and heart rate, neurologic examination, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), flow cytometry (percentages of CD4 and CD8 T-cell subsets and T-cell activation), serum cytokines, gross necropsy findings, organ weights, and histopathologic examinations.

All animals were exposed to the test article after each administration of MGD014. Maximum serum concentration ($C_{max)}$ and area under the curve (AUC) extrapolated up to infinity (AUC_{inf}) increased proportionally with increasing dose of MGD014. Based on the serum concentration profiles at the end of the first weekly dose, there were no significant differences between gender, therefore, male and female animals were grouped for subsequent analyses. Based on the overlapping dose normalized mean serum concentration profiles of the first week for all 3 doses and no significant difference between the total body clearance (CL) and steady-state volume of distribution (V_{ss}) among all 3 doses, MGD014 PK was determined to be linear across the dose range evaluated (0.1-10 mg/kg). By noncompartmental analysis (NCA), mean C_{max} after the first dose was 2, 19, and 180 µg/mL for dose levels of 0.1, 1, and 10 mg/kg, respectively, consistent with the analysis by two-compartment modeling. By NCA, mean AUC_{inf} after the first dose was 74, 769, and 7255 hr•µg/mL for dose levels of 0.1, 1, and 10 mg/kg, respectively, consistent with the analysis by two-compartment modeling. Mean CL by NCA or two-compartment modeling of data after the first dose of MGD014 across all groups were consistent with each other at 1.38 or 1.4 mL/hr/kg, respectively, substantially lower than the glomerular filtration rate of cynomolgus monkeys, as would be expected for a protein of this size (111.8 kDa). Mean V_{SS} by NCA after the first dose of MGD014 across all doses was 141 mL/kg and by two-compartment modeling was 152 mL/kg, or about 3-fold larger than the plasma space (~45 mL/kg), but less than the extracellular space (~200 mL/kg) of cynomolgus monkeys. This indicates some extravasation into the extracellular space. Average mean residence time (MRT) after the first dose of MGD014 was 105 hours (4.4 days) by NCA and 117 hours (4.9 days) by two-compartment modeling. By simulation of 6 weekly doses using two-compartment modeling with PK parameters derived

from the first cycle of data, accumulation by a factor of 1.29 would be expected assuming PK parameters remained constant.

Anti-drug antibodies (ADA) were confirmed in 10 out of 30 animals that received administration of MGD014. Of these, ADA was first detected in 4 animals during the dosing period (between Days 29 and 36) and in 6 animals during the recovery period (between Days 50 and 91). Although ADA were detected in 10 animals, no obvious changes in the PK profile were observed in these animals except for one animal from the 10 mg/kg dose group.

There were no noteworthy MGD014-related increases in serum concentrations of cytokines (IFN-γ, IL-2, IL-4, IL-5, IL-10, or TNF-α).

There also were no noteworthy MGD014-related changes in the frequencies of circulating CD4 and CD8 T cells, nor in the frequencies of CD4 and CD8 T cells expressing markers of activation or exhaustion (CD25, CD69, PD-1, TIM-3), as determined by flow cytometry. Assessment of MGD014 binding to CD4 and CD8 T cells demonstrated that binding to CD3 was 1-2% of maximal at 0.1 mg/kg, ~30% of maximal at 1 mg/kg, and maximal at 10 mg/kg, when measured at 24-hours post-infusion. Binding to CD3 was transient and nearly completely reversed for the low- and mid-dose groups and ~50% reversed for the high-dose group by 7-days post-infusion.

Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 10 mg/kg/dose, which correlated to C_{max} of 180 µg/mL and AUC_{last} of 5604 hr•µg/mL.

A GLP tissue cross-reactivity study performed on a panel of normal human tissues demonstrated that MGD014 staining was observed in the membrane and cytoplasm of lymphocytes in human lymphoid and nonlymphoid tissues (**MGD014 IB**). Nearly identical staining was observed with RSV x CD3, a control DART molecule retaining the anti-CD3 specificity of MGD014, but lacking the anti-HIV env specificity, indicating that the observed staining with MGD014 solely represented reactivity of the CD3 binding domain of MGD014. The staining of these lymphocytes was expected based on the known expression of CD3 by T cells [27]. No unanticipated cross-reactivity of MGD014 was observed. These findings are consistent with those observed in a separate GLP tissue cross-reactivity study in which a panel of HIV-uninfected human tissues was evaluated with HIV_{A32} x RSV, a control DART molecule retaining the anti-HIV env specificity of MGD014 but lacking the anti-CD3 specificity (Study 20058390). There was no staining of human tissues by the HIV_{A32} x RSV molecule, confirming that the anti-HIV env specificity of MGD014 is not reactive with antigens expressed by normal (i.e., uninfected) human tissues.

2.3 Summary of Known and Potential Risks and Benefits of MGD014

The addition of MGD014 to a person's ART regimen or the donation of one's blood cells to this research project provide no direct benefit to participants. However, participation makes it possible to continue research on HIV, potentially resulting in new treatments for HIV infection. Systemic cytokine release is a known potential risk of T-cell redirected therapies. For mAbs, most infusion-related events occur within the first 24 hours after dosing. Specifically, with regard to cytokine release syndrome (CRS) reactions, these most commonly occur within the first few hours of beginning the infusion with licensed therapeutic mAbs, CRS is managed based on the

severity of reaction, including temporarily stopping the infusion, administering histamine blockers, corticosteroids, and restarting the infusion at a slower rate [31]. Severe reactions such as anaphylaxis, angioedema, bronchospasm, hypotension, and hypoxia are infrequent and more often associated with mAbs targeted to human proteins or with a non-human mAb, such as a murine mAb [32].

The probability of inducing substantial cytokine release by a T-cell redirecting DART molecule like MGD014 is dependent on the extent of formation of synapses between antigen-expressing target cells and CD3-expressing effector T cells. The probability of synapse formation will be proportional to the frequency of target cells, the amount (density) of antigen on surfaces of the target cells, the number of effector T cells, the binding affinities of the monovalent arms of the DART molecule and the amount of DART molecule. In PLWH on suppressive ART, env antigen-expressing infected CD4 target cells are rare – exact frequencies are not known, but likely to range between 1 per 10^4 (0.01%) and 1 per 10^6 (0.0001 %) CD4 T cells [29]. The amount of env antigen on the surface of HIV-1 infected cells in PLWH on ART is not well characterized, but low env antigen densities are observed on human CD4 cells infected with HIV-1 in vitro, especially when a transmitted/founder HIV-1 isolate is utilized (**MGD014 IB**), which is consistent with the low number of env antigen spikes (average of only 14) per HIV-1 virion [33, 34], which are released from the surface of infected cells. While the levels of CD4 and CD8 T cells in PLWH on ART are close to the normal range, the paucity of env-expressing CD4 target cells infers that MGD014-dependent synapses will also be proportionally rare. Thus, the likelihood for induction of CRS in PLWH on ART resulting from MGD014-mediated synapse formation appears to be extremely low. In PLWH maintained on ART, HIV-1 viral loads are low to undetectable (generally <20 or <50 copies/mL depending on which commercial assay is used, but typically <5 copies/mL with more highly sensitive research assays). The HIV binding arm of MGD014, based on A32 mAb which recognizes a CD4-inducible epitope in the C1-C2 regions of gp120, binds to env on the surface of infected CD4 cells, but does not bind to envelope on the surface of virions [**MGD014 IB**]. This unique property will minimize the sequestration of MGD014 by circulating virions following its administration and avert any potential toxicities that could result from DART:virion complexes.

The risk for induction of T-cell activation and cytokine release resulting from the binding (in a monomeric fashion) of MGD014 to $CD3^+$ T cells in the absence of envelope-antigen expressing target cells (no target engagement) also appears to be low, as shown by both in vitro data and the absence of detectable cytokine release (or other sign of toxicity) in monkeys treated with up to 10 mg/kg of MGD014, a condition that led to maximal binding to the CD3 receptors on T cells.

Finally, the risk of off-target binding by MGD014 is negligible. In a GLP human tissue cross-reactivity study, MGD014 (HIV_{A32} x CD3) and a CD3-targeted control DART molecule (RSV x CD3) exhibited nearly identical staining of lymphocytes in the periphery and tissues, as predicted. In addition, in a second GLP human tissue cross-reactivity study, the HIV-1 envelope-targeted control DART molecule (HIV_{A32} x RSV) exhibited no staining, as predicted. Thus, there is no evidence of unanticipated off-target cross-reactivity in human tissues.

2.4 Dose Selection

2.4.1 Selection of Maximum Recommended Starting Dose (MRSD)

The initial MGD014 dose proposed for the FIH trial was carefully selected primarily using dose selection principles based on estimation of the MABEL in accordance with the Food and Drug Administration (FDA) guidance for Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (July 2005), the recommendations for determining a starting dose based on FDA's Guidance for Industry: S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (March 2010), and recent publications by Saber et al. 'An FDA oncology analysis of immune activating products and FIH dose selection' [**35**] and Dudal et al. 'Application of a MABEL Approach for a T cell-Bispecific mAb: CEA TCB' [**36**].

A dose of 0.1 µg/kg was selected as the starting dose for the proposed Phase 1 study.

Because MGD014 has an anti-CD3 arm for engaging T cells, the primary potential concern associated with the mechanism of action of MGD014 is CRS.

For in vitro assays conducted in the absence of HIV-1 env-expressing target cells, there was no notable MGD014-dependent cytokine release, such as when PBMCs from normal, uninfected donors were incubated with MGD014 at concentrations up to 10 µg/mL. Moreover, neither cytokine release nor T-cell activation occurred in cynomolgus monkeys that received MGD014 at dose levels as high as 10 mg/kg, which resulted in C_{max} concentrations as high as 180 µg/mL and achieved maximal binding to CD3 on T cells. Thus, there is no evidence supporting monovalent MGD014 engagement of CD3 on T cells as a safety concern. When presented in immobilized form to PBMCs from normal donors, MGD014 at concentrations of 400 ng/mL or greater induced detectable levels of IFN-γ, TNF-α and IL-6, as expected, since immobilization results in high localized concentrations that have an increased potential to interact multivalently with CD3 on T cells and induce their activation. This latter condition, however, is paraphysiologic and does not mimic the environment of nonviremic HIV-infected individuals on ART.

The most physiologically relevant data on the potential for MGD014-dependent cytokine release were obtained from in vitro studies conducted with PBMCs from aviremic donors with HIV-1 on ART, which contain immeasurably low, but nonetheless representative, frequencies of circulating HIV-infected env-expressing CD4 target cells. No cytokine release was induced when these PBMC samples were incubated with MGD014 at concentrations up to 1000 ng/mL. Similarly, no MGD014-dependent cytokine release occurred when the PBMCs were supplemented with autologous, activated CD4 cells infected in vitro by HIV-1 BaL at an E:T (PBMC:CD4) ratio of 100:1. Since ~20% of the CD4 cells were infected, the infected target cell frequencies in the co-mixtures were ~0.2%, which exceeds the anticipated frequencies of target cells in HIV^+ PLWH on ART (0.0001-0.01%) [**29**, **30**] by 20-fold or more. Thus, there was no MGD014-dependent cytokine release under either physiologically relevant or substantially exaggerated in vitro conditions.

With PBMCs from viremic, PLWH naïve to ART (which are expected to contain higher frequencies of circulating HIV-infected env-expressing target cells and have a more highly activated effector T-cell population due to the unsuppressed HIV-1 viral infection), no cytokine

release was induced at MGD014 concentrations up to 1000 ng/mL. Moreover, no MGD014-dependent cytokine release occurred when these PBMC samples were supplemented with autologous CD4 cells infected in vitro by HIV-1 BaL at the E:T (PBMC:CD4) ratio of 100:1. Thus, there was no MGD014-dependent cytokine release under substantially exaggerated in vitro conditions that could mimic an unintended, worst-case clinical study situation in which MGD014-treated, PLWH may have discontinued their ART treatments.

Under more highly exaggerated in vitro conditions, MGD014-dependent cytokine release was observed, which is consistent with its mechanism of action. First, when PBMCs from normal HIV- donors were incubated with an env^{high} target cell line at an E:T (PBMC:target cell) ratio of 20:1 (corresponding to a target cell frequency of 5%, which exceeds that anticipated for PLWH on ART by 500-fold or more), moderate levels of IFN-γ, TNF-α, IL-10 and IL-6 were released in response to MGD014. Mean E_{max} (maximal cytokine level) values were 55-359 pg/mL and the mean EC_{50} value was 26.2 ng/mL. Under the same conditions, the EC_{50} for MGD014-mediated cytolytic activity against the env-expressing target cells was 1.4 ng/mL. Second, when PBMCs from aviremic HIV^+ donors on ART were supplemented with autologous activated, HIV-infected CD4 cells at E:T (PBMC:CD4) ratios of 30:1 or 10:1 (corresponding to target cell frequencies of ~0.7 or ~2%, respectively, which exceed those anticipated in PLWH on ART by 70 or 200-fold, respectively), moderate levels of IFN-γ, TNF-α and IL-10 were released in response to MGD014, but only with 1 of the 4 donors tested. Mean E_{max} values were 187-359 pg/mL and the mean EC_{50} value was 24.6 ng/mL. Under similar conditions, the EC_{50} for MGD014-mediated cytolytic activity against the infected target cells was 2.1 ng/mL. Third, when PBMCs from viremic HIV^+ donors naïve to ART were similarly supplemented with autologous activated, HIV-infected CD4 cells at E:T (PBMC:CD4) ratios of 30:1 or 10:1, moderate levels of IFN-γ, TNF-α and IL-10 were released in response to MGD014 for 2 of the 3 donors tested. Mean E_{max} values were 111-628 pg/mL and the mean EC_{50} value was 0.42 ng/mL.

Based on the lack of cytokine release at MGD014 concentrations up to 1000 ng/mL under conditions that were either most directly relevant to PLWH on ART or were exaggerated by the addition of infected CD4 target cells at frequencies exceeding those estimated for PLWH on ART by 20-fold or more, the MABEL would be considered to be 1000 ng/mL. Allometric modeling of the cynomolgus monkey PK data (**Table 1**) projects that a first dose C_{max} concentration of 1000 ng/mL in human participants would result from an MGD014 dose of 58 µg/kg. Based on the theoretical CD3 RO calculations (**Table 1**), this C_{max} concentration is projected to result in 56% RO (and/or T-cell binding). The data from the cynomolgus monkey toxicology study demonstrated that maximal binding of MGD014 to CD3 on T cells was not associated with any toxicological findings. However, since MGD014 is the first T-cell redirecting DART molecule to be administered to PLWH, it is prudent to select a FIH dose projected to yield a lower RO value.

The in vitro assays for MGD014-mediated cytolytic activity by CD8 T cells directed against autologous HIV-infected CD4 target cells yielded EC_{50} values of 1.4 ng/mL (HIV $seronegative^-$ donors) and 2.1 ng/mL (aviremic PLWH on ART). Based on these EC_{50} values, MABEL values of 1.4-2.1 ng/mL were used to guide selection of the FIH starting dose. This represents a highly conservative approach, because MABEL values based on assays conducted under non-physiologic conditions with elevated frequencies of infected target cells must be considered to be artificially low. Based on allometric modeling of the cynomolgus monkey PK data, a starting

MGD014 dose of 0.1 µg/kg is projected to yield a C_{max} concentration of 1.7 ng/mL, which falls within the range of the MABEL values, and a theoretical RO of 0.03%.

By comparison, a conventional toxicology-based approach to selecting the FIH dose level based on a NOAEL of 10 mg/kg in the GLP toxicology study in normal cynomolgus monkeys, using a body surface area conversion factor of 0.32 for cynomolgus monkeys (see Table 1 of July 2005 FDA Guidance on estimating Maximum Recommended Starting Dose [MRSD]) would have suggested 310 µg/kg as the starting dose if a 10-fold safety factor was applied (projected to yield C_{max} of 5,323 ng/mL and theoretical RO of 87.3%), or alternatively, 31 µg/kg as the starting dose if a more conservative 100-fold safety factor was applied (projected to yield C_{max} of 532 ng/mL and theoretical RO of 40.8%).

In summary, the proposed starting dose of 0.1 µg/kg was determined using a highly conservative approach to dose selection relying on the determination of MABEL values based on supra-physiological conditions in which HIV-1 infected CD4 target cells were present at frequencies that exceeded those anticipated for PLWH on suppressive ART by 70 to 500-fold or more. At a dose of 0.1 µg/kg, human C_{max}, AUC, and CD3 RO are projected to be 1.7 ng/mL, 83 ng/mL•h, and 0.2%, respectively, which are >105,000-fold, >67,000-fold and ~500-fold lower than the C_{max} (180 µg/mL), AUC_{last} (5,604 µg/mL•h), and CD3 RO (100%), respectively, observed during the first dose cycle at 10 mg/kg in cynomolgus monkeys, the NOAEL dose, thus providing a very generous safety margin for first human exposure.

2.4.2 Dose Escalation Strategy

The dose escalation strategy for the single ascending dose phase (Part 1) is summarized in **Table 1**. It depicts dose escalation by half-log increments and shows predicted C_{max} and $C_{trough(7\text{-}day)}$ serum concentrations and theoretical percentages for CD3 RO. The $C_{trough(7\text{-}day)}$ serum concentrations are shown because MGD014 will be administered at once every 2 weeks (Q2W) intervals in the multi-dose expansion cohort (Part 2).

The top dose of 300 µg/kg is 33-fold lower than the NOAEL dose (10 mg/kg) derived from the GLP toxicology study in cynomolgus monkeys, which resulted in C_{max} concentrations of 180 µg/mL and 100% CD3 RO at 24-hours post-infusion. From in vitro studies conducted with CD8 T cells obtained from HIV^+ donors on ART as effector cells and autologous CD4 cells infected by subtype B HIV-1 isolates as target cells with an E:T (CD8:CD4) ratio of 33:1, the mean EC_{90} value for MGD014-dependent cytolytic activity was 11.6 ng/mL with values ranging from 1.0 to 119 ng/mL. While these in vitro conditions are exaggerated and not considered to be directly representative of the physiological conditions of PLWH on ART, the EC_{90} values provide a useful reference point; MGD014 doses that yield $C_{trough(7\text{-}day)}$ serum concentrations exceeding the upper range of the EC_{90} values for in vitro cytolytic activity (projected to be achieved at doses 100 µg/kg and higher) are more likely to exhibit intended levels of biologic activity in vivo.

Targeting MGD014 doses beyond what is expected to achieve $C_{trough(7\text{-}day)}$ serum concentrations exceeding the EC_{90} values for in vitro cytolytic activity, however, may be advantageous; env antigen-expressing HIV-infected target cells are expected to be very rare and many target cells may be situated in localized anatomical sites [B-cell follicular regions of lymph nodes, gut-associated lymphoid tissue, bone marrow, genital tract, central nervous system (CNS) [**1**, **37**]

with potentially reduced penetrance by MGD014 [38, 39]. For example, there is increasing evidence that the brain harbors latent HIV-1 infected cells capable of being reactivated [37, 40, 41, 42], and it may be particularly challenging for MGD014 to gain access to the CNS due to the limits imposed by the blood-brain-barrier (BBB). T cells are capable of trafficking to the CNS [43, 44] and are known to be present in the cerebral spinal fluid (CSF) of both seronegative individuals and PLWH [45, 46]. However, antibody molecules are only able to cross the BBB inefficiently; following IV infusion, CSF to serum concentration ratios of 1:200 to 1:800 have been reported [38, 39]. MGD014, which bears a mutated IgG1 Fc domain for extended serum half-life, would also be expected to cross the BBB inefficiently; thus, the higher serum concentrations resulting from the higher doses will favor the attainment of CSF concentrations that could enable MGD014-mediated targeted cytolytic activity in the CNS compartment.

In summary, MGD014 doses as high as 300 µg/kg are expected to be adequately tolerated in PLWH on ART and capable of mediating activity against env antigen-expressing HIV-infected target cells, possibly even against those residing in 'sanctuary' compartments.

Table 1 MGD014 Dose Escalation Scheme

Cohort	Dose (µg/kg)	C_{max} (ng/mL)	$C_{trough\ (7\text{-}day)}$ (ng/mL)	Theoretical RO at C_{max} (%)	Theoretical RO at $C_{trough\ (7\text{-}day)}$ (%)
1	0.1	1.7	0.27	0.2	0.03
2	0.3	5.2	0.8	0.7	0.1
3	1.0	17.2	2.7	2.2	0.3
4	3.0	51.5	8.0	6.3	1.0
5	10.0	171.7	26.8	18.2	3.4
6	30.0	515.1	80.3	40.0	9.4
7	100.0	1717.1	267.5	69.0	25.7
8	300.0	5151.4	802.6	87.0	51.0

Projected C_{max} and $C_{trough\ (7\text{-}day)}$ values were derived from allometric modeling of cynomolgus monkey PK data, using allometric exponents of 0.75 for clearance and 1.0 for volumes of distribution under the assumption of linearity to estimate PK in humans. Theoretical CD3 RO values were calculated from the Hill equation ($RO = [C] / (K_D + [C])$) using K_D = 6.9 nM for human CD3 binding.

2.4.3 Post-Infusion Monitoring

Infusion related reactions (IRR) and CRS following infusion of mAb therapy, when they do occur, manifest rapidly, with a typical onset within hours of infusion, and generally appear in the dose finding phase of studies [47, 48, 49, 50] and have not been observed in participants through Cohort 8 in Part 1. Safety profiles of similar MacroGenics-produced DART products currently in Phase 1 oncology trials show that all participants who experienced IRR/CRS became symptomatic within a 6-hour post-infusion monitoring period.

The data together suggests that a 12-hour observation period following MGD014 in Part 1 of the trial will be sufficient to ensure both the safe administration of the study drug as well as management of potential IRR. As an additional conservative measure, the first participant of

each dose cohort to receive the specified MGD014 dose level will be monitored for 24 hours following MGD014 infusion. Subsequent participants of each dose cohort of Part 1 will be monitored for 12 hours.

In Part 2, each participant will be monitored for 6 hours following the first MGD014 infusion and for 4 hours following subsequent infusions.

2.4.4 Every 2 Week Administration

For the multi-dose expansion cohort in Part 2, MGD014 at 300 mcg/kg will be administered IV Q2W for a total of three doses over 4 weeks. The Q2W administration of MGD014 is supported by the repeat-dose toxicology study in cynomolgus monkeys (Study 20093423) in which MGD014 was administered weekly for 6 weeks by 2-hour IV infusions. Simulations based on the allometric modeling of the cynomolgus monkey PK data predicts that the concentration profiles in human participants will reach steady-state between the third and fourth dosing intervals and that the accumulation factor for exposure following the last (sixth) dose will be 1.84.

3 STUDY PURPOSE AND OBJECTIVES

3.1 Primary Objective

The objective of this study is to characterize the safety and tolerability of MGD014 administered IV to PLWH maintained on suppressive ART.

3.2 Secondary Objectives

- Assessment of PK and immunogenicity (ADA) of MGD014.
- Assessment of serum cytokine levels following MGD014 administration.

3.3 Exploratory Objectives

- Explore the impact of MGD014 administration on the immunologic response to HIV.
- Explore correlations between virologic and immunologic responses to MGD014.
- Assess the ability of MGD014 to alter markers of persistent HIV-1 infection.

The results of exploratory objectives may not be included in the clinical study report (CSR) or database lock unless they represent meaningful findings.

4 STUDY DESIGN

4.1 Overview of Study Design

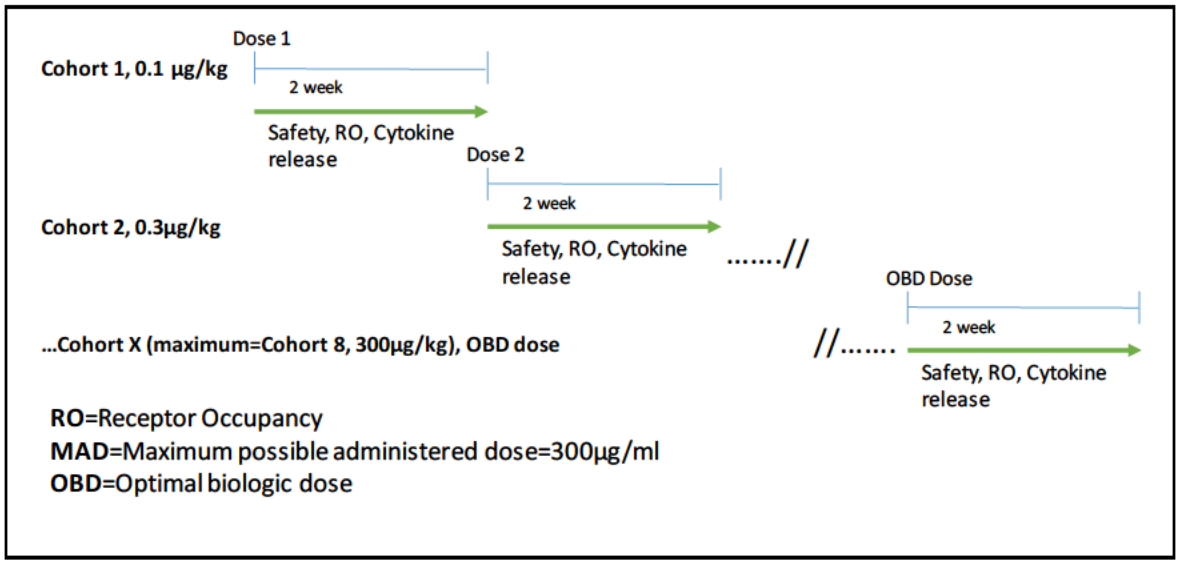
This is a Phase 1, single-center, open-label study of MGD014 in PLWH infection on stable ART. PLWH who began ART during either chronic HIV infection or acute HIV infection with plasma HIV RNA < 50 copies/mL for 24 months prior to screening will be consented to the study. The screening procedures and initial evaluations that follow the consent determine eligibility for study entry. Eligible participants continue their baseline ART regimens throughout the study and receive either one infusion (Part 1) or an IV infusion Q2W for a total of three infusions of 300 mcg/kg of MGD014 for 4 weeks (Part 2).

4.2 Part 1 – Dose Escalation Phase

Single Ascending Dose (Cohort 1 & 2: n= 1 to 4 participants per dose cohort; Cohorts 3- 8: n= 3 to 6 participants per dose cohort). Part 1 is a single ascending dose study with a 1+3 design for cohorts 1 and 2, and a 3+3 design with staggered accrual for cohorts 3-8, with an aim of determining the safety, PK, and pharmacodynamics (PD) of ascending doses up to either the Optimal Biologic Dose (OBD) or the maximum administered dose. ***During Part 1, the OBD is identified. The OBD is defined as the MGD014 dose that does not exceed the MTD (see Section 4.2.1) and achieves either maximum RO of CD3 >95% in all participants within the dose cohort, or is at the maximum administered dose (MAD) level of 300 µg/kg.***

Part 1 has 8 unique dose cohorts: 0.1, 0.3, 1.0, 3.0, 10, 30, 100, and 300 (µg/kg). For cohorts 1 and 2, each dose cohort will consist of 1 participant, unless a dose limiting toxicity (DLT) is encountered, which will prompt expansion of the dose cohort to an additional 3 participants (see **Section 4.2.1**). A 2-week DLT period will be observed prior to escalation of the dose to the next dose cohort level. For dose cohorts 3-8, each dose cohort will consist of 3 participants, with at least 24 hours between the dosing of each participant within the cohort. If a DLT is experienced in one of the three participants, the dose cohort will be expanded to 3 additional participants. Following infusions, the study will monitor safety parameters as well as the effects of MGD014 on clinical chemistry, hematology, serum cytokines, T-cell phenotype, CD3 RO, PK, ADA and SCA.

Figure 4 **Part 1: Single Ascending Dose Phase Schema**



Note: Cohort X represents any cohort number

Step 1 Screening, Eligibility and Optional Baseline Leukapheresis (Pretreatment Phase)

There are two study visits associated with Step 1. At Visit 1, participants review and sign the informed consent and complete the screening requirements. At Visit 2, eligible participants enroll and baseline research assays are collected.

Note: Participants, who consented to the optional leukapheresis procedure, may be asked to complete a leukapheresis procedure. The completion of the leukapheresis procedure may occur at or at any time after the enrollment (Visit 2) but prior to receiving their MGD014 dose. The leukapheresis procedure obtains resting CD4 T cells for determination of the baseline frequency of resting CD4 T-cell infection by QVOA.

Step 2 Treatment Phase: In the MGD014 treatment phase (infusion of DART® molecule), participants continue to take their ART and receive 1 infusion of MGD014 at a given dose level based on their assigned dose cohort. The first participants of each dose cohort are monitored for 24 hours on site following infusion; subsequent participants at the same dose level will be monitored for 12 hours on site following infusion. A minimum of 24 hours is required between each participant infusion in a dose cohort. Assessment of clinical and laboratory parameters for safety, including cytokine release, occurs after the MGD014 infusion. PK, PD, and RO data are also collected after the MGD014 infusion. A 2-week DLT period follows each dose cohort and the decision to escalate to the next dose cohort level depends on the results of the testing done during this period. Reference the study schema for Part 1 in **Figure 4**.

Step 3 Post-treatment Phase: Participants progress to Step 3 two (2) weeks after completion of their infusion. This phase is 4 weeks in length and continues monitoring each participant for safety. Serial blood samples collected during this time will analyze the PK, PD and RO measures, and the impact on T-cell phenotype.

4.2.1 Dose Escalation Rules

Dose escalation from one dose cohort to the next dose cohort level depends upon the clinical safety profile (e.g., evaluation of AEs, VS, ECGs, and clinical laboratory parameters) of the dose administered up to and including the preceding dose cohort. Participants will not be dosed at the next higher dose level until all the safety data collected following each dose through Day 14 is reviewed by the principal investigator (PI) (or designee) in conjunction with the medical monitor and are determined to demonstrate acceptable safety and tolerability.

Dose escalation continues until the OBD is achieved, provided MTD is not exceeded. The PI (or designee) may also decide to halt dose escalation if, upon review of available RO data, the RO of CD3 is >95% in all participants within the dose cohort level, and further dose escalation is not expected to provide any additional biologic utility due to saturation of the CD3 receptor. There are three possible outcomes after the infusion of MGD014 in each dose cohort:

Scenario 1: No DLT is encountered, available data on binding to T cells shows CD3 RO is ≤ 95%. Dose escalation to next dose cohort occurs.

Scenario 2: No DLT is encountered, but available data on binding to T cells demonstrates CD3 RO is >95% in all participants at this dose level. Further dose escalation will halt, and study proceeds to Part 2, using the identified OBD dose.

Scenario 3: DLT is encountered in at least one participant. Dose cohort is expanded to an additional 3 participants. **Dosing of the first additional participant will be staggered,** so that the safety and tolerability of MGD014 is evaluated over the entire 2-week DLT in the first additional participant, at the dose in question, prior to dosing any additional participants at the same dose level.

a. If the first additional participant does not experience a DLT during this 2-week DLT period, the 2 other additional participants can proceed to receive MGD014 at this dose level with a minimum of 24 hours between the dosing of each participant. If none of the 3 additional participants experience a DLT, dose escalation to the next dose cohort proceeds.
b. If any of the 3 additional participants experiences a DLT (so in total ≥ 2 of the participants experience a DLT within the same dose cohort), no further participants will receive a dose at this dose level, as the maximum tolerated dose (MTD) will have been exceeded. Part 2 will proceed with the MTD (the dose preceding the dose level at which MTD was exceeded). If only 1 participant was enrolled at the prior dose level, an additional 3 participants will be enrolled at the prior dose level for evaluation of the MTD.

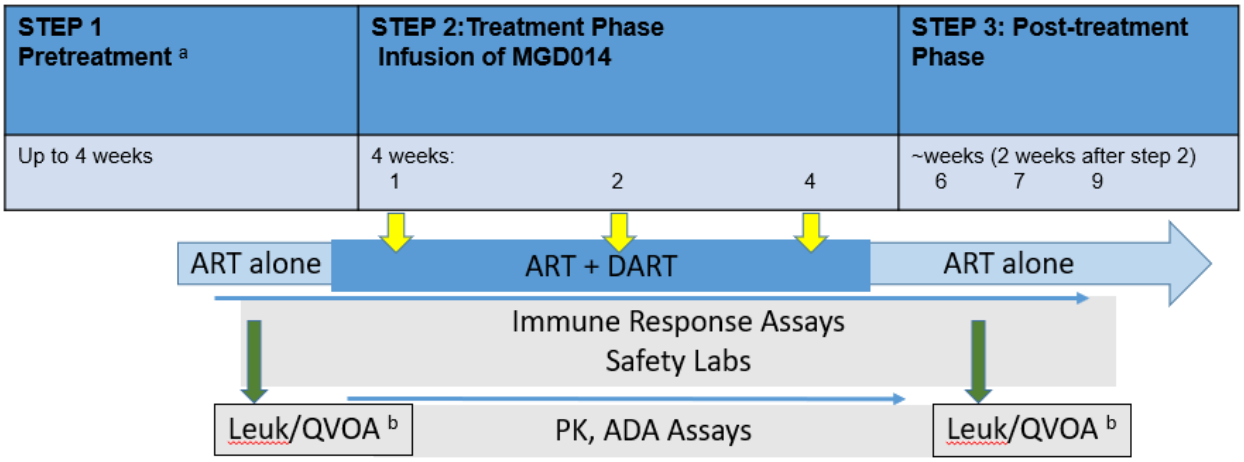
4.3 Multi-Dose Cohort Expansion Phase (Part 2)

Part 2 is a multi-dose expansion cohort with repeat administrations of MGD014 at 300 mcg/kg; see Study Part 2 Schema, **Figure 5**. Up to 6 patients will be enrolled in Part 2.

Participants previously enrolled in and having completed Part 1 may be considered for enrollment in Part 2, provided they continue to meet all eligibility criteria, did not experience any DLT in Part 1, and do not have any detectable ADA at the completion of Part 1.

In Part 2, additional optional assessments on the effects of MGD014 on HIV latent infection parameters include measurements of resting cell infection (frequency of persistent infection of resting CD4 T cells) by QVOA, SCA, and T-cell phenotype and functional properties.

Figure 5 Part 2: Dose Expansion Study Schema



(a) Screening, eligibility and optional baseline leukapheresis (b) optional leukapheresis post-treatment for frequency of persistent infection of resting CD4 T cells.

Abbreviations: ADA = anti-drug antibody; ART = antiretroviral therapy; leuk = leukapheresis; PK = pharmacokinetics; QVOA = quantitative viral outgrowth assay.

Step 1 Optional Baseline Leukapheresis: After obtaining the informed consent and confirmation that the participant qualifies for the study, the participant enrolls in the study. If the participant gives consent, an optional baseline leukapheresis is completed. The resting CD4 T cells obtained in the leukapheresis will determine the baseline frequency of resting CD4 T-cell infection. Additionally, baseline measurements at 2 independent, pre-MGD014 time points will determine baseline T-cell function and SCA levels. Note: if the frequency of resting CD4 T cell infection is ≤ 0.3 infected cells per million (IUPM), as measured by QVOA, a further decrease from this low frequency of infection cannot be definitively measured given the QVOA assay threshold and variance [51].

Step 2 Treatment phase: Eligible participants will continue their ART regimen and receive 3 infusions of MGD014 at the dose of 300 mcg/kg. Participants are monitored for 6 hours on site following their first infusion. Participants will be monitored for 4 hours on site following subsequent infusions. Clinical and laboratory parameters for safety, including clinical assessment

of cytokine release, will be assessed after each MGD014 infusion. PK and PD data will be collected, and serial blood draws will be obtained to assess the impact on T cell functional properties.

Step 3 Post-treatment Phase: This phase begins following the Day 28 MGD014 infusion and includes the 14 days between Day 28 and Day 42, with the first post-treatment study visit at Day 42. Step 3 is conducted over a 6-week period. During Step 3, if a baseline leukapheresis was performed, a second and final leukapheresis procedure is completed 2 weeks (+/- 2 weeks) following the final MGD014 infusion, for assessment of potential reduction in the frequency of resting CD4 T cell infection by QVOA. Plasma HIV-1 RNA as measured by SCA may be assessed. Serial blood draws will be obtained to determine PK and PD measures, and impact on T cell function.

4.4 Dose Limiting Toxicity

DLT will be defined based on drug-related AEs that occur during the DLT period following MGD014 administration. For Part 1, the DLT period is 2 weeks following the single MGD014 infusion. For Part 2, the DLT period is defined as the period from initial infusion of MGD014 through 2 weeks following the last IV MGD014 infusion.

The severity of all AEs will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected Version 2.1, July 2017, which can be found on the DAIDS Regulatory Support Center Web site: http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

A DLT is any ≥ Grade 2 drug-related AE, with the following exceptions, based on the medical judgement of PI (or designee) and medical monitor:

- Grade 2 laboratory abnormality that lasts <72 hours and is not otherwise associated with clinical complications.
- Grade 2 fatigue that lasts <7 days.

In general, for participants who experience an AE that meets criteria for a DLT, subsequent administration of the study drug to that participant should be held pending management and/or resolution of the event and assessment of attribution to the study drug.

In Part 1, if a given dose level is found to exceed the MTD, meaning that ≥ 2 participants experience a DLT in a single dose cohort, Part 2 will proceed with the MTD (the dose preceding the dose level at which MTD was exceeded). If only 1 participant was enrolled at the prior dose level, an additional 3 participants will be enrolled at the prior dose level for evaluation of the MTD.

In Part 2, if ≥ 2 participants experience the same DLT, subsequent administration of the study drug to any participant should be held pending review by the PI (or designee), sponsor, and independent Safety Monitoring Committee (SMC). If toxicity is unacceptable, the study will be discontinued.

All participants who discontinue study treatment or follow-up procedures should comply with end of study procedures. The sponsor or its designee must be notified about discontinuation within 24 hours of such an event.

4.5 Study Duration and End of Trial

For each participant, the study duration will be approximately either 13 weeks (Part 1), or 19 weeks (Part 2). This includes a post treatment period of 6 weeks following the final MGD014 infusion through end of study, which is approximately 5 times the anticipated 8-day half-life based on preclinical animal studies. As participant accrual will be staggered so that the full 2-week DLT period will occur prior to dose escalation in Part 1, the overall study duration will be approximately 36 months. The end of trial is the date that all participants enrolled have completed their end of study visit. The end of trial is when the clinical study database is locked after the last participant in the study completes discharge procedures at the last visit and the study forms have been entered, monitored, reviewed, and approved by PI.

4.5.1 Definition of End of Study

The end of study will occur after the last patient has met off-study criteria and the data collection process is completed (time of study database lock).

End of study for each patient is defined as follows: The date that the participant meets discontinuation criteria or is lost to follow-up.

5 STUDY PROCEDURES

The eligibility criteria for this study have been carefully considered to ensure the safety of the study participants and to ensure that the results of the study can be used. It is imperative that participants meet all eligibility criteria and qualifications to participate in the study. No exceptions to these criteria will be granted by the sponsor.

5.1 Inclusion Criteria

1. Aged ≥ 18 years and ≤ 65 years of age.
2. Ability and willingness of participant to provide written informed consent.

   Note: Due to the lack of foreseeable benefit to study participants, no enrollment of illiterate or mentally incompetent persons allowed.

3. HIV-1 infection, documented by any FDA-approved rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral load.

   Note: The term "licensed" refers to a US FDA-approved kit, which is required for all investigational new drug studies.

   The World Health Organization and Centers for Disease Control and Prevention guidelines mandate confirmation of the initial test result with a second distinct assay. For example, a reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA assay.

4. On continuous antiretroviral therapy (ART defined below) for at least 24 months prior to screening.

   Note: For study eligibility – participant must not have missed more than 9 total days in the 3 months prior to screening.

5. Permitted ART regimens include:

   a. At least 3 ART agents (not counting ritonavir if less than 200 mg total daily dose or cobicistat as one of the agents).

      Note: One of the agents must include an integrase inhibitor, NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitors), or a protease inhibitor.

      OR

   b. Two (2) ART agents in which one of the agents is either a boosted protease inhibitor or an integrase inhibitor, that are FDA approved or are recommended by the Department of Health and Human Service Treatment Guidelines.

Note: Other potent fully suppressive antiretroviral combinations will be considered on a case-by-case basis.

Note: Changes in drug formulation or dose are allowed (e.g., tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF), ritonavir to cobicistat, or separate ART agent dosing to fixed-dose combination), but none within 30 days prior to screening.

Note: Prior changes in, or elimination of, medications for easier dosing schedule, intolerance, toxicity, improved side effect profile or within a drug class are permitted but none within 30 days prior to screening if an alternative suppressive regimen was maintained.

6. Able and willing to adhere to protocol therapy and treatment schedule.
7. Agrees not to enroll in another study of an investigational research agent for the duration of the participant's study participation.
8. Plasma HIV-1 RNA viral load < 50 copies/mL at two time points in the previous 12 months prior to screening (one time point can be screening) and never ≥ 50 copies/mL on 2 consecutive time points in the last 24 months.

   Note: The documented plasma HIV-1 RNA viral load must be performed by any United States laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent certification or accreditation.

9. Plasma HIV-1 RNA viral load < 50 copies/mL obtained at screening, performed at US laboratory that has a CLIA certification or its equivalent certification or accreditation.
10. CD4 cell count > 350 cells/mm^3 obtained at screening, performed at any US laboratory that has a CLIA certification or an equivalent certification or accreditation.
11. Hepatitis C virus (HCV) antibody negative result at study screening or, if the HCV antibody result is positive, a negative HCV RNA result at study screening.
12. Negative Hepatitis B surface antigen result obtained at study screening.
13. When participating in sexual activity that could lead to pregnancy, male participants with partners of childbearing potential must agree to consistently use 2 reliable forms of contraception simultaneously from the time of consent through 6 months after their last infusion of study drug. Such methods include: condoms (male or female) with or without a spermicidal agent; diaphragm or cervical cap with spermicide; intrauterine device (IUD); hormone-based contraception. NOTE: For female partners who are receiving ritonavir or cobicistat, estrogen-based contraceptives are not reliable and an alternative method should be suggested.
14. Ability and willingness of participant to continue ART throughout the study.
15. Ability and willingness to provide adequate locator information.
16. Ability and willingness to communicate effectively with study personnel; considered reliable, willing, and cooperative in terms of compliance with the protocol requirements.

17. Adequate vascular access for MGD014 infusion and leukapheresis.

    Exception: Participants who opt out of the leukapheresis procedure, are not required to have adequate vascular access for a leukapheresis procedure.

18. Participant must have adequate organ function as indicated by the following laboratory values, at the screening visit:

Laboratory Values Required for Study Eligibility	
Test Name	**Laboratory Value**
Hematological	
Absolute neutrophil count	≥ 1,500 /mcL
Platelets	≥ 125,000 / mcL
Hemoglobin	≥ 12 g/dL (male) and ≥ 11 g/dL (females)
Coagulation	
Prothrombin Time or INR	≤ 1.1 x ULN
Chemistry	
K+ levels	Within normal limits
Mg++ levels	Within normal limits
Glucose	Screening serum glucose ≤ Grade 1 (fasting or non-fasting)
Albumin	≥ 3.5 g/dL
Renal	
Creatinine clearance determined by the CKD-Epi equation found at: https://www.qxmd.com/calculate/calculator_251/egfr-using-ckd-epi	eGFR > 60 mL/min
Hepatic	
Serum total bilirubin	Total bilirubin < 1.5 times the ULN range. If total bilirubin is elevated, direct bilirubin must be < 2 times the ULN range. NOTE: If participant is on an atazanavir-containing therapy, then a direct bilirubin should be measured instead of the total bilirubin and must be ≤ 1.0 mg/dL.
AST and ALT	≤ 1.25 X ULN
ALK-P	≤ 1.25 X ULN
Lipase	< 1.1 X ULN
Serum Pregnancy	Negative

Abbreviations: ALK-P = Alkaline Phosphatase; ALT = Alanine Transaminase; AST = aspartate aminotransferase; CKD-Epi = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; INR = international normalized ratio; K+ = potassium; Mg++ = magnesium; ULN = upper limit of normal.

Labs/procedures completed during a routine clinical care appointment that are the same as the study screening labs and/or procedures and completed within the 14 days preceding the screening visit can be used to qualify the participant upon approval by the study PI or designee.

5.2 Exclusion Criteria

1. Women of Child-Bearing Potential (WOCBP) are excluded as the in vivo teratogenic potential of this compound is unknown. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization or menopause.
    a. WOCBP must have documentation from a medical record or physician of successful surgical sterilization, i.e. hysterectomy, bilateral tubal ligation, ESSURE procedure, or bilateral oophorectomy
    b. Post menopause is defined as: amenorrhea ≥ 12 consecutive months without another cause or, for women with irregular menstrual periods and on hormone replacement therapy, a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL.
2. Any HIV-1 RNA viral load > 1000 copies/mL within 6 months prior to screening.
3. History or other evidence of severe illness, immunodeficiency other than HIV, or any other condition that would make the potential participant unsuitable for study in the opinion of the PI (or designee).
4. History or other evidence of any condition or process for which signs or symptoms could be confused with reactions to MGD014.
5. History of any HIV immunotherapy or HIV vaccine except for MGD014 within 12 months prior to screening.
6. History of clinically significant cardiovascular disease including, but not limited to:
    a. Myocardial infarction or unstable angina within the 6 months prior to the initiation of study drug.
    b. Clinically significant cardiac arrhythmias.
    c. Uncontrolled hypertension: systolic blood pressure (SBP) > 180 mmHg, diastolic blood pressure (DBP) >100 mmHg that is sustained on repeat measurement (without intervention).
    d. Deep vein thrombosis, pulmonary embolism, stroke, or transient ischemic attack within the 6 months prior to the initiation of study drug.
    e. QTc prolongation > 480 msec.
    f. Congestive heart failure (New York Heart Association class III-IV).
    g. Pericarditis/clinically significant pericardial effusion.
    h. Myocarditis.

7. Evidence of active viral, bacterial, or systemic fungal infection requiring parenteral antibiotic, antiviral, or antifungal treatment within 7 days prior to the initiation of study drug. Participants requiring any systemic antiviral, antifungal, or antibacterial therapy for active infection must have completed treatment no less than one week prior to the initiation of study drug
8. Active COVID-19/SARS-CoV-2 infection. While SARS-CoV-2 testing is not mandatory for study entry, testing should follow local clinical practice guidelines/standards. Participants with a positive test result for SARS-Cov-2 infection, known asymptomatic infection, or suspected infection are excluded.
9. Active, untreated syphilis (defined as rapid plasma reagin (RPR) positive at screening visit, without any documented history of appropriate treatment).

   Note: If positive at screening without history of treatment, participant will be allowed one rescreen following documentation of recent, appropriate treatment.

10. Known allergic hypersensitivity to recombinant proteins, or any excipient contained in the drug or vehicle formulation for MGD014.
11. History of a severe allergic reaction with generalized urticarial, angioedema, or anaphylaxis within 2 years of study entry or history of hereditary angioedema, acquired angioedema, or idiopathic angioedema.
12. History of malignancy within the past 5 years or current malignancy that may require chemotherapy or radiation therapy.

    Note: a history of non-melanoma skin cancer (e.g. basal cell carcinoma or squamous cell skin cancer) with documentation of complete resection or resolution per licensed and board-certified dermatology consultant following topical therapy is not exclusionary.

13. Seizure disorder: History of seizure(s) within the past two years.

    Note: history of seizure disorder controlled on anti-epileptic therapy, with no seizure within the past two years, does not exclude participant.

14. History of organ or tissue transplantation.
15. History of autoimmune disease, including type I diabetes mellitus, with the specific exceptions of:
    a. Vitiligo.
    b. Resolved childhood atopic dermatitis.
    c. Psoriasis (with the exception of psoriatic arthritis) not requiring systemic treatment (within the past 2 years).
    d. Graves disease with subsequent return to a euthyroid state (clinically and by laboratory testing).

16. Known psychiatric or substance abuse disorders that preclude compliance with the protocol as assessed by the study PI (or designee). Specifically excluded are persons with psychoses within the past 3 years, ongoing risk for suicide, or history of suicide attempt or gesture within the past 3 years.
17. Participation in another investigational clinical research study (with the exception of an antiretroviral treatment trial that uses FDA approved antiretroviral agents) within 60 days prior to study screening.

    Note: Co-enrollment in the ACTG 5332 REPRIEVE study (NCT02344290) and using FDA approved pitavastatin is permitted provided participant enrolled on ACTG 5332 and has taken the study provided medication ≥ 4 months.

    Note: Enrollment in investigative trials using FDA approved medications may be reviewed on a case-by-case basis.

18. History of unstable asthma, including sudden acute attacks occurring without an obvious trigger or asthma requiring hospitalization. Additional criteria for exclusion include:

    In the past year has either of the following:

    a. >1 exacerbation of symptoms treated with oral/parenteral corticosteroids;
    b. Emergency care, urgent care, hospitalization, or intubation for asthma.

19. Bleeding disorder diagnosed by a doctor (e.g., clotting factor deficiency, coagulopathy, or platelet disorder requiring special precautions).
20. Use of any of the following within 90 days prior to screening: receipt of any blood product, immune globulin, immunomodulatory therapy, cytokine therapy, or growth stimulating factors such as systemic corticosteroids, cyclosporine, methotrexate, azathioprine, anti-CD25 antibody, interferon (IFN), interleukin-2 (IL-2), systemic cytotoxic chemotherapy, or investigational therapy. Intent to use immunomodulators (e.g., IL-2, IL-12, interferons or TNF modifiers) during the course of the study.
21. Current use of the following antiretrovirals: maraviroc and/or enfuvirtide.
22. Positive ADA (anti-MGD014) obtained during screening in Part 2.
23. Any vaccination with the exception of the flu vaccine, within 30 days prior to screening.

    Note: Individuals who require vaccination will delay screening for the study until 30 days after receiving the last injection.

5.3 Guidelines for Discontinuation of Participants from Study Drug Administration

Under certain circumstances, an individual participant's infusions will be prematurely or permanently discontinued. Specific events that will result in stopping a participant's infusion schedule in either Part 1 or Part 2 of the study include:

- Failure to meet requirements established for safety assessment
- Pregnancy
- Development of a DLT at any time following MGD014 infusion
- Investigator discretion
- HIV RNA > 150 copies/mL on 2 consecutive determinations

If the PI (or designee) decides that a participant should be withdrawn from study treatment, the sponsor must be alerted within 24 hours. All participants who discontinue treatments should comply with protocol specified visits and follow-up as required by the protocol. The only exception to this requirement is when a participant withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a participant is withdrawn before completing the study, the reason for withdrawal must be documented appropriately in the study documents.

5.3.1 Participant Follow-up after Discontinuation

Participants for whom infusions are discontinued should be counseled on the importance of continuing with the study and strongly encouraged to participate in follow-up visits and protocol-specified procedures.

The study will replace all participants who withdraw for reasons unrelated to drug toxicity. If participant withdrawal occurs in Part 1 before completion of the DLT period, these participants will have inadequate data to support dose escalation, therefore “new” replacement participants can enroll at the same dose level as the withdrawn participant.

The withdrawn participant will continue on study for safety assessments per the end of study visit (see **Section 9.18**). Analysis will be completed on all participant samples, including blood, collected at the end of treatment study visit. The data may or may not be included in the final PK, PD, or ADA analyses but all clinical safety data will be included in the final CSR.

5.3.2 Guidelines for Discontinuation of Participant from Study

Participants who are no longer on treatment but are still followed on the study (with safety evaluations obtained per the Time and Events Schedule in **Appendix 1**) can be terminated from the study for the following reasons:

- Uncontrolled intercurrent illness that prevents continuing study follow-up or regular study visits impossible.
- Noncompliance with protocol-required evaluations.
- Participant request for discontinuation from the study, i.e., withdrawal of consent.
- The sponsor, PI, or regulatory agency terminates the study.

5.3.3 Lost to Follow Up Status

Participants classified as lost to follow up (LTFU) need to meet both of the following criteria:

- Failure to respond or reply to 3 documented phone contact attempts.
- Failure to respond to a certified letter sent to the address provided by the participant.

Only after documentation of these failed attempts to connect with the participant, will the participant be determined to be LTFU.

5.4 Guidelines for Withdrawal of Participant from Study

A participant may withdraw or be withdrawn from the study if any of the following occurs:

- Failure by the participant to attend multiple clinic visits.
- Failure to receive the first MGD014 infusion.
- Failure to meet study advancement criteria.
- Development of an illness that requires treatment with certain medications not allowed in this study.
- Poor adherence to ART as judged by the site PI (or designee).
- Request by the participant to withdraw from the study and study procedures.
- Request of the participant's primary care provider if she/he thinks the study is no longer in the best interest of the participant.
- Participant judged by the PI (or designee) to be at significant risk of failing to comply with the provisions of the protocol, as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the Institutional Review Board/Ethics Committee, FDA, National Institutes of Health (NIH), Office of Human Research Protection (OHRP), other government agencies as part of their duties, Investigator, or industry supporter.

6 STUDY TREATMENT PROCEDURES

Study treatment is MGD014 (also referred to as AEX2028, HIV_{A32} x CD3, or A32 x hXR32 MP3) and is the only investigational drug administered in this study. Participants are required to continue their baseline ART throughout the study. ART will not be provided by the study. **Appendix 1** details the schedule of assessments by study day.

Administration of MGD014 takes place over 2 hours via IV infusion. In Part 1, each participant receives a single MGD014 infusion based on his/her assigned dose escalation cohort. In Part 2, all participants receive multiple MGD014 doses at the same dose as determined in Part 1.

6.1 Regimen

Part 1: Dose escalation cohort (n= at least 20 participants) is a single ascending dose study with an aim of determining the safety, PK, and PD of ascending doses up to either the OBD or the MAD.

Part 2: Dose expansion cohort (n= up to 6) is a multi-dose expansion cohort with repeat Q2W IV administrations of MGD014 at the OBD determined in Part 1. This dose was determined to be 300 mcg/kg.

6.2 Method of Assigning Participants to Treatment Groups

Participants will be assigned sequentially to the dose escalation and multi-dose expansion cohorts as specified in **Section 4.2** and **Section 4.3**, respectively. Participants in the cohort expansion phase will receive the MGD014 dosage based upon results from the dose escalation phase (see **Section 4.3**). A predetermined number of participants will then be enrolled at the selected dose.

6.3 Blinding

This is an open-label study.

6.4 Emergency Unblinding

Not applicable. This is an open-label study.

6.5 Study Drug and Supplies

6.5.1 MGD014

MGD014 will be administered by IV infusion after dilution in vehicle.

6.5.2 Vehicle

6.6 Study Drug Preparation and Administration

6.6.1 General Guidelines and Precautions

MGD014 is administered to participants at very low doses. All doses employed in this study are described in units of micrograms/kilogram: A microgram (μg) is 1 millionth ($1/10^6$) of a gram (g), 1 thousandth ($1/10^3$) of a milligram (mg).

MGD014 is a CD3-targeting therapy. Therefore, it is possible that MGD014 may induce severe/fatal CRS when administered to humans. Errors in dilution could result in severe/fatal CRS.

Every reasonable precaution should be exercised in the preparation, verification, and administration of the MGD014 dose. Independent verification of participant weight, the calculated dose, and the IV pump setting must be reviewed and documented by a second individual trained in these procedures before study drug administration commences.

6.6.2 Study Drug Preparation

Instructions on the preparation of the study drug infusion are detailed in the Pharmacy Manual.

The University of North Carolina (UNC) Investigational Drug Services (IDS) Pharmacy stores, distributes, and maintains accountability for MGD014. The dispensing of each dose will be participant specific and by signed prescription. Upon receipt of the MGD014 doses from IDS, the study coordinator infuses the MGD014 to the participant in the research clinic according to the dose, schedule, and supportive care guidelines.

MGD014 is administered as an open-label IV solution.

Administer the calculated dose based on the participant's actual weight at each dosing visit. Significant (≥ 10%) change in body weight from Visit 2 should prompt recalculation of dose.

Study drug administration

Reference MGD014 SOP entitled 'MGD014 Product Infusion Guidelines and Emergency Management Plan' for details.

The following is performed prior to administration of MGD014:

- Initiate, maintain, and verify IV access.

- Pre-dose assessments completed as listed in the Time and Events Schedule (**Appendix 1**) and the Blood Sampling Schedule (**Appendix 2**).
- Calculate the dose based on the participant's actual weight at the Enrollment Visit in Step 1 (Visit 2). On infusion days, if there is a significant (≥ 10%) change in body weight from Visit 2, promptly recalculate the dose for administration.
- Complete required ECGs in triplicate (approximately 1 minute apart) within 30 minutes of the infusion.
- Pre-medicate with the following study provided medications approximately 30 to 60 minutes prior to infusion:
    - Diphenhydramine 25- 50 mg IV or equivalent H1-antihistamine.
    - Acetaminophen 650 mg oral administration (PO).

    Note: Contact study PI (or designee) for pre-medication doses if participant weighs less than 60 kg.

For administration of MGD014:

- MGD014 will be administered as an IV infusion over 120 minutes. The infusion rate may vary based on the total volume needed to administer the full dose. The total time needed to administer the dose may be longer than 120 minutes based on factors such as participant tolerance but should be completed no more than 6 hours after the product is prepared. Infusion access should be maintained and the participant observed for a minimum of 120 minutes following completion of the infusion (see **Section 6.6.3** for details). The MGD014 should be visually inspected for particulate matter and discoloration prior to administration. The vial should be returned if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow or pale brown color), or there is foreign particulate matter.
- Administer MGD014: Reference MGD014 SOP entitled 'MGD014 Product Infusion Guidelines and Emergency Management Plan' for details.
    - Do not mix the study drug with, or administer as an infusion with, other medicinal products, with the exception of normal saline IV solution.
    - All doses of MGD014 will be administered as an IV infusion over 120 minutes

Administration of the study drug should begin immediately after preparation but no later than 4 hours after preparation when stored at room temperature (see Pharmacy Manual). If there is a delay in administration of study drug such that it will not be administered on the day of preparation, the medical monitor should be notified immediately. Instructions on how to proceed will be provided.

6.6.3 Monitoring Post-administration

Infusion or allergic reactions may occur with the infusion of protein-based therapeutics such as MGD014. Precautions for anaphylaxis should be observed during MGD014 administration. Supportive measures will follow guidelines established in the MGD014 SOP and may include, but are not limited to: epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine or equivalent H1-antihistamine, and acetaminophen. Please refer to **Section 7.1.2** for specific guidelines regarding the management of infusion reactions. Supportive care measures consistent with optimal patient care will be provided throughout the study according to institutional standards.

The duration of monitoring following MGD014 infusions will vary from 2 to 24 hours post-infusion depending on participant stage in the protocol and cohort assignment:

- **For Part 1:** The first participant within each dose cohort to receive MGD014 will be monitored on-site for 24 hours post-infusion. Monitoring will occur in both the Clinical and Translational Research Center (CTRC), and in the adjoining main UNC hospital in a pre-allocated hospital provided research bed. Subsequent participants within the same dose cohort level will be monitored for 12 hours post-infusion in the CTRC.
- **For Part 2:** Each participant will be monitored in the CTRC for 6 hours on-site following receipt of their first MGD014 infusion. The duration of direct monitoring may be reduced to 4 hours for subsequent infusions. Participants are required to return to the CTRC at designated times for blood collections.

During the monitoring period, participants are observed for clinical AEs and the following procedures are performed:

- Vital Signs (VS), Part 1: Taken immediately before infusion (approximately 3 minutes before the start of the infusion); at 15, 30, and 60 minutes after the start of infusion; at end of infusion; and following the infusion, every 15 minutes up to 60 minutes, then at 2, 4, and 6 hours after the completion of infusion. VS will then be taken every 4 hours for the remaining post-infusion monitoring period, unless a clinical event necessitates more frequent VS monitoring. Participants admitted to an inpatient bed for completion of the 24-hour observation period will have VS completed per hospital unit policy for every 4 hour assessments or more frequently as clinically indicated.
- VS, Part 2: Taken immediately before infusion (approximately 10 minutes prior to start of infusion); at 15, 30, and 60 minutes after the start of infusion; at end of infusion; and following the infusion, every 15 minutes up to 60 minutes, then every 60 minutes up to 6 hours after the completion of first infusion and up to 4 hours for subsequent infusions.
- Blood samples for PK, PD, and cytokine release per **Appendix 1** and **Appendix 2**.
- ECG: Perform 2 ECGs after the infusion is completed; 1) within 30 minutes of end of infusion and 2) 60 minutes after infusion.

In Part 1, the study coordinator will see participants at 24- and 48-hours post-infusion (± 5 hours). Contact will be maintained for follow-up of complications and other participant concerns that arise during this time.

In Part 2, the study coordinator will see participants at 24-hours post-infusion (± 5 hours) and on Day 3. Telephone or contact participants via their preferred way of communication for study visits conducted remotely after infusion to inquire about any reactions or potential treatment emergent adverse events (TEAEs). Participants will be instructed to contact the study coordinator or Investigator if any signs or symptoms of an AE occur not only after the infusions but at any time during the study.

6.7 Treatment Compliance

MGD014 will be administered by trained study site personnel under the supervision of the PI (or designee). Records of MGD014 dose calculation, administration, and dosing regimen will be accurately maintained by site staff. Study drug accountability will be maintained and monitored during the study and at the completion of the study. Accurate accounting of MGD014 must be maintained. The PI, in collaboration with IDS Pharmacy, is accountable for study drug. Study drug disposition records must be kept in compliance with applicable guidelines and regulations.

6.8 Packaging and Labeling

MGD014 study drug will be labelled according to U.S. requirements. Please see the Study Specific Pharmacy Manual for detailed information about the packaging and labeling of the study drug.

6.9 Storage and Accountability

6.9.1 MGD014 Storage

MGD014 will be stored and dispensed by the UNC Hospitals IDS Pharmacy by prescription on a participant specific basis. The clinical supplies storage area at the site will be monitored by the IDS staff for temperature consistency.

Vials containing study drug should be stored upright under refrigeration at 2 - 8°C (36 - 46°F) in an appropriate, locked room accessible only to pharmacy personnel, the PI (or designee), or duly designated personnel. The IDS staff's responsibilities include maintaining, monitoring, and documenting the temperature in the pharmacy supply storage area per institutional guidelines.

Vials should be protected from light during storage and should not be shaken or frozen.

The clean-up and disposal of spilled, wasted, or unused medication and used syringes must be documented appropriately (i.e., witnessed) in accordance with applicable federal regulations, Good Clinical Practice (GCP) procedures, and the procedures for handling biohazardous substances. The IDS Pharmacy follows hospital and standard practices for avoidance of contact when preparing the study drug (UNC Hospital Policy (EHA 0024) called "Handling and

Disposal of Hazardous Drugs (Antineoplastic, Biologic, Cytotoxic, and Immunosuppressant Drugs).

Accurate accounting of all study drug must be maintained. The IDS will keep an inventory of study drugs using the institution's drug accountability logs. Study drug disposition records are kept in compliance with applicable guidelines and regulations.

When the study is completed, copies of all study drug accountability records must be provided to the sponsor. Original study drug accountability records must be maintained with the rest of the documentation for inspection by the study monitors.

6.10 Return or Destruction of Study Drug

Upon completion or termination of the study, all unopened vials of MGD014 study drug and vehicle must be returned to MacroGenics or its representative, unless the site has received written authorization from MacroGenics to destroy study drug and/or vehicle at the site. All study drug returns to MacroGenics or its representative must be accompanied by the appropriate documentation and be clearly identified by protocol number on the outermost shipping container.

Additional details regarding storage, handling, and accountability can be found in the Pharmacy Manual.

7 POTENTIAL ADVERSE EVENTS AND SUPPORTIVE CARE MEASURES

7.1 Infusion Related Reactions Including Cytokine Release Syndrome

MGD014 is an immune-modulation agent that may lead to T cell activation and killing of HIV-infected cells. Activation of T cells can be associated with the production of various cytokines. IRR (including CRS) may occur with MGD014. These reactions may manifest with signs and symptoms that may include, but are not limited to, fever, chills, headache, rash, pruritus, arthralgia, hypo- or hypertension, bronchospasm, or other symptoms.

IRR (including CRS) associated with MGD014 administration should be managed according to the standard practice of medicine. General guidelines for the management of such reactions are provided in the SOP. However, severe reactions may require more intensive interventions (e.g., steroids, anti-TNFα antibodies, and/or IL-6 inhibitors).

Participants will be monitored closely for the development of IRR during infusions. The infusion room/area will have immediate access to medications and supportive measures for the treatment of severe hypersensitivity reactions, inclusive of resuscitation equipment and other supplies for the emergency management of an allergic/toxic reaction. All supportive measures consistent with optimal patient care will be provided throughout the study according to institutional standards.

Symptoms of fever or chills will be carefully assessed and treated based on the assessment of the PI (or designee). An evaluation for infection including COVID-19 should be performed. Please refer to **Section 7.1.2** for guidance regarding the management of infusion reactions.

7.1.1 Grading of Infusion Reactions

Infusion reactions should be graded according to the criteria for acute systemic allergic reaction located in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected Version 2.1, July 2017, which can be found on the DAIDS Regulatory Support Center Web site: http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

7.1.1.1 Premedications and Prophylaxis

In clinical testing of other CD3-based bispecific molecules, including BITE (blinatumomab) and DART® molecules used for oncology indications, administration of pre-medications has proven to be helpful in ameliorating symptoms associated with cytokine release. Although the risk of induction of cytokine release should be low in participants treated with MGD014, as a precaution, participants will be premedicated with antipyretics and/or antihistamines prior to dosing with MGD014 (see **Section 6.6.2**). The use of corticosteroids will be reserved for those circumstances where cytokine release symptoms develop despite the administration of premedication prior to dosing with MGD014 (**Section 7.1.2**).

7.1.2 Management of Observed Infusion Reactions

All changes in the infusion of MGD014, including interruption of the infusion and its duration, as well as reductions in infusion rate and duration must be recorded.

The treatment guidelines (which may be modified as needed by the responsible PI (or designee) according to the best practices of medicine) for MGD014 infusion reactions will be in the study SOP.

Grade 1:

- Slow the infusion rate by 50%.
- Monitor the participant for worsening of condition.
- If the infusion reaction recurs and/or persists at the decreased rate of infusion, the rate of the infusion may be further reduced by 50% one additional time only.
- Continue rate at 50% reduction and increase dose rate to the original rate by doubling the infusion rate after 30 minutes, as tolerated.
- If symptoms persist but do not worsen, completion of the infusion will be at the discretion of the site PI (or designee) with careful monitoring.

Grade 2:

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PARTICIPANT. NO FURTHER MGD014 SHOULD BE ADMINISTERED.
- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING – ASPIRATE RESIDUAL DRUG FROM THE CATHETER.
- Administer antihistamines and corticosteroids per SOP, and other medications/treatment as medically indicated.
- IV fluids, supplemental oxygen, and bronchodilators should be considered as appropriate.

Grade 3:

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PARTICIPANT. NO FURTHER MGD014 SHOULD BE ADMINISTERED.
- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING – ASPIRATE RESIDUAL DRUG FROM THE CATHETER.

- Administer antihistamines and corticosteroids per SOP and other medications/treatment as medically indicated.
- IV fluids, supplemental oxygen, and bronchodilators should be considered as appropriate.

Grade 4:

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PARTICIPANT. NO FURTHER MGD014 SHOULD BE ADMINISTERED.
- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING – ASPIRATE RESIDUAL DRUG FROM THE CATHETER.
- Administer antihistamines and corticosteroids per SOP and other medications/treatment as medically indicated. Consider additional medications as per SOP (e.g., an IL-6 receptor inhibitor or IL-6 inhibitor, an IL-2 receptor inhibitor, and/or an anti-TNF antibody).
- Give epinephrine or bronchodilators as indicated.
- Support ventilation and blood pressure as indicated.

7.2 COVID-19/SARS-CoV-2 Infection

The following guidelines apply to participants with confirmed (positive by regulatory authority approved/authorized test) or presumed (test pending/clinical suspicion) coronavirus disease 2019 (COVID-19)/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection:

For participants with active SARS-CoV-2 infection, study drug should be delayed for at least 14 days from the start of symptoms.

Prior to restarting study drug, participants should be afebrile for 72 hours and SARS-CoV-2–related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. The sponsor should be informed when resuming study drug.

The sponsor must be informed within 24 hours of awareness of a participant with COVID-19/ SARS-CoV-2 infection.

8 CONCOMITANT THERAPY AND RESTRICTIONS

8.1 Concomitant Therapy

All concomitant medications, including ART and prophylactic pre-infusion medications administered during the participant's participation in the study until the end of treatment visit must be recorded in the source document. All changes in infusions of study drug, including interruptions and their duration, as well as reductions in rate and duration, must be recorded.

Medications taken within 4 weeks prior to administration of each infusion must also be recorded on the source documentation.

8.1.1 Prohibited Therapy

The following rules concerning concurrent treatment(s) will apply in this study:

- Participants may not receive other investigational drugs during the period of study participation.
- Participants may not be switched to an ART regimen containing maraviroc and/or enfuvirtide.
- The use of other immune-suppressive agents is prohibited, unless they are being used to treat an AE.
- Restrictions on medications taken prior to enrollment in the study are described in **Section 5.2**.
- Vaccinations, inclusive of flu vaccines, prohibited within 4 days prior to Day 0 through 5 days after last infusion of study drug.
- Participants requiring any systemic antiviral, antifungal, or antibacterial therapy for active infection must have completed treatment no less than one week prior to initiation of study drug.

8.1.2 Permitted Therapies

Participants may receive the following concurrent therapy:

- Regularly prescribed medications such as antipyretics, analgesics, antidepressants, sleep medications, megestrol acetate, testosterone, and other medications for chronic conditions that do not interact with MGD014;
- Oral and topical antibiotics for bacterial infections;
- Intermittent use of inhaled corticosteroids (e.g., for chronic obstructive pulmonary disease [COPD], asthma) is only permitted for participants not receiving ritonavir or cobicistat as part of their current ART regimen and after consultation with the study PI or designee).

- Sporadic topical use of corticosteroids (e.g., creams) to small areas of the skin (15 cm^2) after consultation with the PI (or designee) is only permitted for participants who are not receiving ritonavir or cobicistat as part of their current ART regimen; and
- For treatment of IRR (Grade 1 and Grade 2) flu-like symptoms, non-steroidal anti-inflammatory drugs (NSAIDs) may be used to alleviate symptoms under a physician's guidance and for a limited period of time.

9 STUDY PROCEDURES

This section provides a general description of the procedures and assessments associated with this study. The timing of the study procedures is presented in **Appendix 1**.

9.1 Study Visits

During the COVID-19 pandemic, alternative methods for conducting study assessments should be considered when compliance, feasibility, and safety can be assured. These methods may include:

- Remote visits, e.g., via telephone/video (using compliant video-conference tools as permitted by HIPAA regulations)
- Use of primary care centers and local laboratories for blood draws and imaging/radiographs

If alternative methods are used, local laboratory reference ranges will be documented and submitted to the sponsor. If local laboratory testing other than McLendon or LabCorp are used, their results and laboratory accreditation should be retrieved and documented in the participant's study records.

9.2 Informed Consent

Prior to performing any study-related procedure or assessments, the study coordinator discusses the study with the potential participant and obtains signed informed consent. This communication will be documented. Labs/procedures completed during a routine clinical care appointment that are the same as the study screening labs and/or procedures and completed within the 14 days preceding the screening visit can be used to qualify the participant upon approval by the study PI or designee.

9.3 Screening Period

Screening evaluations will be performed within 8 weeks (56 days) prior to study drug administration on Day 0 unless otherwise specified. At the 1st screening visit, participants will screen for the study. Only those participants who meet all eligibility criteria specified in **Section 5.1** Inclusion Criteria and **Section 5.2** Exclusion Criteria will be enrolled. A unique PID will be assigned during the screening visit. Participants who had previously completed Part 1 and are being considered for Part 2 will maintain the same PID and will be assigned a new study-specific identifier (SID).

Participants who are unable to meet protocol defined eligibility criteria at the Screening Visit (Step 1, Visit 1) may be eligible to re-screen again at the PI (or designee)'s discretion. In such cases, the same PID will be used. If a screen failure or the failure to enroll is due to the inability to meet one of the laboratory parameters (hematology, chemistry, HIV RNA, or CD4 T cell count), a laboratory retest of the failed criteria may be performed one time only. If the repeat value is within eligibility requirements, the participant can enroll on the study.

9.4 Enrollment and Registration

Step 1 Visit 1 determines eligibility and enrollment at Visit 2. Once the potential participant has been determined to be eligible for enrollment into the study, the participant must be registered with MacroGenics. The following information should be provided during registration:

- Year of birth
- Date of signed informed consent
- Planned date of first administration

Instructions for the registration process are provided in the Study SOP.

9.5 Medical History

Significant medical history should be obtained during the screening visit. All concurrent medical conditions in the last 60 days and any significant medical conditions (e.g., hospitalizations, surgeries, prior medical history) should be collected. Medical history obtained at Screening will include demographic information (e.g., date of birth, gender, race, and ethnicity, etc.), participant's medical history, HIV testing history (CD4 and VL) and HIV medication history, inclusive of prior genotypes (if available). Safety updates will occur at all clinical visits, according to **Appendix 1**.

During the Step 1 screening period (prior to MGD014 administration), any untoward event that occurs should be collected as a concurrent medical history and not as an AE, unless it is due to a protocol-related procedure. Thereafter (i.e., after the time of study drug administration), any untoward event should be collected as an AE.

9.6 Prior and Concomitant Medications

All concomitant medications administered during screening and the participant's participation in the study until the end of study visit must be recorded in the source. Concomitant medications will be reviewed at every study visit.

Prescription and non-prescription medications taken within 4 weeks prior to screening must be recorded on the source document.

9.7 ART Adherence

ART adherence will be reviewed at every visit. Non-adherence will be defined as having missed more than 9 total days in the 3 months prior to screening. Assess any missed doses while on study and discuss with PI (or designee). Continuance on study will be contingent on ART adherence.

9.8 Physical Examination

Complete physical examination will include examination of skin, head, eyes, ears, nose, throat, lymph nodes, heart, chest, lungs, abdomen, extremities, and neurologic system according to schedule specified in **Appendix 1**. A directed physical exam will be performed at the visits indicated in the SOE, according to **Appendix 1**, and includes VS. The targeted or directed physical exam addresses any previously identified or new event that the participant experiences since the last study visit or any unresolved signs or symptoms previously experienced. In addition to the VS, this assessment includes updates to signs and symptoms, and clinical assessment of HIV disease.

9.9 Vital Signs

At each study visit, the VS (body temperature (T), pulse (P), respiratory rate (RR), seated blood pressure (BP)) and weight will be recorded according to the schedule specified in **Appendix 1**. Height is only required at Step 1, Visit 1.

Repeat VS (T, P, RR, BP) may also be captured as necessary to elucidate the course of any untoward event or AE and may be inclusive of all or individual VS components as required to address monitoring of the AE.

9.10 Leukapheresis

Part 1:

The leukapheresis is optional in Part 1. Participants consenting to this optional procedure will have the procedure at Visit 2 or at any time point between Visit 2 and the day of the infusion.

Part 2:

The leukapheresis is optional in Part 2. Participants consenting to this optional procedure will undergo 2 leukapheresis procedures in Part 2. The first leukapheresis occurs at baseline completed at Visit 2. The second leukapheresis procedure will occur in Step 3, the post treatment phase, approximately 2 weeks post-completion of MGD014 therapy (± 2 weeks).

All leukapheresis products will be transported on the day of collection to the [redacted] Laboratory on the UNC campus.

NOTE: Refer to the Apheresis SOP and Study Specific Lab Manual for procedures specific to this study.

Participants who experience a Grade 3 or higher toxicity during the leukapheresis will be evaluated on a case by case basis to understand the cause of the Grade 3 event. If the clinical situations (i.e., vaso-vagal response) that lead to the discontinuation of the leukapheresis procedure is determined by the study PI in collaboration with the apheresis medical director to be situational and poses no apparent harm to the participant, the leukapheresis procedure may be repeated. However, if determined by the study PI, apheresis medical director, or the medical monitor that repeated leukapheresis would be harmful to the participant, then he/she will be terminated from the study.

The only exception to this discontinuation policy will be related to elevations in BP. Elevated BP observed during the leukapheresis procedure will be monitored via apheresis Lab policies. These will be noted and documented but will not be used to discontinue study participation.

9.11 Clinical Laboratory Tests

Blood and urine specimens will be collected according to the schedule specified in **Appendix 1**. Safety laboratory tests can be performed up to 7 days prior to the infusion and must be reviewed before study drug administration.

Monitoring HIV RNA levels

In the event of HIV-1 viral load of ≥ 50 copies/mL after the infusion of MGD014, the following should occur per standard of care:

- Adherence to ART should be carefully assessed and documented.
- A standard HIV RNA assay should be repeated within 1-4 weeks.
- HIV resistance testing will be performed at the time of drawing a confirmatory sample.
- In the event of HIV-1 viremia ≥ 150 copies/mL, the participant may continue with study treatment if repeat testing is < 100 copies/mL within 4 weeks and < 50 copies/mL within 12 weeks.
- HIV RNA will be repeated every 2 weeks, or sooner as clinically indicated, until <50 copies/mL.
- In the event of confirmed HIV-1 viremia and documented adherence to ART, ART should be managed by the primary care provider in discussion with the study team. The results of the HIV resistance tests will be shared with the participants and their care providers.

9.12 Central Laboratory Assays

Study specific safety and research samples will be collected at the research visit. Safety and clinically relevant assays will be performed at UNC McLendon Laboratories or LabCorp. Research assays will be processed and stored in associated research laboratories. Additional details on collection, processing, storage, and shipping of samples will be provided in the Study Specific Laboratory Manual.

9.13 Pharmacokinetics

Blood samples for MGD014 PK and ADA will be collected at the time points shown in **Appendix 1** and **Appendix 2**. Further details of blood collection and processing will be provided in the Study Specific Laboratory Manual. Actual collection date and time must be recorded in the source documents.

9.14 Immunogenicity

Blood samples will be collected from the participant's arm contralateral to the site of IV infusion. If an indwelling catheter is used, the fluid in the indwelling catheter will be removed and discarded prior to the collection of blood sample for ADA assessment.

9.15 Pharmacodynamics

Appendix 1 and **Appendix 2** lists the sampling schedule to be followed for the assessment of the PD activity of MGD014. Further details of blood collection and processing will be provided in the Study Specific Laboratory Manual. Actual collection times must be recorded in the source documents.

9.16 Sample Collection, Storage, and Shipping

All blood samples acquired for PK and ADA described in **Section 10** will be processed at the UNC CFAR HIV/STD Laboratory Core (CHSLC) and shipped to MacroGenics for analysis.

All blood samples acquired for serum cytokine assays described in **Section 10.3.2** will be processed at CHSLC and shipped to Duke University for analysis.

Samples for RO, T cell phenotype, resting CD4 T Cell infection, and exploratory research assays (**Sections 10.3.1**, **10.3.3**, and **11.1.1**, respectively) will remain at UNC for processing and storage.

Samples for Plasma HIV-1 RNA SCA assays described in **Section 11.1.2** will be processed at UNC CHSLC, stored, and shipped in batch to National Cancer Institute (NCI) for analysis.

Details on laboratory specimen processing, storage, and shipping will be provided in the Study Specific Laboratory Manual.

9.17 Electrocardiography Monitoring

Twelve-lead ECGs will be obtained according to **Appendix 1** in order to evaluate the potential cardiac effects of MGD014, including QT interval. There are no requirements for fasting and no restrictions for fluid and food intake by the participants during this study. ECGs will be obtained as per **Appendix 1**.

9.18 End of Study Visit

End of study visit occurs after the last dose of study drug. See **Appendix 1**, Time and Events Schedule.

10 ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

10.1 Pharmacokinetics Assessments

Serum concentrations of MGD014 will be monitored. Single and multiple dose PK parameters of C_{max}, time to maximal concentration (T_{max}), area under the concentration-time curve for a dosing interval (AUC_{tau}), trough concentration (C_{trough}), CL, V_{ss}, and terminal half-life ($t_{1/2}$) will be derived from serum concentration versus time data. Population PK analyses may be conducted using data from this study alone or combined with data from other studies.

10.2 Immunogenicity Assessments

Blood samples for immunogenicity assessments (ADA) will be collected at the time points shown in **Appendix 2**.

10.3 Pharmacodynamic Assessments

10.3.1 Receptor Occupancy and/or T-cell Binding

The receptor occupancy of MGD014 binding sites on CD3-expressing T cells in peripheral blood will be estimated. The percentages of T cells in peripheral blood with MGD014 bound will be measured.

% RO = (MFI of anti-MGD014 events with saline)/(MFI of anti-MGD014 events with excess MGD014) ×100. An event is defined as either a CD4-expressing or CD8-expressing T cell that has MGD014 binding to the T cell as detected by an anti-MGD014 antibody.

10.3.2 Serum Cytokine Analysis

Serum samples will be analyzed for concentrations of serum cytokines, which will include, but not be limited to, IFN-γ, IL-2, IL-5, IL-6, IL-10, and TNF-α.

10.3.3 T cell Phenotype and Function

Flow cytometry panels for T cell phenotyping will include: T cell subsets, surface expression levels of activation of T cells, and exhaustion of T cells. Functional changes to circulating CD8 T cells by flow cytometry may be assessed.

11 ASSESSMENT OF EFFICACY

11.1 Efficacy Assessments

Efficacy will be assessed by examination of the ability of MGD014 administration to alter markers of persistent HIV-1 infection in individuals on ART if the participant consents to the optional leukapheresis through evaluation of: a) the frequency of resting CD4 T cell infection by QVOA and b) levels of plasma HIV-1 RNA, as measured by SCA.

11.1.1 Resting CD4 T Cell Infection

Lymphocytes by continuous-flow leukapheresis (samples obtained as per **Appendix 1**) and resting CD4 T cells are isolated as previously described [**52**].

Quantitative viral outgrowth assay measurements determine the frequency of CD4 resting cell infection, expressed as infectious units per million (IUPM). The resting cell infection frequency is a measure of the lowest detectable HIV reservoir. A statistically significant decline in the HIV reservoir would be considered evidence of a reduction in the HIV reservoir.

11.1.2 Plasma for SCA

Residual low-level HIV-1 viremia by SCA, as evidence suggests that such HIV-1 viremia originates in persistently infected cells, and low-level HIV-1 viremia might be reduced by an augmented antiviral immune response.

12 ADVERSE EVENT REPORTING AND ASSESSMENT OF SAFETY

The safety assessment will be based on the evaluation of all AEs that occur from the time of initiation of administration of study drug through the End of Treatment Visit or 30 days after the last dose of study drug (whichever is later) and will be determined based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled participants, as appropriate.

If an AE occurs, the study coordinator, in collaboration with the PI, will evaluate the severity and seriousness of the AE and the relationship to the study drug, and will document the findings.

All adverse events will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected Version 2.1, July 2017, which can be found on the DAIDS Regulatory Support Center Web site: http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

AEs reported between the time the potential participant signs the informed consent form (ICF) and the administration of the first dose of study drug will be captured as medical history unless the AEs are attributed to protocol-specified procedures that are not part of standard of care that occur during this time period, in which case the AEs will be collected on the Source Document Adverse Event Form. Protocol-related AEs and SAEs will be collected from the time the participant has consented to study participation.

SAEs considered related to study drug may be reported at any time, even after the participant's final treatment visit.

The reporting of laboratory abnormalities as both laboratory findings and AEs should be avoided. Laboratory abnormalities should not be reported as AEs unless any one of the following are met:

- Any criterion for an SAE is fulfilled
- The laboratory abnormality causes the participant to discontinue from the study treatment
- The laboratory abnormality causes the participant to interrupt the study treatment
- The laboratory abnormality causes the participant to modify the dose of study treatment
- The laboratory abnormality requires intervention
- The PI (or designee) determines the laboratory value as an abnormal change from baseline and is of clinical significance for that participant
- Laboratory values consistent with the DAIDS designation of Grade 3 (events as severe or medically significant) and Grade 4 (events as life-threatening), should be reported as AEs or SAEs, as appropriate.

12.1 Definitions

12.1.1 Adverse Event

AE means any untoward medical occurrence in a participant or clinical trial participant associated with the use of a drug in humans, whether or not considered drug related. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example, see **Section 12.2.1**), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

12.1.2 Adverse Drug Reaction

Adverse drug reaction (ADR) is a noxious and unintended response to the medicinal product related to any dose. As used herein, the phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

12.1.3 Adverse Event of Special Interest

An AE of special interest (AESI) is an event of scientific and medical interest or concern to the sponsor, for which ongoing monitoring and rapid communication to the sponsor could be appropriate. It may be a serious or non-serious AE, which may require further investigation in order to characterize and understand it.

12.1.4 Attribution/Assessment of Causality

Attribution/Assessment of Causality is a determination that describes the relationship or association of the study drug with an adverse event.

This assessment of causality or relationship of AEs to the study drug is provided by the PI and is determined by 1) temporal relationship of the event to the administration of study drug; 2) whether an alternative etiology has been identified, and 3) biological plausibility.

The causality assessment categories that will be used for this study are described below.

Causality assessments that are considered **not related** to study drug:

> *Not related:* The event is related to an etiology other than the study drug (the alternative etiology must be documented in the participant's medical record).
>
> *Unlikely:* The event is unlikely to be related to the study drug and likely to be related to factors other than study drug. An alternate explanation is more likely (e.g., concomitant drugs, concomitant disease), or the relationship in time suggests that a causal relationship is unlikely.

If an AE or SAE is considered "unlikely" or "unrelated" to study drug, the PI should offer his/her clinical opinion as to what factor(s), agent(s), or process(s) were the likely causative mechanism for the event.

Causality assessments that are considered **related** to study drug:

Possible: There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug; but there may also be alternative etiology, such as characteristics of the participant's clinical status or underlying disease.

Probable: There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and the event could not be reasonably explained by known characteristics of the participant's clinical status or an alternative etiology is not apparent.

Definite: There is an association between the event and the administration of study drug; a plausible mechanism for the event to be related to the study drug, causes other than the study drug have been ruled out, and/or the event re-appeared on re-exposure to the study drug.

12.1.5 Serious Adverse Events

An SAE is any AE that results in any of the following outcomes:

- Death
- Life-threatening (immediate risk of death)
- Inpatient hospitalization for longer than 24 hours or prolongation of existing hospitalization (even if the event is Grade 1)
- Persistent or significant disability or incapacity
- Congenital anomaly/birth defect
- Important medical events

12.1.6 Severity Criteria

Event *severity* will be assigned according to the assessment of the PI using Division of AIDS (DAIDS) grading table Version 2.1.

Severity Grade for Parameters Not Identified in the Grading Table:
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as Grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

12.2 Adverse Event Collection and Documentation

12.2.1 All Adverse Events

Adverse Events (AEs) leading to discontinuation, potential autoimmune events, AEs of ≥ Grade 3 severity, related adverse events, and lab abnormalities as well as safety concerns, will be communicated in a timely manner to the UNC IRB, MacroGenics, National Institute of Allergy and Infectious Diseases (NIAID), and FDA per the reporting requirements of each body/authority. The sponsor of this study is MacroGenics. The PI at UNC-CH will be responsible for reporting to MacroGenics, who in turn, will be responsible for reporting to NIAIDs, and FDA per the reporting requirements of each body/authority. AEs occurring after the participant undergoes early termination or completes the trial need not be reported unless the event is serious, and the PI believes that the event may have been caused by the study drug or a protocol procedure.

All participants who receive at least one dose of study drug will be considered evaluable for safety. AEs will be determined based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled participants as appropriate.

All AEs whether serious or non-serious, will be evaluated from the time a signed and dated ICF is obtained until 30 days following the last dose of study drug. AEs and SAEs reported between the time the participant signs the ICF and the administration of the first dose of study drug will be captured as concurrent medical history unless the events are attributed to protocol-specified procedures. AEs attributed to protocol-specified procedures will be recorded in the database and provided to the sponsor. Additionally, the IRE form will be completed and provided, as appropriate.

All AEs must be reported, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the AE source document. AEs will be coded to the Preferred Term using the current version of MedDRA available at study initiation. All records will need to capture:

- The details of the duration, severity, and seriousness of each AE,
- The action taken with respect to the study drug(s),
- The PI attribution/causality assessment concerning the relationship of the AE to study therapy,
- The outcome of the event.

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). All treatment measures that are required for AE management must be recorded in the source document. The intensity (severity) of AEs will be assessed and serious events will be determined by the definition provided in **Section 12.1.5** above.

Clinical Laboratory Changes: Safety laboratory assessments will be carried out locally at UNC and evaluated by the PI to ensure participant safety. The PI is responsible for reviewing the results of all laboratory tests as they become available.

- Laboratory values that fall outside of a clinically accepted reference range or values that differ significantly from previous values must be evaluated by the Investigator (or designee) for clinical significance. The Investigator (or designee) may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests.
- If the Investigator determines the laboratory value is an abnormal change from baseline and is of clinical significance for that participant, it is considered an AE.
- Generally, Grade 1 and Grade 2 laboratory findings need not be reported as AEs unless deemed clinically significant by the Investigator.
- Consistent with the DAIDS designation of Grade 3 events as severe or medically significant and Grade 4 events as life-threatening, Grade 3 and Grade 4 laboratory findings should be reported as AEs or SAEs, as appropriate.
- The test result or finding should be reported as the AE. Such laboratory values should generally be recorded as “increased” or “decreased” (e.g., change from baseline potassium of 5.0 to 3.5 mEq/L =potassium decreased).

The sponsor has responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the Investigator (or designee) all suspected unexpected serious adverse reactions (SUSARs). The Investigator (or designee) must report SUSARs to the UNC IRB, unless otherwise required and documented by the IRB.

12.2.2 Immediately Reportable Events

IREs are AEs that must be reported immediately to MacroGenics within 24 hours of the study site's awareness of the event:

- All SAEs
- Pregnancy in a study participant or partner of a study participant.
- The following AESI: ≥ Grade 2 CRS /IRR
- Administration of a dose significantly greater (specifically, + 20 % or higher) than the planned dose, and results in an event of clinical consequence.
- AEs leading to permanent discontinuation of study drug in an individual participant.
- Withdrawal of the participant from study drug administration for any reason
- Product quality issues with an associated clinical consequence.
- Participant diagnosed with COVID-19/SARS-CoV-2 infection.

In those cases, in which the IRE is considered related to study drug, the study drug may be discontinued, and the participant will continue participation in the study for observational safety and analysis (except for cases where the participant is withdrawn from the study by the PI (or designee) or withdrew the consent). At any time after completion of the study, if an PI (or designee) becomes aware of a SAE that s/he suspects is related to study drug, the PI (or designee) should report the event to MacroGenics Product Safety.

12.2.3 Serious Adverse Events

All SAEs occurring during the study must be reported to MacroGenics and the UNC IRB per the MacroGenics and UNC IRB reporting requirements. A written report (IRE Form) will be faxed or emailed to MacroGenics within 24 hours. Additional information will be supplied as requested. All SAEs occurring during the study will be reported by MacroGenics to DAIDS following guidelines for expedited AE (EAE) reporting and to the FDA according to those regulatory bodies' guidelines.

After 30 days following the last dose of study drug administration only SAEs the PI (or designee) considers related to study drug or a protocol procedure, should be reported to the sponsor.

Information regarding SAEs will be transmitted to the sponsor using the IRE Form, which must be completed and signed by the PI from the study site and transmitted to the sponsor within 24 hours of the site becoming aware of the serious adverse event.

All Grade 3 or Grade 4 SAEs considered related to study drug must be followed until recovery to baseline or Grade 1 with the date of resolution recorded in the source documents. In addition, the investigator should report all reportable Grade 3 or Grade 4 SAEs to the IRB. Resolution of an

event is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to etiology other than the study drug or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant 's participation in a study must be reported as a SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term facility).
- Surgery or procedure planned before entry into the study (must be documented in the source document).

12.2.4 Protocol-specific Adverse Events of Special Interest (AESI)

Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities by the sponsor. All AEs will be reported in the database. The sponsor will be notified of these events within 24 hours of awareness by the site, if grade 2 or greater, regardless of seriousness (i.e., serious and non-serious adverse events).

- CRS
- IRR

12.2.5 Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the Immediately Reportable Event form. Additionally, the Pregnancy Notification Form should be completed. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal

death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the IRE Form. Any participant who becomes pregnant during the study must discontinue further study drug administration.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male participants included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event. If the female partner of a male participant becomes pregnant within 24 weeks after the last MGD014 infusion, a request to the partner will be made to complete a Pregnant Partner Consent Form so that the pregnant partner, fetal and/or newborn information can be collected.

Upon confirmation of the pregnancy with a serum pregnancy test, the participant will be followed for the outcome of pregnancy. All live newborns will be followed at six months after the birth, and all necessary information will be collected to assess the effects of study drug on the newborn. If necessary, the follow-up period will be extended for the newborn.

12.2.6 Reporting of Adverse Events to the Sponsor and DAIDS

Throughout the study, the Investigator must document all AEs in the source documents (and database) in a timely manner. IREs, as defined in **Section 12.2.2** are events that must be reported immediately to MacroGenics Product Safety or designee within 24 hours of being identified and be entered into the database within 5 calendar days. The sponsor, MacroGenics, is responsible for reporting to DAIDS.

All reportable AEs must have their severity graded along with attribution to study drug recorded.

AEs leading to discontinuation, potential autoimmune events, AEs of ≥Grade 3 severity related to MGD014, as well as safety concerns will be communicated within 24 hours to MacroGenics and the UNC IRB, as required. MacroGenics will report to the DAIDS and FDA per their reporting requirements.

All AEs and SAEs must be followed until resolution, or they become chronic, or stable. The resolution status of such an event must be documented. In addition, the PI should report all follow-up for reportable AEs and SAEs to the UNC IRB and MacroGenics. MacroGenics will report all follow up to DAIDS and FDA.

The PI (or designee) will immediately complete and transmit the *Immediately Reportable Event (IRE)* Report Form, within 24 hours of identifying the event, to MacroGenics Product Safety or designee. The IRE Report Form and Completion Guidelines, and Contact Information for Reporting IREs, are found in the Study Procedures Manual.

For reports of pregnancy, the IRE Report Form **AND** the MacroGenics Pregnancy Exposure Form must be completed and transmitted. The Investigator must attempt to follow the pregnancy to term or termination in order to report the outcome and health status of the mother and child. The Pregnancy Exposure Form is found in the Study Procedures Manual.

Please refer to the **Table 2** for reporting timeframes by event type:

Table 2 Safety Reporting by UNC by Event Type

Event Type	Report to MG via Immediately Reportable Event Form within 24 hours of awareness	Pregnancy Exposure Form (within 24 hours of awareness) to MG	Adverse Event Form (UNC database)	Report to UNC IRB
All SAEs	X		X	X
Pregnancy in a study participant or partner of a study participant	X	X	X	X
AESIs: ≥ Grade 2 Cytokine Release Syndrome/Infusion-Related Reaction	X		X	X
Administration of a dose significantly greater (specifically, + 20% or higher) than the planned dose, and results in an event of clinical consequence.	X		X	X
AEs leading to permanent discontinuation of study drug in an individual participant.	X		X	X
Withdrawal of the participant from study drug administration for any reason	X		X	X
Product quality issues with an associated clinical consequence.	X		X	X
COVID-19/SARS-CoV-2 Infection	X		X	X
Non-serious AEs			X	

13 PRODUCT QUALITY COMPLAINT AND HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1 Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel, after being made aware of the event, and those that are associated with clinical consequences must be reported within 24 hours.

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to **Section 12.2.3**). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2 Contacting Sponsor Regarding the Product Quality

The name(s) (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Study Specific Procedure Manual.

14 PLANNED STATISTICAL METHODS

The majority of the statistical summaries for this Phase 1 trial will be descriptive. Summary statistics will consist of absolute and relative frequencies of each category of discrete variables of means, standard deviations, coefficient of variations, medians, and minimum and maximum values of continuous variables.

14.1 Determination of Sample Size

The number of participants is not based on statistical power calculations. A 1+3 design is utilized in the first two dose levels of Part 1 because the starting dose is considered biologically conservative and the anticipated risk of DLT is low. A 3+3 design is used for dose cohorts 3-8. The total sample size of Part 1 is at least 20, but will depend upon the occurrence of DLTs and potential need for expanded dose level cohorts (see **Section 4.2.1**). Part 2 of the study will have six (n=6) participants. This study overall plans to have approximately 26 HIV-1 infected, ART suppressed participants in total (Part 1 + Part 2). No inferential statistics will be calculated in Part 1. This sample size is considered biologically sufficient to evaluate the primary objective of this study (first in human evaluation of safety and tolerability of MGD014).

14.2 Analysis Populations

All participants who receive any MGD014 infusion will be included in the safety data sets. Participants enrolled in the Part 1 single-dose cohort will contribute to analysis of the OBD and MTD. Participants enrolled in the Part 2 multi-dose cohort will contribute to multi-dose safety, PK, and PD analyses.

14.3 Demographics and Baseline Characteristics

Participant disposition, demographics, baseline characteristics, disease history, medical history, concomitant medications, and study drug exposure data will be summarized using descriptive statistics. Key demographic and baseline characteristics include biological sex, race/ethnicity, age, baseline ART regimen, years on ART, and nadir CD4.

14.4 Safety Endpoints

14.4.1 Adverse Events

Adverse events will be coded to the Medical Dictionary for Regulatory Activities (MedDRA). Events prior to treatment (e.g., due to study-related procedure) will be listed separately in an appendix to the final CSR.

The following tables of AE data will be created to summarize the number and percent of participants who experience at least one event of each of the following types:

- All AEs
- Drug related AEs by severity grade

- AEs by severity grade
- All SAEs (this may be a listing if there are few events)
- Drug-related SAEs
- Fatal AEs (this may be a listing if there are few events)
- AEs that result in study discontinuation
- AEs that lead to withdrawal of study drug
- AEs categorized as AESI and/or IREs
- AEs with severity grade 3 or greater
- Drug-related AEs with severity grade 3 or greater

All of these tables will display the number and percent of participants that experience the given event and will display events by System Organ Class (SOC) and Preferred Term (PT). Events will be displayed alphabetically for SOC and in descending order of overall PT incidence within each SOC.

14.4.2 Laboratory Values

Summaries of abnormal laboratory values will display descriptive statistics for numerically quantified labs. Summaries will be grouped by lab panel (e.g., hematology, blood chemistry, and urinalysis) and will be displayed by visit for each lab parameter. Graphs of mean values over time or individual values at each time point may be used. Mean change from baseline may also be graphed. Graphs of individual values are preferred when feasible due to the small sample size of this study.

In cases where an abnormality resulted in a repeat lab test, the repeat value will be used for the summaries. A list of repeated labs including original values and repeat values will be included.

Shift tables will be used to display the number and percent of participants who have a shift in their lab values from normal at baseline to each post-baseline visit by severity grade.

14.4.3 Other Safety Endpoints

Electrocardiograms will be collected and analyzed for evidence of cardiac toxicity, especially prolongation of QT interval. Vital signs will be summarized with descriptive statistics at each visit and time point where they are collected.

14.5 Efficacy Endpoints

14.5.1 Quantitative Viral Outgrowth Assay

For participants who completed the optional leukapheresis, a comparison of pre-MGD014 and post-MGD014 frequency of HIV infection per million resting CD4T cells will be performed

using a non-parametric 2-sided exact sign test to assess whether or not a significant decrease of IUPM is observed. The primary comparison will be between the leukapheresis taken at baseline and approximately 2 weeks following the last MGD014 infusion in Part 2 (at Day 42 ± 2 weeks). The sign test used for this analysis makes minimal statistical assumptions and is based solely upon whether each participant is observed to have a decrease in HIV infection within resting CD4 cells following MGD014 treatment. Results will be presented as the proportion with decreased IUPM and the corresponding confidence interval (CI). If the observed proportion with decreased IUPM is 100% (6/6 participants) the corresponding 95% CI will span from [0.541, 1.000]; this CI would exclude a null hypothesis of no change (H_0: probability of decrease=0.50).

Precision calculations for QVOA analysis

Number of participants with decrease in IUPM	Binomial 95% CI (Clopper-Pearson)
6 of 6 (100%)	[0.541, 1.000]
5 of 6 (83%)	[0.359, 0.996]

IUPM=infectious units per million CI=confidence interval

14.5.2 Single Copy Assay

For participants who completed the optional leukapheresis, a comparison of pre-MGD014 and post-MGD014 measurements of residual low-level HIV-1 viremia quantified by SCA using a nonparametric 2-sided exact sign test will be performed to assess whether or not a significant decrease in plasma HIV-1 viremia is observed. Left-censored observations (SCA < 1 copy) are anticipated and the sample size is six (6) participants. Based on background data from the AIDS Clinical Trials Group (ACTG) trial A5244, we assume a 10% probability that participants (with plasma HIV-1 RNA <50 copies/mL at screening, per eligibility) will have a SCA measurement below the limit of detection (<1 copy) at the pre-MGD014 measurement [**54**]; it is unknown how large of an effect MGD014 will have upon SCA levels post-therapy. The precision calculations provided above in the QVOA analysis section apply here, i.e., if the observed proportion with decreased low-level HIV-1 viremia as measured by SCA is 100% (6/6 participants) the corresponding 95% CI will span from [0.541, 1.000] and the null hypothesis can be rejected.

14.5.3 Exploratory Endpoints

Additional exploratory endpoints are defined as change in a quantitative measure from baseline to post-MGD014 administration. Using a two-sided 0.05 significance level, 10,000 empirical simulations from a normal distribution with mean change equal to 2 standard deviations (SD) with n=6 evaluable participants achieved 86 % power to detect a statistically significant change from baseline to post-infusion using an exact Wilcoxon signed-rank test (for paired data). Observed virologic and immunologic measurements may not be normally distributed or may be partially censored due to assay limits of quantification. A Wilcoxon signed-rank test will be used for continuous outcome measures when appropriate; otherwise, an exact sign test will be utilized. Potential immune correlates of antiviral impact will be assessed graphically (e.g., scatter plots, correlate heat map) and estimated with a non-parametric rank based correlation method. Additionally, association between antiviral impact of MGD014 and baseline participant clinical

characteristics, such as stage of HIV infection (acute vs. chronic) at initiation of ART, will also be described and examined. Correlation including one or more measures from the same participant may be assessed using Kendall's tau for clustered data [53]. Exploratory analyses will be conducted using a two-sided 0.05 significance level with no adjustment for multiplicity.

14.6 Pharmacokinetic Endpoints

Geometric means and percent coefficients of variation may be reported for C_{max}, AUC, and C_{trough}; arithmetic means and standard deviations may be reported for $t_{1/2}$, CL, and V_{ss}; and medians, minimum, and maximum will be reported for T_{max}.

14.7 Pharmacodynamic Endpoints

Summary statistics for biomarkers, such as but not limited to those listed under **Section 10.3** and corresponding changes from baseline, will be summarized and may also be presented graphically as will possible associations between changes in PD measures of interest and MGD014 dose and exposure.

14.7.1 Serum Cytokines

Data will be tabulated and summarized by dose panel and time. Plots of serum cytokine levels versus time may be provided. Additional analyses may be conducted in order to characterize the relationship between the MGD014 serum concentrations and serum cytokines (e.g., an exposure-response analysis), if deemed appropriate.

14.8 Immunogenicity Endpoints

The proportion of participants who are negative for MGD014 ADA at baseline and become positive in this assay, the proportion of participants who are negative at baseline and remain negative, and those who have positive ADA at baseline that increases or decreases in titer over the course of treatment will be summarized. Positive samples will be evaluated for neutralizing capacity and the incidence of neutralizing antibodies will also be summarized. The impact of immunogenicity on safety, PK, and PD will be summarized and explored graphically.

14.9 Cohort Analyses and Monitoring

As described in **Section 4.2.1**, the decision to escalate doses from cohort to cohort will only occur based on consensus supporting escalation by PI (or designee) and the medical monitor. The medical monitor and the PI (or designee) will review aggregate safety data up through Day 14 from all dosed participants from the prior dose cohort.

An independent Safety Monitoring Committee (SMC) will receive monthly study progress and safety monitoring reports. Study feasibility and the achievement of study milestones will be assessed in these reports. Additionally, accrual, baseline characteristics, conduct of the study (including premature study discontinuations), any interruptions of ART, virologic failures, and all reported toxicities and events will be monitored during the study on a monthly basis. The

individual safety data will be reviewed monthly to assess relation of all reported toxicities and AEs to the study treatment. The monthly data will be shared with the SMC for review.

If at any time during the study, two or more participants experience a toxicity that is Grade 3 or higher and definitely, probably, or possibly related to study treatment (as judged by the protocol team), or two or more participants experience the same DLT that is Grade 2 or higher, then enrollment into the study will be temporarily suspended and the independent SMC will be asked to review all safety data; review the relation to study treatment of the event(s); and recommend how the study should proceed with respect to resuming enrollment and continuing study treatment.

14.10 Primary Analysis

Not applicable.

14.11 Final Analysis

Final analysis of all data will be carried out at the End of the Study.

15 QUALITY CONTROL AND ASSURANCE

Quality review activities will be undertaken to ensure accurate, complete, and reliable data. MacroGenics Inc. or designees will do the following:

- Provide instructional material to the study site, as appropriate.
- Sponsor a start-up training session (Investigator Meeting or Study Initiation Visit) to instruct the Investigator and study coordinators. This session will give instruction on the protocol, and study procedures.
- Make periodic visits to the study site to monitor protocol compliance and general Good Clinical Practice (GCP) compliance.
- Be available for consultation and stay in contact with the study site personnel by mail, e-mail, telephone, and/or fax.
- Conduct a quality review of the database.

15.1 Monitoring, Auditing and Inspections

To ensure the safety of participants in the study, compliance with applicable regulations, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and participant medical records in the participant files as source documents for the study.

An independent study monitor will monitor the study on a regular basis throughout the study period according to the study monitoring plan. The Investigator will allocate adequate time for such monitoring activities. The study monitor periodically will conduct a review of a sample of the participant data recorded on source documents at the study site. The Investigator will also ensure that the monitor is given access to all the above noted study-related documents, source documents (regardless of media) and study-related facilities (e.g., investigational pharmacy, etc.), and has adequate space to conduct the monitoring visit. Queries may be raised if any datum is unclear or contradictory. The Investigator and site personnel must address all queries in a timely manner.

Participation as an Investigator in this study implies acceptance of the potential for inspection by the study sponsor/representatives, US or non-US government regulatory authorities, IRB/IEC and applicable compliance and quality assurance offices. The Investigator will permit study-related audits and inspections and will provide access to all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g., investigational pharmacy, CTRC, etc.).

15.2 Data Entry and Computerized Systems

An electronic data capture system will be used in this trial. Other data assessments, such as central laboratory assessments, will be managed by MacroGenics or central vendors for transfer to MacroGenics Inc. or representative for use in the study analysis.

16 ADMINISTRATIVE CONSIDERATIONS

16.1 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

The Investigator should provide the sponsor with a statement of compliance from the IRB/IEC indicating compliance with the applicable regulations in the region and International Conference on Harmonization (ICH). Any documents that the IRB/IEC may need to fulfill its responsibilities, such as the protocol and any amendments, Investigator's Brochure (IB), and information concerning participant recruitment, payment or compensation procedures, or information from the sponsor will be submitted to the UNC IRB. The IRB's written approval of the study protocol and the ICFs will be in the possession of the Investigator and the sponsor before the study drug is initiated at the Investigator's site. The Investigator will transmit the IRB's approval statement to the sponsor. This approval must include the date of review and refer to the study by protocol title and/or study number and version number and refer to the ICFs by version number or date. If the IRB or institution uses its own unique number for the protocol instead of the sponsor's number, that unique number should be noted on the approval statement. The date of approval and/or expiration must be included.

Protocol modifications or changes may not be initiated without approval from the sponsor, except when necessary to eliminate immediate hazards to the participants. Such modifications will be submitted to DAIDS; written verification that the modification was submitted and approved should be obtained. Modifications should then be submitted to the IRB and PRO prior to implementation.

The Investigator must, where required by local regulations, submit to the IRB:

- The protocol and the IB and any amendments or updates.
- The informed consent form(s) and any amendments or changes.
- Any documents given to participants or potential participants (e.g., recruitment materials, diary cards) and the plan for distribution/use.
- Revisions of other documents originally submitted for review or for notification.
- Serious and/or unexpected AEs occurring during the study.
- New information that may adversely affect the safety of participants or conduct of the study.
- At minimum, an annual update and/or request for re-approval of study, unless otherwise specified by IRB.
- Protocol deviations.
- Notification when the study has been completed.
- Proof of indemnity/liability insurance.
- Other documents required by the IRB.

16.2 Ethical Conduct of the Study

The investigational study will be conducted according to the Protection of Human Subjects (21 CFR 50), IRBs (21 CFR 56), Obligations of Clinical Investigators (21 CFR 312.60 – 312.69), the current ICH Guideline for Good Clinical Practice (ICH E6), and all other applicable regulations.

16.3 Participant Information and Consent

It is the responsibility of the Investigator to obtain and document written informed consent (IC) from the participant. IC in compliance with the principles of informed consent in ICH E6 and all applicable local regulations should be obtained before any protocol-specified procedures or interventions are conducted. The sponsor reserves the right to delay initiation of the study at a site where informed consent forms (ICFs) do not meet the standards of applicable local regulations or ICH E6.

Information should be given to the participant in both oral and written form, and participants must be given ample opportunity to inquire about details of the study.

The ICF generated by the Investigator must be approved by the IRB. The Investigator will provide the sponsor with a copy of the IRB-approved ICF and a copy of the IRB's written approval before the start of the study.

Informed consent forms must be written (and appropriately translated in the participant's native language or language in which the participant has fluency) so as to be understood by the prospective participant. Informed consent will be documented by the use of a written consent form approved by the IRB. The ICF must be signed and dated by the participant and by the person who conducted the discussion of the informed consent.

All versions of each participant's signed ICF must be kept on file by the Investigator for possible inspection by regulatory authorities and/or authorized MacroGenics monitoring and regulatory compliance persons. The participant should receive a copy of the signed and dated written ICF and any other written information provided to the participants.

16.4 Participant Confidentiality

To maintain confidentiality of participants, all research laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number. Clinical information will not be released without written permission of the participant, or an individual with legal decision-making authority for the participant or the participant's interests, except as necessary for monitoring by the relevant regulatory authorities, the sponsor of the clinical study, or the sponsor's representative. The Investigator must also comply with all local applicable privacy regulations [e.g., US Health Insurance Portability and Accountability Act of 1996 (HIPAA)], on protection of individuals with regard to personal data.

16.5 Case Report Forms and Study Records

Source data in a clinical study are the original records or certified copies where clinical observations are first recorded, which may include, but are not limited to, the participant's medical file, original laboratory reports, histology, and pathology reports (as applicable). The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be entered onto source documents designed to capture data pertinent to the clinical investigation. Data should be recorded on paper source documents or electronic medical records system. The electronic database should be completed in their entirety by the Investigator or his/her designee. Prior to database lock, the Investigator will verify the completeness and accuracy of the data and indicate that he/she has done so by providing an electronic signature on the appropriate document. The Investigator will retain a copy of all source documents.

16.6 Access to Source Documentation

The Investigator and study center will permit the sponsor, its representatives, IRB and all relevant regulatory agencies access to all original source data and documents regardless of media, for study monitoring audits and inspections.

16.7 Retention of Data

Per ICH guidelines, all essential documents, including source documents (regardless of media), signed ICFs, and laboratory test results, should be retained by the Investigator for at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. There may be other circumstances for which MacroGenics Inc. is required to maintain study records for longer periods; therefore, MacroGenics Inc. should be contacted before study records are removed from the control of the investigational site for any reason. The Investigator must obtain written permission from MacroGenics Inc. prior to destruction of study documents.

16.8 Sample Retention and Further Testing

Samples acquired for protocol-specified assays will be retained for at least 1 year following the end of the study and may be retained up to 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. If potential participants consent, or an individual with legal decision-making authority for the participant or the participant's interests consent, to the use of their study samples for non-study research purposes, these samples may also be used for exploratory testing (including assay development/ optimization).

A separate IRB application will be submitted for future analysis involving these blood samples. These stored samples will only be used for research including genetic studies of the stored samples, after specific further review and approval by the UNC IRB.

Any remaining specimens that will be stored for future research will be stored safely and securely in a research specimen storage laboratory at the University of North Carolina at Chapel Hill (UNC-CH). No protected health information (PHI) will be included with the samples. The samples will be identified by coded number to maintain participant confidentiality. The link between Participant Identifier Code on the samples and PHI is maintained in a secured file on a secured server in the control of the principal Investigator at UNC-CH. Future researchers would not have access to this link. Only study personnel, people who work at the research specimen storage laboratory at UNC-CH and IRB approved researchers will have access to the participants' samples. Since all the stored specimens are de-identified, the people who work at the research specimen storage laboratory will not have any personally identifying information that would link to a participant. The IRB approved researchers who receive the specimens may receive information pertaining to lab assay values, age, and sex of the specimen donor, but will not be given the name or any other information that identifies the donor/participant. These samples will be stored up to 15 years.

16.9 Financial Disclosure

The Investigator and Sub-Investigators will be required to disclose any applicable financial arrangement as defined in US regulation (i.e., 21 CFR 54).

The following information will be collected about the Investigators, their spouse and each dependent child: any significant payments of other sorts from MacroGenics, Inc., or any alliance partner, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in the study drug; and any significant equity interest in MacroGenics, Inc., as defined in 21 CFR 54. Investigators are obliged to update the sponsor with any changes in reported information up to 1 year following the end of the study.

In addition, Investigators and Sub-Investigators will be required to disclose if they are an employee of MacroGenics, or an immediate family member of a MacroGenics employee, officer, or director. This is in order to assist MacroGenics with its compliance with Securities and Exchange Commission rules requiring disclosure of certain transactions with related persons as defined in 17 CFR 229.404. "Immediate family member of a MacroGenics employee" means a child, stepchild, parent, stepparent, spouse, sibling, mother-in-law, father-in-law, son-in-law, brother-in-law, or sister-in-law of any MacroGenics employee, officer, or director or any person sharing the household of such MacroGenics employee, officer, or director.

In consideration of participation in the study, MacroGenics, Inc., will pay the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator agreement.

Financial disclosure information will be documented in writing and signed and dated by the Investigator. This information will be collected prior to that Investigator taking part in the research.

16.10 Publication and Disclosure Policy

This policy will be codified in the agreement between the site and the sponsor. This includes authorship issues, scheduling analyses, prioritizing analyses for reports, publications, presentations, and developing a review and approval process.

16.11 Discontinuation of the Study or Study Site

16.11.1 Discontinuation of Study Site

Site participation may be discontinued if MacroGenics, Inc., the Investigator, a regulatory authority, or the IRB/IEC of the study site deems it necessary for any reason.

16.11.2 Discontinuation of the Study

The study may be discontinued by a regulatory authority or at the discretion of the sponsor.

The Investigator maintains the right to discontinue his/her participation in the study should his/her clinical judgment so dictate. The Investigator will notify the IRB of any study discontinuation. Study records must be retained as noted above.

16.12 Identification of the Principal Investigator

[redacted] will be the Principal Investigator for this study. As part of her responsibilities, the Principal Investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the Principal Investigator.

17 REFERENCES

1. **Archin NM, Sung JM, Garrido C, Soriano-Sarabia N, Margolis DM**. Eradicating HIV-1 infection: seeking to clear a persistent pathogen. Nature reviews Microbiology 2014; 12:750-64.

2. **Chun TW, Carruth L, Finzi D, et al**. Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection. Nature 1997; 387:183-8.

3. **Chun TW, Davey RT, Jr., Engel D, Lane HC, Fauci AS**. Re-emergence of HIV after stopping therapy. Nature 1999; 401:874-5.

4. **Cartwright EK, Spicer L, Smith SA, et al**. CD8(+) Lymphocytes Are Required for Maintaining Viral Suppression in SIV-Infected Macaques Treated with Short-Term Antiretroviral Therapy. Immunity 2016; 45:656-68.

5. **Chowdhury A, Hayes TL, Bosinger SE, et al**. Differential Impact of In Vivo CD8+ T Lymphocyte Depletion in Controller versus Progressor Simian Immunodeficiency Virus-Infected Macaques. Journal of virology 2015; 89:8677-86.

6. **Davey RT, Jr., Bhat N, Yoder C, et al**. HIV-1 and T cell dynamics after interruption of highly active antiretroviral therapy (HAART) in patients with a history of sustained viral suppression. Proceedings of the National Academy of Sciences of the United States of America 1999; 96:15109-14.

7. **Root AR, Cao W, Li B, et al**. Development of PF-06671008, a Highly Potent Anti-P-cadherin/Anti-CD3 Bispecific DART Molecule with Extended Half-Life for the Treatment of Cancer. Antibodies. Vol. 5, 2016:6.

8. **Sung JA, Pickeral J, Liu L, et al**. Dual-Affinity Re-Targeting proteins direct T cell-mediated cytolysis of latently HIV-infected cells. The Journal of clinical investigation 2015; 125:4077-90.

9. **Sloan DD, Lam CY, Irrinki A, et al**. Targeting HIV Reservoir in Infected CD4 T Cells by Dual-Affinity Re-targeting Molecules (DARTs) that Bind HIV Envelope and Recruit Cytotoxic T Cells. PLoS pathogens 2015; 11:e1005233.

10. **Moore PL, Crooks ET, Porter L, et al**. Nature of nonfunctional envelope proteins on the surface of human immunodeficiency virus type 1. Journal of virology 2006; 80:2515-28.

11. **Munro JB, Gorman J, Ma X, et al.** Conformational dynamics of single HIV-1 envelope trimers on the surface of native virions. Science 2014; 346:759-63.

12. **Sung JA, Pickeral J, Liu L, et al**. Dual-Affinity Re-Targeting proteins direct T cell-mediated cytolysis of latently HIV-infected cells. J Clin Invest 2015; 125:4077-90.

13. **Lewis GK, Pazgier M, DeVico AL**. Survivors Remorse: antibody-mediated protection against HIV-1. Immunological reviews 2017; 275:271-84.

14. **Acharya P, Tolbert WD, Gohain N, et al**. Structural definition of an antibody-dependent cellular cytotoxicity response implicated in reduced risk for HIV-1 infection. Journal of virology 2014; 88:12895-906.

15. **Moore JP, McCutchan FE, Poon SW, et al**. Exploration of antigenic variation in gp120 from clades A through F of human immunodeficiency virus type 1 by using monoclonal antibodies. Journal of virology 1994; 68:8350-64.

16. **Guan Y, Pazgier M, Sajadi MM, et al**. Diverse specificity and effector function among human antibodies to HIV-1 envelope glycoprotein epitopes exposed by CD4 binding. Proceedings of the National Academy of Sciences of the United States of America 2013; 110:E69-78.

17. **Veillette M, Desormeaux A, Medjahed H, et al**. Interaction with cellular CD4 exposes HIV-1 envelope epitopes targeted by antibody-dependent cell-mediated cytotoxicity. Journal of virology 2014; 88:2633-44.

18. **Santra S, Tomaras GD, Warrier R, et al**. Human Non-neutralizing HIV-1 Envelope Monoclonal Antibodies Limit the Number of Founder Viruses during SHIV Mucosal Infection in Rhesus Macaques. PLoS pathogens 2015; 11:e1005042.

19. **Yasmeen A, Ringe R, Derking R, et al**. Differential binding of neutralizing and non-neutralizing antibodies to native-like soluble HIV-1 Env trimers, uncleaved Env proteins, and monomeric subunits. Retrovirology 2014; 11:41.

20. **Poignard P, Moulard M, Golez E, et al**. Heterogeneity of envelope molecules expressed on primary human immunodeficiency virus type 1 particles as probed by the binding of neutralizing and nonneutralizing antibodies. Journal of virology 2003; 77:353-65.

21. **Parren PW, Burton DR, Sattentau QJ**. HIV-1 antibody--debris or virion? Nature medicine 1997; 3:366-7.

22. **Blattner C, Lee JH, Sliepen K, et al**. Structural delineation of a quaternary, cleavage-dependent epitope at the gp41-gp120 interface on intact HIV-1 Env trimers. Immunity 2014; 40:669-80.

23. **Finnegan CM, Berg W, Lewis GK, DeVico AL**. Antigenic properties of the human immunodeficiency virus envelope during cell-cell fusion. Journal of virology 2001; 75:11096-105.

24. **Ferrari G, Pollara J, Kozink D, et al**. An HIV-1 gp120 envelope human monoclonal antibody that recognizes a C1 conformational epitope mediates potent antibody-dependent cellular cytotoxicity (ADCC) activity and defines a common ADCC epitope in human HIV-1 serum. Journal of virology 2011; 85:7029-36.

25. **Smith-Garvin JE, Koretzky GA, Jordan MS**. T cell activation. Annual review of immunology 2009; 27:591-619.

26. **Guy CS, Vignali DA**. Organization of proximal signal initiation at the TCR:CD3 complex. Immunological reviews 2009; 232:7-21.

27. **Chetty R, Gatter K**. CD3: structure, function, and role of immunostaining in clinical practice. The Journal of pathology 1994; 173:303-7.

28. **Moore PL, Crooks ET, Porter L, et al**. Nature of nonfunctional envelope proteins on the surface of human immunodeficiency virus type 1. J Virol 2006; 80:2515-28.

29. **Eriksson S, Graf EH, Dahl V, et al**. Comparative analysis of measures of viral reservoirs in HIV-1 eradication studies. PLoS pathogens 2013; 9:e1003174.

30. **Crooks AM, Bateson R, Cope AB, et al**. Precise Quantitation of the Latent HIV-1 Reservoir: Implications for Eradication Strategies. The Journal of infectious diseases 2015.

31. **Vogel WH**. Infusion reactions: diagnosis, assessment, and management. Clinical journal of oncology nursing 2010; 14:E10-21.

32. **Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ**. The safety and side effects of monoclonal antibodies. Nature reviews Drug discovery 2010; 9:325-38.

33. **Schiller J, Chackerian B**. Why HIV virions have low numbers of envelope spikes: implications for vaccine development. PLoS Pathog 2014; 10:e1004254.

34. **Zhu P, Liu J, Bess J, Jr., et al**. Distribution and three-dimensional structure of AIDS virus envelope spikes. Nature 2006; 441:847-52.

35. **Saber H, Gudi R, Manning M, Wearne E, Leighton JK**. An FDA oncology analysis of immune activating products and first-in-human dose selection. Regul Toxicol Pharmacol 2016; 81:448-56.

36. **Dudal S, Hinton H, Giusti AM, et al**. Application of a MABEL Approach for a T cell-Bispecific Monoclonal Antibody: CEA TCB. J Immunother 2016; 39:279-89.

37. **Gama L, Abreu CM, Shirk EN, et al**. Reactivation of simian immunodeficiency virus reservoirs in the brain of virally suppressed macaques. Aids 2017; 31:5-14.

38. **Curtin F, Vidal V, Bernard C, Kromminga A, Lang AB, Porchet H**. Serum pharmacokinetics and cerebrospinal fluid concentration analysis of the new IgG4 monoclonal antibody GNbAC1 to treat multiple sclerosis: A Phase 1 study. mAbs 2016; 8:854-60.

39. **Stemmler HJ, Schmitt M, Willems A, Bernhard H, Harbeck N, Heinemann V**. Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood-brain barrier. Anti-cancer drugs 2007; 18:23-8.

40. **Bednar MM, Sturdevant CB, Tompkins LA, et al**. Compartmentalization, Viral Evolution, and Viral Latency of HIV in the CNS. Current HIV/AIDS reports 2015; 12:262-71.

41. **Marban C, Forouzanfar F, Ait-Ammar A, et al**. Targeting the Brain Reservoirs: Toward an HIV Cure. Frontiers in immunology 2016; 7:397.

42. **Gray LR, Roche M, Flynn JK, Wesselingh SL, Gorry PR, Churchill MJ**. Is the central nervous system a reservoir of HIV-1? Current opinion in HIV and AIDS 2014; 9:552-8.

43. **Ransohoff RM, Engelhardt B**. The anatomical and cellular basis of immune surveillance in the central nervous system. Nature reviews Immunology 2012; 12:623-35.

44. **Ransohoff RM, Kivisakk P, Kidd G**. Three or more routes for leukocyte migration into the central nervous system. Nature reviews Immunology 2003; 3:569-81.

45. **Ho EL, Ronquillo R, Altmeppen H, Spudich SS, Price RW, Sinclair E**. Cellular Composition of Cerebrospinal Fluid in HIV-1 Infected and Uninfected Subjects. PloS one 2013; 8:e66188.

46. **Kowarik MC, Grummel V, Wemlinger S, et al**. Immune cell subtyping in the cerebrospinal fluid of patients with neurological diseases. Journal of neurology 2014; 261:130-43.

47. **Winkler U, Jensen M, Manzke O, Schulz H, Diehl V., Engert A**. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (rituximab, IDEC-C2B8). Blood 1999; 94:2217-2224.

48. **Baldo BA**. Adverse events to monoclonal antibodies used for cancer therapy: Focus on hypersensitivity responses. Oncoimmunology 2013; 2:e26333.

49. **Rosello S, Blasco I, Garcia Fabregat L, Cervantes A, Jordan K, Committee EG**. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. Annals of oncology: official journal of the European Society for Medical Oncology 2017; 28:iv100-iv118.

50. **Lenz HJ**. Management and preparedness for infusion and hypersensitivity reactions. The Oncologist 2007; 12:601-609.

51. **Crooks AM, Bateson R, Cope AB, et al**. Precise Quantitation of the Latent HIV-1 Reservoir: Implications for Eradication Strategies. The Journal of infectious diseases 2015; 212:1361-5.

52. **Archin NM, Eron JJ, Palmer S, et al**. Valproic acid without intensified antiviral therapy has limited impact on persistent HIV infection of resting CD4+ T cells. Aids 2008; 22:1131-5.

53. **Lorenz DJ, Datta S, Harkema SJ**. Marginal association measures for clustered data. Statistics in medicine 2011; 30:3181-91.

54. **Gandhi RT, Zheng L, Bosch RJ, Chan ES, Margolis DM, Read S, et al**. The effect of raltegravir intensification on low-level residual viremia in HIV-infected patients on antiretroviral therapy: a randomized controlled trial. PLoS Med 2010,7.

Appendix 1 Time and Events Schedule

Part 1	Step 1-Pre-Treatment		Step 2 – Infusion					Step 3 – Post Treatment		End of Study Visit [3]
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit Event	**Screen**	**Enroll [2]**	**Day 0**	**Day 1 (24 hr)**	**Day 2 (48 hr)**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 42**
Study Week	**Within 8 weeks of Day 0**		**0**			**1**	**2**	**3**	**4**	**6**
Window period			≤56 days of screen	± 5 hour	± 5 hour	±2 day	±2 day	±2 day	±2 day	±5 days
Study Drug Administration										
MGD014 Infusion [4]			X							
Clinical Procedures										
Informed Consent [1]	X									
Collect Locator information	X									
Assign PID [5]	X									
Enrollment/Assign SID [6]		X								
Assign Dose Cohort [7]			X							
Medical History [8]	X									
Physical Exam [9]	X									X
Vital signs [10]	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X							
Height	X									
Review of ART treatment history [11]	X									
Assess Karnofsky score	X									
Directed Assessment [12]			X	X	X	X	X	X	X	
Assess ART and ART adherence [13]	X	X	X	X	X	X	X	X	X	X
Assess venous access	X									
Concomitant Medications [14]	X	X	X	X	X	X	X	X	X	X
ECG [15]	X		X							X
Signs, symptoms and diagnosis of illnesses and diseases [16]		X	X	X	X	X	X	X	X	X
Pre-Infusion Medications and anaphylactic medications [17]			X							

Part 1	Step 1-Pre-Treatment		Step 2 – Infusion					Step 3 – Post Treatment		End of Study Visit [3]
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Assess for Adverse Events		X	X	X	X	X	X	X	X	X
Post-Infusion Assessment [18]			X	X	X	X	X	X	X	X
Leukapheresis Procedure (Optional) [23]		X								
Clinical Lab Procedures										
CBC with differential	X	X [22]	X	X		X		X		X
Chemistry Panel [19]	X		X	X		X		X		X
Calculated Creatinine Clearance	X									
Albumin & Lipase	X									
Fasting Lipids & Triglycerides	X									X
Pregnancy test (serum) [20]	X									
Pregnancy test (urine/POCT) [20]			X							
FSH; optional for proof of menopause	X									
PT, INR and aPTT	X									
CD4/CD8	X									X
HIV-1 RNA	X									X
RPR	X									
Hepatitis B and Hepatitis C	X									
Complete Urinalysis with microscopic exam	X									X
Research Laboratory Sample Collection										
HLA		X								
Anti-Drug Antibody (ADA) [21]			X				X		X	X
Pharmacokinetics (PK) [21]			X	X	X	X	X	X	X	X
PD: Receptor Occupancy (RO) Measurements [21]			X	X	X	X				
PD: Serum Cytokines [21]			X	X	X	X				
PD: T Cell Phenotype [21]			X	X		X				
Resting CD4 T Cell Infection by QVOA [23]		X [23]								
Single Copy Assay	X	X		X						X

Part 2	Step 1 Pre-Treatment		Step 2 – Treatment					Step 3 – Post Treatment			End of Study [3]
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Visit Event	**Screen**	**Enroll [2]**	**Day 0**	**Day 1**	**Day 3**	**Day 14**	**Day 28**	**Day 42**	**Day 49**	**Day 63**	**Day 77**
Study Weeks	Within 8 weeks of Day 0		**0**	**1**	**1**	**2**	**4**	**6**	**7**	**9**	**11**
Window period (+ or – days)		≤ 56d screen	≤ 56d screen	0	0	1	1	1	1	3	3
Study Drug Administration											
MGD014 [4]			X			X	X				
Clinical Procedures											
Informed Consent [1]	X										
Collect Locator information	X										
Assign PID [5]	X										
Enrollment/Assign SID [6]		X									
Medical History [8]	X										
Physical Exam [9]	X										X
Vital signs [10]	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X			X	X				
Height	X										
PI review of ART treatment history [11]	X										
Directed Physical Assessment [12]			X	X	X	X	X	X	X	X	
Assess ART and ART adherence [13]	X	X	X	X	X	X	X	X	X	X	X
Assess venous access	X										
Concomitant Medications [14]	X	X	X	X	X	X	X	X	X	X	X
ECG [15]	X		X			X	X				X
Signs, symptoms and diagnosis of illnesses and diseases [16]		X	X	X	X	X	X	X	X	X	X
Pre-Infusion Medications [17]			X			X	X				
Assess for Adverse Events		X	X	X	X	X	X	X	X	X	X
Post-Infusion Assessment [18]			X		X	X	X				
Optional Leukapheresis [23]		X						X			

Part 2	Step 1 Pre-Treatment		Step 2 – Treatment					Step 3 – Post Treatment			End of Study [3]
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Clinical Lab Procedures											
CBC with differential	X	X [22]	X			X	X	X [22]		X	X
Chemistry Panel [19]	X		X			X	X			X	X
Calculated Creatinine Clearance	X										
Albumin & Lipase	X									X	X
Fasting Lipids & Triglycerides	X									X	X
Pregnancy test (serum) [20]	X										
Pregnancy test (urine/POCT) [20]			X			X	X			X	
FSH; optional for proof of menopause	X										
PT, INR and aPTT	X										X
CD4/CD8	X										X
HIV-1 RNA	X										X
RPR	X										
Hepatitis B and Hepatitis C	X										
Complete Urinalysis with microscopic exam	X										
Research Laboratory Sample Collection											
HLA		X									
Anti-Drug Antibody (ADA) [21]	X					X	X				X
Pharmacokinetics (PK) [21]			X	X	X	X	X	X			X
PD: Receptor Occupancy (RO) Measurements [21]			X	X		X	X				X
PD: Serum Cytokines [21]			X	X	X	X	X				
PD: T Cell Phenotype [21]			X	X		X	X				X
Resting CD4 T Cell Infection by QVOA [23]		X						X			
Single Copy Assay [23]		X		X				X			X

1 **Consent:** Obtain prior to obtaining any study-associated procedure.

2 **Study Enrollment:** Determination of study eligibility by the inclusion and exclusion criteria occurs in the Step 1, Visit 1 Screening.

3 Perform the **End of Study Visit** (Visit 10, Day 42, of Part 1 and Visit 11, Day 77 of Part 2) unless participant discontinues study earlier than Day 63, then conduct End of Study Visit 30 days after last dose of study drug.

4 **MGD014 Infusion**: MGD014 will be administered by staff competent in antibody infusion; the PI (or designee) or a licensed physician assistant (PA), nurse practitioner (NP) or Research Nurse. A research assistant (RA) may obtain and record vital signs and provide other participant care necessary during the MGD014 infusion.

Part 1: The first participants of each dose cohort are monitored for 24 hours on site following infusion; subsequent participants at the same dose level will be monitored for 12 hours on site following infusion.

Part 2: Participants are monitored for 6 hours on site following their first infusion. Participants will be monitored for 4 hours on site following subsequent infusions.

5 **Participant identifier (PID) assignment**: This is a computer generated 5-digit number assigned to each participant after the informed consent is signed.

6 **Study-specific identifier (SID) assignment**: This is a sequential study specific number assigned to each participant at enrollment.

7 **Dose Cohort Assignment**: Part 1 only: This assignment occurs at the time of infusion and determined by the prior participant's safety data collected during their 2-week DLT period following the dose.

8 **Medical History**: Medical history obtained at screening will include demographic information (date of birth, gender, race, ethnicity), participant's medical history, and HIV medication history, and (CD4 nadir and peak HIV-1 viral load, if available).

9 **Physical Exam:** Includes a complete review of systems, and vital signs. Obtain the weight at screening, and prior to the dose of MGD014 at each infusion.

10 **Vital Signs:**

a. Screening visit: T, P, BP, and RR and includes height and weight measurements.

b. Infusion Visits: vital signs include T, P, BP, and RR. The weight is only taken upon arrival at the clinic. Vital signs are taken before infusion (approximately 10 minutes before the infusion); at 15, 30, and 60 minutes after the start of infusion; at end of infusion; then every 15 minutes up to and including 60 minutes, then every 60 minutes up to 6 hours after the completion of first infusion and up to 4 hours for subsequent infusions after the completion of infusion. Vital signs have a +/- 5-minute window.

c. Repeat VS (T, BP, P and RR) with a +/- 5-minute window, may also be captured as necessary to elucidate the course of any untoward event or AE and may be inclusive of all or individual VS components as required to address AE monitoring.

d. Part 1 participants staying in the hospital as an inpatient will have VS assess Q 4 hours with a +/- 5-minute window per hospital unit policy or more frequently as clinically indicated.

e. All other visits: vital signs include T, P, BP, and RR.

11 **PI Review of ART History**: if available the most recent HIV-1 genotype should be obtained and presented to PI for review at this time.

12 **Directed Physical Assessment:** Guided by review of systems and participant history and addresses any previously identified or new event that the participant experiences since the last study visit or any unresolved signs or symptoms previously experienced.

13 **ART and ART adherence:** Non-adherence will be defined as having missed more than 9 total days in the 3 months prior to screening. Assess any missed doses while on study and discussed with Study PI (or designee). Continuance on study will be contingent on adherence.

14 **Concomitant medications:** Include all current medications and any as needed (PRN) medications used.

a. All medications taken within 4 weeks of study screening.

b. After study entry, record only new over-the-counter, herbal, dietary and vitamin supplements, and prescription medications. Mark any discontinued medications.

c. Document all doses of MGD014 treatments and permanent discontinuation.

15 **ECG:** Perform in triplicate (approximately 1 minute apart).

a. Screening Visit:

a. Part 1; Performed within 28 days of the first dose of MGD014.

b. Part 2: Performed within 56 days of the first dose of MGD014.

b. Infusion Visits: pre-infusion (within 30 min), end of infusion (within 30 min of the End of Infusion (EOI), 1 hour after the EOI (+/- 5 minutes after EOI).

c. End of Study Visit

16 **Signs and Symptoms and Diagnosis**:

a. Screening: record all diagnosis and disease, record all graded baseline labs, signs and symptoms that occurred within 28 days of screening. Untoward events due to protocol-related procedures should be recorded as AEs.

b. After study entry: Record all AEs related to study drug product regardless of grade.

17 **Pre-MGD014 Infusion Medications (Diphenhydramine or equivalent H1-antihistamine and Acetaminophen) and other medications administered for hypersensitivity Anaphylactic Reaction:**

a. Diphenhydramine (IV) or equivalent H1-antihistamine and the Acetaminophen (oral) administered by licensed study staff.

b. Administration of medications for treatment of adverse reactions to the MGD014 will follow hospital policy and the UNC HIV Cure Center SOP entitled “DART Infusion Guidelines and Emergency Management Plan”.

18 **Post-Infusion Assessment**: Participants provided with instructions to contact study staff about any reactions that occur after receipt of MGD014. Part 1 participants will return to the clinic on Days 1 and 2. Part 2 participants will return for Day 3 assessment and for post-infusion Day 14 and Day 28 to be contacted approximately 2 to 3 days after the study drug administration to inquire about reactions or any potential treatment emergent adverse events (TEAEs). Infusion reactions graded per the DAIDS Toxicity Table.

19 **Chemistries:** Na, K, Cl, bicarbonate, BUN, creatinine, glucose, Ca, total protein, AST, ALT, alkaline phosphatase, total bilirubin, and Mg. Indirect bilirubin required if participant on atazanavir. Clinical labs scheduled for the day of infusion (this is inclusive of CBC) can be obtained within 7 days of infusion.

20 **Pregnancy test:** Serum pregnancy test done on all women at screening. Urine pregnancy test/POCT done on all women at or within 72 hours of each infusion. Test results must be negative, documented and reviewed by study PI or designee prior to each infusion.

21 **For ADA, PK, PD, RO, Serum Cytokine, and T Cell Phenotype measurements**, please refer to **Appendix 2** for detailed schedule.

22 **CBC** done for leukapheresis procedure only.

23 **Optional Leukapheresis** procedure. The QVOA samples will be collected as part of the leukapheresis product for participants having the optional procedure.

Abbreviations: ART= antiretroviral therapy; BMI = body mass index; CBC = complete blood count; DAIDS = Division of AIDS; ECG = electrocardiogram; FSH = follicle stimulating hormone; HLA = human leukocyte antigen; INR = international normalized ratio; IUPM = infectious units per million; IV = intravenous; PI = principal investigator; PD = pharmacodynamics; PID = Participant identifier; POCT = point of care testing; PRN = as needed; PT/aPTT = prothrombin time/activated partial thromboplastin time; QVOA = quantitative viral outgrowth assay; RNA = ribonucleic acid; RPR = Rapid Plasma Reagin; SID = Study-specific identifier; SOP = standard operating procedure; VL = viral load; VL = vital signs.

Appendix 2 PK, Immunogenicity, and PD Biomarkers Blood Sampling Schedule: Part 1 and 2

PART 1 Pharmacokinetics, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule for MGD014						
MGD014 Dosing	**Treatment Day**	**PK Sampling Time (Hours) [a]**	**ADA Sampling Time (Hours)**	**Receptor Occupancy (Hours)**	**Serum Cytokines [b] (Hours)**	**T cell Phenotype (Hours)**
X	0	0 [c] (Pre-infusion)	0 [c] (Pre-infusion)	0 [c] (Pre-infusion)	0 [c] (Pre-infusion)	0 [c] (Pre-infusion)
	0	EOI (within 5 min. before EOI)				
	0	1 (post EOI)		1 (post EOI)		1 (post EOI)
	0	4 (post EOI)		4 (post EOI)	4 (post EOI)	4 (post EOI)
	1	24 +/- 5 hour (post EOI)		X (post EOI)	X (post EOI)	X (post EOI)
	2	48 +/- 5 hour (post EOI)		X	X	
	7	166 +/- 2 day (post EOI)		X	X	X
	14	334 +/- 2 day (post EOI)	X			
	21	502 +/- 2 day (post EOI)				
	28	670 +/-2 days (post EOI)	X			
	42 (EOT visit)	1006 +/- 5 days (post EOI)	X			

a Do not collect PK samples from infusion port. Obtain PK samples as follows: Pre-infusion: Before start of infusion on visit day (dosing day) or day before. When collecting multiple samples, collect the PK sample first.

b Additional samples may be obtained selectively at additional time points in participants who experience signs and symptoms of cytokine release.

c All pre-dose PK, ADA, Receptor Occupancy including T-cell binding, cytokines, and T-cell Phenotype samples will be collected prior to start of MGD014 infusion; the start of MGD014 infusion is designated as time = 0 hour.

Note: Actual start and end of infusion times, PK, and ADA sample collection times will be recorded on the source documents. All sample time points are hours after EOI, unless otherwise specified. Samples required at EOI can be drawn up to 5 minutes before the infusion is complete, post EOI samples can be drawn +/- 5 minutes; duration of infusion = 120 minutes. 24 - and 48-hour samples will be drawn on Day 1 and 2 respectively.

Abbreviations: ADA = Anti-drug antibody; EOI = end of infusion; PK = Pharmacokinetic.

PART 2 Pharmacokinetics, Immunogenicity, and Pharmacodynamic Biomarkers Blood Sampling Schedule for MGD014						
MGD014 Dosing	**Treatment Day**	**PK [a] Sampling Time (Hours)**	**ADA Sampling Time (Hours)**	**Receptor Occupancy [b] (Hours)**	**Serum Cytokines [c] (Hours)**	**T cell Phenotype (Hours)**
X	0	0 [d] (Pre-infusion)		0 [d] (Pre-infusion)	0 [d] (Pre-infusion)	0 [d] (Pre-infusion)
	0	EOI				
	0	1 (post EOI)				
	0	4 (post EOI)		4 (post EOI)	4 (post EOI)	4 (post EOI)
	1	24 +/- 5 hours (post EOI)		24 +/- 5 hours (post EOI)	24 +/- 5 hours (post EOI)	24 +/- 5 hours (post EOI)
	3	72 +/- 5 hours (post EOI)			72 +/- 5 hours (post EOI)	
X	14	0 (Pre-infusion)	0 (Pre-infusion)	0 (Pre-infusion)		0 (Pre-infusion)
	14	EOI		4 (post EOI)	4 (post EOI)	4 (post EOI)
X	28	0 (Pre-infusion)	0 (Pre-infusion)	0 (Pre-infusion)		0 (Pre-infusion)
	28	EOI		4 (post EOI)	4 (post EOI)	4 (post EOI)
	42	1008 hours +/- 1 day				
	77 (EOS visit)	1848 hours +/- 3 days	X	X		X

a Do not collect PK samples from infusion port. Obtain PK samples as follows: Pre-infusion: Before start of infusion on visit day (dosing day) or day before. When collecting multiple samples, collect the PK sample first.

b If at any time in Step 3 RO reaches below the limit of detection, at the discretion of the PI or designee, further measurement of RO may be deemed unnecessary.

c Additional samples may be obtained selectively at additional time points in participants who experience signs and symptoms of cytokine release.

d All pre-dose PK, ADA, Receptor Occupancy including T-cell binding, cytokines, and T-cell Phenotype samples will be collected prior to start of MGD014 infusion; the start of MGD014 infusion is designated as time = 0 hour.

Abbreviations: ADA = Anti-drug antibody; EOI = end of infusion; PK = Pharmacokinetic.

Note: Actual start and end of infusion times, PK, and ADA sample collection times will be recorded on the source documentation. All sample time points are hours after EOI, unless otherwise specified. Samples required at EOI can be drawn up to 5 minutes before the infusion is complete, post EOI and 4 hr post EOI samples can be collected +/- 5 minutes; duration of infusion = 120 minutes. 24- and 72-hour samples will be drawn on Day 2 and 4, respectively.

Appendix 3 Principal Investigator's Agreement

Study Title: A Phase 1 Study to Evaluate the Safety, Immunologic and Virologic Responses of MGD014 Therapy in HIV-Infected Individuals on Suppressive Antiretroviral Therapy

Study Number: CP-MGD014-01

I have read the protocol described above.

I have fully discussed the objectives of this trial and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution of the ethical review of the study, without written authorization from MacroGenics, Inc. It is, however, permissible to provide information to a participant in order to obtain consent.

I agree to conduct this trial according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the trial in accordance with ICH guidelines on GCP and with the applicable regulatory requirements.

I understand that the sponsor may decide to suspend or prematurely terminate the trial at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the trial, I will communicate my intention immediately in writing to the sponsor.

Signed: _____

Date: _____

Name (printed): _____

Title: _____

Affiliation: _____

Address: _____

Phone Number: _____

CP-MGD014-01 Protocol Amendment 6 (31-Mar-2021)

This is the electronic signature page for the above referenced document.

User Task: eSignatories Approval	Data Management/Statistics Approval (Intended or Designee) 31-Mar-2021 18:13:56 GMT+0000

User Task: eSignatories Approval	arch Approval (Intended or Designee) 02-Apr-2021 06:28:38 GMT+0000

User Task: eSignatories Approval	Management/Statistics Approval (Intended or Designee) 06-Apr-2021 10:18:04 GMT+0000

User Task: eSignatories Approval	esearch Approval (Intended or Designee) 06-Apr-2021 13:25:55 GMT+0000

User Task: eSignatories Approval	Research Approval (Intended or Designee) 06-Apr-2021 15:38:34 GMT+0000