CLINICAL STUDY PROTOCOL: CP-MGD020-01
PROTOCOL AMENDMENT 1

Study Title:	A Phase 1 Study of MGD020 as a Single Agent or in Combination with MGD014 in Persons with HIV-1 on Antiretroviral Therapy
Study Number:	CP-MGD020-01
Study Phase:	Phase 1
Product Number:	MGD020, MGD014
IND Number:	
EudraCT Number:	Not applicable
DAIDS Document ID:	
Indication:	Persons with human immunodeficiency virus-1 on antiretroviral therapy
Coordinating Principal Investigator:	
Sponsor:	MacroGenics, Inc. 9704 Medical Center Drive Rockville, MD 20850 301-251-5172
Sponsor's Medical Monitor:	Refer to study contact list

Confidentiality Statement

REVISION HISTORY

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

SPONSOR SIGNATURES

Study Title:	A Phase 1 Study of MGD020 as a Single Agent or in Combination with MGD014 in Persons with HIV-1 on Antiretroviral Therapy
Study Number:	CP-MGD020-01
DAIDS Document ID:	38879

This clinical study protocol has been approved by the sponsor:

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

Vice President, Clinical Development
MacroGenics, Inc.

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

Executive Director, Biostatistics
MacroGenics, Inc.

LIST OF ABBREVIATIONS

The list of abbreviations of specialist terms does not include standard scientific abbreviations of temperature, weight, and volume.

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time zero to infinity
AUC_{tau}	area under the concentration-time curve for a dosing interval
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CRS	cytokine release syndrome
CSR	clinical study report
C_{trough}	trough concentration
DAIDS	Division of AIDS
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DP	drug product
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
E/CIA	enzyme or chemiluminescence immunoassay
EDC	electronic data capture
env	envelope; specifically, the HIV-1 env glycoprotein
EOSV	end of study visit
Fc	fragment crystallizable
FcγR	fragment crystallizable-gamma receptor
FDA	Food and Drug Administration
FSH	follicle stimulating hormone

GCP	Good Clinical Practice
gp	glycoprotein
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus-1
HLA	human leukocyte antigen
IB	investigational brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN-γ	interferon gamma
IgG	immunoglobulin G
IL	interleukin
IND	Investigational New Drug
INR	international normalized ratio
IOCBP	individual of childbearing potential
IPDA	intact proviral DNA assay
IRB	Institutional Review Board
IRR	infusion related reaction
IUPM	infectious units per million
IV	intravenous(ly)
K_D	equilibrium binding constant
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NIAID	National Institute of Allergy and Infectious Diseases
NNRTI	non-nucleoside reverse transcriptase inhibitors
NOAEL	no observed adverse effect level
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	pharmacodynamics
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
PO	oral administration
PQC	product quality complaint
PRF	participant registration form
PWH	persons with HIV
Q2W	once every 2 weeks

QVOA	quantitative viral outgrowth assay
rca-RNA	resting CD4+ T-cell-associated HIV-1 gag RNA
RNA	ribonucleic acid
RPR	rapid plasma reagin
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCA	single copy assay
SHIV	simian-human immunodeficiency virus
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
$t_{1/2,\beta}$	beta phase half-life
T_{max}	time to maximal concentration
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
V_{ss}	steady-state volume of distribution

1 SYNOPSIS

Sponsor: MacroGenics, Inc.	**IND Number:**
Name of Product: MGD020, MGD014	
Study Title: A Phase 1 Study of MGD020 as a Single Agent or in Combination with MGD014 in Persons with HIV-1 on Antiretroviral Therapy	
Study Number: CP-MGD020-01	
Study Phase: Phase 1	
Investigators/Centers: The study will be conducted at 3-5 institutions in the United States.	
Primary Objective: • Characterize safety and tolerability of MGD020 as a single agent and in combination with MGD014	
Secondary Objective(s): • Assess pharmacokinetics (PK) and immunogenicity (anti-drug antibody [ADA]) of MGD020 • Assess PK and immunogenicity (ADA) of MGD014 • Assess serum cytokine levels	
Study Drugs: MGD020 (HIV_{7B2} x CD3) and MGD014 (HIV_{A32} x CD3) are Fc-bearing DART molecules identical in structure except for the sequences of the anti-HIV-1 envelope (env) arms, which recognize different epitopes. DART molecules are bispecific, antibody-based molecules that can bind two distinct antigens simultaneously. MGD020 and MGD014 are designed to target HIV-1-infected, env-expressing cells for recognition and elimination by CD3-expressing T lymphocytes as effector cells.	
Study Design: Study CP-MGD020-01 is a phase 1, open-label, dose-escalation, and multi-dose expansion study of MGD020 as a single agent or in combination with MGD014 in persons with HIV-1 (PWH) on antiretroviral therapy (ART). The study is designed to characterize the safety, tolerability, PK, immunogenicity, and pharmacodynamics (PD) of the study drugs. The study consists of 3 parts (Part 1A, Part 1B, and Part 2). In all parts, the participant's standard of care ART regimen is continued throughout the study period. Part 1A evaluates single ascending doses of MGD020 with a 1+3 design for cohorts 1–3, and a 3+3 design for cohorts 4–6. In the 6 cohorts, the MGD020 dose ranges from 1 to 300 mcg/kg. A 2-week dose-limiting toxicity (DLT) period is observed prior to escalation to the next cohort level. Dose escalation proceeds until either the maximum tolerated dose (MTD) or maximum administered dose (MAD) is determined. Part 1B commences only after the MTD or MAD of single-agent MGD020 has been determined in Part 1A. During Part 1B, participants will be enrolled and treated with a single ascending dose of MGD020 in combination with a fixed dose of 300 mcg/kg MGD014. Dose escalation uses a 3+3 design with up to 3 dose cohorts, including 1 dose de-escalation cohort. The first cohort will be treated with a single dose of MGD020, at a dose determined to be one dose level lower than the single-agent MTD/MAD from Part 1A (i.e., one dose level lower	

than MTD_{1A}/MAD_{1A}), and a single 300 mcg/kg dose of MGD014. Dose escalation proceeds until either the MTD or MAD of the combination is determined.

Part 2 commences only after an MTD or MAD of MGD020 in combination with MGD014 has been determined in Part 1B. Part 2 is a multi-dose expansion cohort with sequential infusions of a fixed dose of MGD020 in combination with a fixed dose of MGD014 administered every 2 weeks (Q2W) for 3 combination doses over 4 weeks. MGD020 is dosed at the MTD/MAD determined in Part 1B (i.e., MTD_{1B}/MAD_{1B}); MGD014 is dosed at 300 mcg/kg. Up to 6 participants may be enrolled in Part 2 using a conventional 3+3 design.

The study consists of a screening phase of up to 8 weeks, and an approximately 6-week (Part 1A and Part 1B) or 11-week (Part 2) study period (dosing and follow-up), which concludes with an end of study visit approximately 6 weeks (Part 1A and Part 1B) or 7 weeks (Part 2) after the last dose of study drug. Thus, the total study duration for each participant is approximately 14 weeks (Part 1A and Part 1B) or 19 weeks (Part 2). If a participant is unable to complete the study, but has not withdrawn consent, the end of study visit is conducted 30 days (+3 day window) after the last dose of study drug.

An independent safety monitor will provide study oversight and evaluate cumulative safety and other clinical data at regular intervals.

Dose-limiting Toxicities:

Dose-limiting toxicity (DLT) is defined based on treatment-related adverse events (AEs) that occur during the DLT period following study drug administration. The DLT period is defined as the period from initial infusion of study drug(s) through 2 weeks following the last infusion of study drug(s).

Severity of AEs is graded according to the National Institute of Allergy and Infectious Diseases (NIAID) Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1, July 2017.

A DLT is any ≥ Grade 2 treatment-related AE, with the following exceptions, based on the medical judgement of the investigator (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.

Number of Participants Enrolled:

The study plans to enroll up to approximately 54 participants in total, including up to 30 participants in Part 1A, 18 participants in Part 1B, and 6 participants in Part 2. The exact number of participants cannot be determined precisely in advance but depends upon the occurrence of DLTs and potential need for expanded cohorts.

Study Population/Key Entry Criteria:

The target population consists of PWH (18 to 70 years old) on ART with plasma HIV-1 RNA < 50 copies/mL for 24 months prior to enrollment. Participants must have adequate organ function and no serious concurrent illnesses that would increase the risk to the participant or confound study results.

Duration of Treatment and Study Duration:

For individual participants, the study duration is approximately 14 weeks in Part 1A and Part 1B or approximately 19 weeks in Part 2. The study duration includes screening, dosing, follow-up, and an end of study visit.

The overall study duration is approximately 24 months. This estimate of timing may vary from that observed in the actual conduct of the study.

Criteria for Evaluation:

Safety Assessments

The safety assessment is based on evaluation of AEs occurring from the first administration of study drug(s) through the end of study visit or 30 days after the last dose of study drug(s), whichever is later. The assessment is based on signs, symptoms, physical examination findings, and laboratory test results.

Pharmacokinetic Assessments

Serum concentrations of study drug(s) will be assessed using quantitative validated bioanalytical methods. Single and multiple dose PK parameters 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 sponsor-conducted studies.

Immunogenicity Assessments

Incidence of ADA to study drug(s) will be assessed using validated bioanalytical methods.

Pharmacodynamic Assessments

All study parts: assessment of serum cytokines, T-cell binding, T-cell phenotype and function, and markers of persistent HIV-1 by intact proviral DNA assay (IPDA).
Part 2 only: assessment of markers of persistent HIV-1 by quantitative viral outgrowth assay (QVOA), plasma HIV-1 RNA levels by single copy assay (SCA), and resting CD4+ T-cell-associated HIV-1 gag RNA (rca-RNA).

Analysis Populations:

Study analyses will be performed on the safety population, defined as all participants who received at least one dose of either study drug. This population will be used to summarize safety data. This population will also be used to summarize baseline data for PK, pharmacodynamics, and immunogenicity analyses.

Statistical Methods:

A statistical analysis plan and statistical programming plan will describe the statistical methods and govern the analysis.

Sample Size:

The study plans to enroll up to approximately 54 participants in total, including up to 30 in Part 1A, 18 in Part 1B, and 6 in Part 2. The sample size in Part 1A is based on a 1+3 design with 3 planned cohorts (12 participants) and 3+3 design for 3 cohorts (18 participants). The sample size in Part 1B is based on a 3+3 design with 3 planned cohorts (18 participants). Part 2 of the study may enroll up to 6 participants based on a 3+3 design with 1 cohort.

Safety:

Adverse events will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment-emergent AEs will be summarized in tables and listings. All AEs prior to treatment (e.g., due to study-related procedures) will be presented in listings only. Adverse events will be summarized by system organ class, preferred term, relationship to study drug(s), and highest severity. Summaries of laboratory values will display descriptive statistics for numerically quantified labs.

Efficacy:

Not applicable.

Pharmacodynamics:

Exploratory analyses are described in the protocol body.

2 BACKGROUND INFORMATION

2.1 Disease Background

An estimated 1,173,900 persons (aged ≥ 13 years) in the United States (US) at the year-end 2018 were living with human immunodeficiency virus (HIV) infection (**5**). The prevalence rate was 427 per 100,000 population. Of those with HIV in 2018, about 76% received some HIV care, 58% were retained in care, and 65% were virally suppressed (**6**).

Antiretroviral therapy (ART) for the treatment of HIV-1 infection has improved steadily since the advent of potent combination therapy in 1996. ART has dramatically reduced HIV-1-associated morbidity and mortality and has transformed HIV-1 infection into a manageable chronic condition, with life expectancy approaching that for people without HIV-1 (**12**). Life-long ART is required to prevent rebound of viremia and return of disease, due to the persistence of long-lived viral reservoirs (**13**).

2.2 Rationale for Study

Despite use of ART, HIV-1 persists in a latent, transcriptionally quiescent state. This latent HIV-1 reservoir is the major obstacle to a cure for HIV-1 (**1**, **9**, **10**). Persons with HIV-1 (PWH) are now taking ART over much longer periods of time, and the resulting potential cumulative toxicity that can emerge is not fully understood. Not only could such long-term toxicity lead to poor health status and a diminished quality of life but ART-related adverse events (AEs) that ultimately result in increases in morbidity and mortality risk may contribute significantly to healthcare resource utilization and costs associated with HIV-1 treatment (**8**). Thus, new approaches to deplete persistent HIV-1 infection are needed.

In this study, MGD020 will be evaluated first as a single agent then in combination with MGD014. MGD020 and MGD014 are bispecific DART® molecules that bind HIV-1 envelope (env) glycoprotein antigen and human cluster of differentiation (CD)-3 antigen. DART molecule-mediated co-engagement of HIV-1-infected, env-expressing cells and $CD3^+$ T cells induces cytolysis of HIV-1 infected cells. The combination of MGD020 and MGD014 has the potential to enhance the recognition of rare actively infected cells in individuals that express env glycoproteins encoded by diverse and mutable HIV-1 isolates. This broadened clearance activity is due to the ability of each DART molecule to recognize a distinct, highly conserved epitope of the HIV-1 env antigen.

The combination of MGD014 and MGD020 is justified by in vitro and in vivo nonclinical data. In vitro binding studies demonstrate that MGD014 and MGD020 bind independently (i.e., without competition) to their respective HIV-1 Env epitopes, which will increase the probability of recognition of HIV-1 Env-expressing cells. In vitro studies on redirected CD8 T-cell killing of HIV-1-infected CD4 cells conducted with CD4/CD8 cells from different human donors (HIV-1-infected or uninfected) and different HIV-1 virus isolates demonstrate that the combination of MGD014 + MGD020 mediates potent and high activity across all conditions more consistently than the individual DART molecules. In vivo studies in HIV-1-infected humanized mice on ART demonstrate that treatment with the combination of MGD014 + MGD020 is significantly more

effective than treatment with the individual DART molecules in decreasing levels of cell-associated viral RNA and delaying rebound viremia following ART interruption.

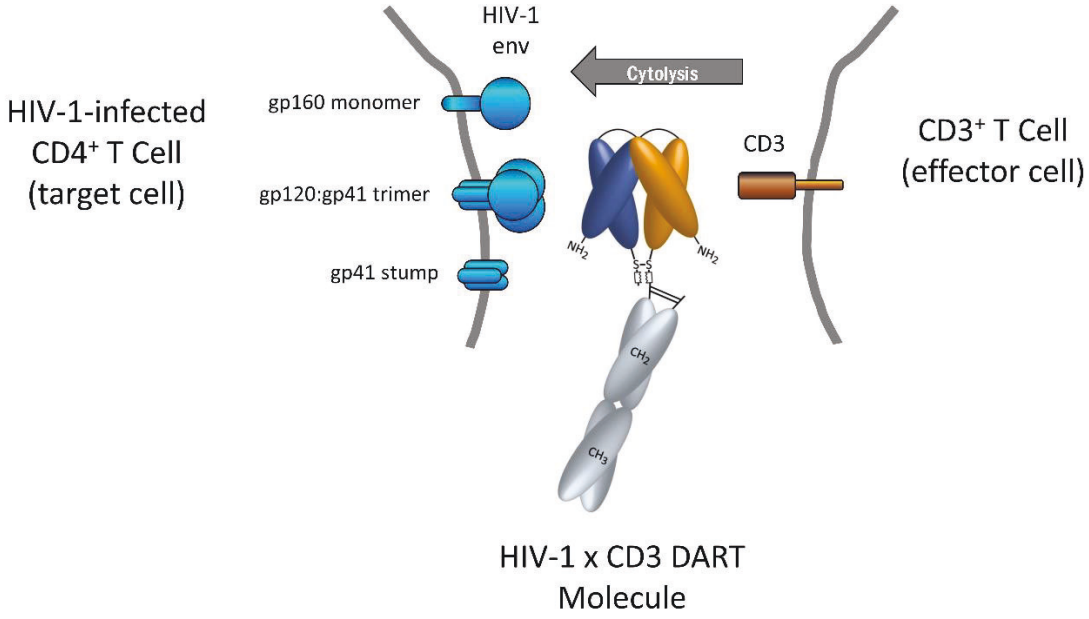
2.3 Background on Study Drugs

The non-clinical studies of MGD020 and MGD014 are summarized in the respective investigator brochures (IBs).

MGD020 (HIV_{7B2} x CD3) and MGD014 (HIV_{A32} x CD3) are fragment crystallizable (Fc)-bearing DART molecules identical in structure except for the sequences of the anti-HIV-1 env arms, which recognize different epitopes of the HIV-1 env. DART molecules are bispecific, antibody-based molecules that can bind two distinct antigens simultaneously. MGD020 and MGD014 are designed to target HIV-1-infected, env-expressing cells for recognition and elimination by CD3-expressing T lymphocytes as effector cells. A schematic depicting the structure and mechanism of action of an HIV-1 x CD3 DART molecule is shown in **Figure 1**.

Prior pre-clinical and clinical studies with MGD014, which is structured exactly like MGD020 except for the identity of the MGD020 anti-HIV-1 env arm, were conducted to evaluate pharmacokinetics (PK) and anti-drug antibodies (ADA). MGD020 and MGD014 are structurally and functionally similar. Therefore, MGD020 will likely have similar PK and ADA in PWH on ART. The first in human dose of MGD020 is based on the minimum anticipated biological effect level (MABEL).

Figure 1 **DART Molecule Structure and Mechanism for Redirected T-cell Cytolysis of Human Immunodeficiency Virus-1-infected Envelope-expressing Cells**



The anti-CD3 arm (orange) of the HIV-1 x CD3 DART molecule binds to CD3 (brown) at the surface of CD3+ T cells (effector cell), and the anti-HIV-1 env arm (dark blue) of the HIV-1 x CD3 DART molecule binds to HIV-1 env antigen at the surface of HIV-1 infected $CD4^+$ T cells (target cell). Cell surface HIV-1 env

glycoprotein (light blue) may be in the form of functional mature trimers or nonfunctional variant forms such as cleaved or uncleaved gp160 monomers or gp41 stumps (17); gp160 is the full-length HIV-1 env precursor which is cleaved by furin to generate gp120 and gp41. HIV-1 x CD3 DART molecule-mediated co-engagement of target and effector cells results in activation of CD3+ T-cell cytolytic responses toward HIV-1-infected, env-expressing target cells.

2.3.1 Background on MGD020

MGD020 (HIV-1_{7B2} x CD3) is an HIV-1 env x CD3 DART molecule. MGD020 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 arm is derived from non-neutralizing human monoclonal antibody (mAb) 7B2, which binds to highly conserved residues (cluster I) in the glycoprotein 41 (gp41) subunit of HIV-1 env and is broadly reactive with HIV-1 env from diverse isolates of HIV-1. The 9 HIV-1 env residues that comprise the linear epitope plus 2 accessory (non-epitope) residues that may influence binding to the 7B2 epitope are conserved at an average frequency of 98.5% (range: 95.5–99.8%) across all HIV-1 subtypes (based on analysis of 5923 HIV-1 env sequences in the Los Alamos National Laboratory database). The anti-CD3 arm of MGD020 is derived from humanized mAb hXR32, which binds to human CD3 and cross-reacts with cynomolgus or rhesus monkey CD3. MGD020 contains a human immunoglobulin G (IgG)-1 Fc domain that was mutated to greatly reduce or eliminate undesired binding to Fc-gamma receptor (FcγR) or complement, while retaining binding to neonatal Fc receptor (FcRn), which allows MGD020 to take advantage of the IgG salvage pathway to prolong the circulating half-life.

2.3.1.1 MGD020 Clinical Experience

No information is available about the effects of MGD020 in humans. Study CP-MGD020-01 is the first-in-human study. No other clinical studies have been conducted with MGD020.

2.3.1.2 MGD020 Non-Clinical Experience

The non-clinical program was designed to characterize the biological activity of MGD020 to support development as a single agent and in combination with MGD014. A summary is provided in the subsections below. Please refer to the **MGD020 IB** for details on non-clinical studies with MGD020.

2.3.1.2.1 Pharmacology

In vitro binding studies with MGD020 demonstrated binding affinities (equilibrium binding constant [K_D] values) of 4.1–41 nM for HIV-1 env glycoproteins and 15.7 or 16.4 nM for human or cynomolgus/rhesus monkey CD3ε protein, respectively. Virion capture studies demonstrated MGD020 binding to HIV-1 virions; this contrasts with MGD014, which binds HIV-1 virions inefficiently. MGD020 binds to primary $CD3^+$ T lymphocytes ($CD4^+$ and $CD8^+$ subsets), HIV-1-env-expressing human cell lines and HIV-1 infectious molecular clone (IMC)-infected human $CD4^+$ cells. MGD020 and MGD014 can bind simultaneously, without competition, to their respective epitopes on purified HIV-1 env protein, HIV-1-env-expressing human cell lines or HIV-1 IMC-infected human $CD4^+$ cells.

MGD020 redirected T cells to lyse human $CD4^+$ cells infected in vitro by IMCs derived from HIV-1 transmitted/founder isolates (subtype B CH040, subtype C 1086c, or subtype C DU151) with high potency; median half-maximal effective concentration (EC_{50}) was 7.0 ng/mL. Similarly, MGD020 redirected T cells to lyse human Jurkat and HEK293 cell lines engineered to express HIV-1 env from different HIV-1 isolates (subtype 01_AE CM244, subtype B JRFL, subtype B HXBc2, or subtype C CH505); median EC_{50} was 7.6 or 12 ng/mL, depending on assay method used. T-cell activation (CD25 upregulation and tumor necrosis factor-α [TNF-α] production) was induced concomitantly with redirected T-cell cytolytic activity. However, with target cells expressing very low levels of HIV-1 env, MGD020 had minimal or no effect on T-cell activation yet mediated potent redirected cytolysis. These data are consistent with mechanistic studies demonstrating that induction of cytokines may not be required for cytotoxic T-cell activity mediated by CD3-bispecific antibodies (**16**).

A 1:1 combination of MGD020 plus MGD014 generally mediated redirected T-cell cytolytic activity in vitro with greater potency than MGD020 alone; median EC_{50} values for the combination ranged from 1.0 to 3.7 ng/mL. The MGD020 plus MGD014 combination consistently mediated cytolytic activity that was comparable to that of the more active individual DART molecule, which varied depending on HIV-1 isolate or T-cell donor. Thus, MGD020 and MGD014 effectively complemented each other to maximize redirected cytolysis regardless of target cell or effector cell identities.

MGD020 mediated antiviral activity in HIV-1-infected humanized mice on suppressive ART. Intravenous (IV) administration of MGD020 significantly reduced cell-associated viral RNA and delayed rebound in viremia following ART interruption. The MGD020 plus MGD014 combination mediated a greater decline in cell-associated viral RNA and longer delay in rebound viremia than MGD020 or MGD014 alone, which supports use of the MGD020 plus MGD014 combination.

2.3.1.2.2 Pharmacokinetics and Toxicology

MGD020 was well tolerated when administered at 1 mg/kg/dose via 30-minute IV infusion once weekly for 6 weeks to simian-human immunodeficiency virus (SHIV)-infected rhesus monkeys maintained on long-term suppressive ART. There were no MGD020-related clinical signs or changes in body weight, hematology parameters, levels of serum cytokines, or activation status of circulating T cells, despite high levels of MGD020 binding to $CD4^+$ or $CD8^+$ T cells at 24 hours post-dosing. Mean MGD020 clearance (CL) was 0.47–0.63 mL/hr/kg, which is lower than the glomerular filtration rate, indicating that renal excretion is not a significant clearance pathway. Mean volume of distribution at steady state (V_{ss}) was 66–106 mL/kg, which is greater than the plasma volume, but less than the extracellular volume of rhesus monkeys, which suggests minimal binding or partitioning into tissues. Mean maximum concentration (C_{max}) was 27.2 mcg/mL. Mean terminal half-life ($t_{1/2}$) was 3.3 days and the beta phase half-life ($t_{1/2,\beta}$) was 7.9 days.

MGD020 did not reduce cell-associated viral RNA or delay rebound viremia in SHIV-infected rhesus monkeys following ART interruption. The absence of MGD020-mediated antiviral activity was likely due to the rarity of target cells (SHIV-infected cells expressing env protein) in

study animals maintained on long-term ART. These results contrast with those from the HIV-1-infected humanized mouse model which used short-term ART.

MGD020 in immobilized form, but not in soluble form, induced cytokines (especially interferon-γ [IFN-γ] and TNF-α) when incubated with peripheral blood mononuclear cells (PBMCs) from healthy or HIV-1-infected human donors. Induction of IFN-γ production was the most sensitive cytokine response; the mean EC_{50} values of 200 or 1800 ng/mL with PBMCs from HIV-1-infected or healthy human donors, respectively, were much higher than those for in vitro redirected T-cell cytolytic activity. There were no additive or synergistic elevations in cytokines when MGD020 and MGD014 were combined. Induction of cytokine production by PBMCs with MGD020 in immobilized form is expected because of formation of artificial molecular aggregates at high concentrations that allow the monovalent anti-CD3 arms to interact multivalently with CD3 receptors on T cells and induce their activation. However, cytokine responses measured by these supra-physiologic conditions in vitro are not predictive of systemic cytokine responses in vivo, as evidenced by the lack of increase in serum cytokines following MGD020 administration at 1 mg/kg to SHIV-infected rhesus monkeys, which resulted in a mean C_{max} serum concentration of 27,200 ng/mL.

In vitro binding studies demonstrated MGD020 interactions with cardiolipin-containing phospholiposomes. No binding was observed with MGD020 at 10 mcg/mL, but weak to moderate binding was observed with MGD020 at 50 or 100 mcg/mL. MGD014 exhibited a similar binding profile. This binding property resides within the anti-CD3 portion of the DART molecules. The potential for clinical adverse effects due to phospholiposome binding by MGD020 is minimal. The anticipated clinical maximal administered dose (MAD) for MGD020 is 300 mcg/kg, which will yield C_{max} of ~5 mcg/mL, a concentration below the threshold for detection for binding to cardiolipin-containing phospholiposomes.

No unexpected cross-reactivity was detected for MGD020 by a GLP tissue cross-reactivity study conducted on a standard panel of normal human tissues. In addition, no off-target interactions were identified for MGD020 or MGD014 by screening a cell-based microarray consisting of ~5900 human plasma membrane proteins, secreted proteins tethered to the cell surface, and heterodimeric receptors.

In summary, administration of MGD020 via IV infusion once weekly for 6 weeks was well tolerated at 1 mg/kg/dose in SHIV-infected, ART-suppressed rhesus monkeys. All animals survived to the end of the study. There were no MGD020-related clinical signs or changes in body weight, hematology parameters, levels of serum cytokines, or activation status of circulating T cells.

2.3.2 Background on MGD014

MGD014 (HIV_{A32} x CD3) is an HIV-1 env x CD3 DART molecule. 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 non-neutralizing mAb that recognizes highly 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 24

HIV-1 env residues that comprise the conformational epitope plus 12 accessory residues that may influence binding to the A32 epitope are conserved at an average frequency of 99.0% (range: 95.2-99.9%) across all HIV-1 subtypes (based on analysis of 5923 HIV-1 env sequences in the Los Alamos National Laboratory database). The anti-human CD3 component of MGD014 is derived from mAb hXR32, which is cross-reactive with similar affinity to cynomolgus or rhesus 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 FcγRs and complement, while retaining binding to the neonatal Fc receptor to take advantage of the IgG salvage pathway mediated by this receptor.

A schematic depicting MGD014 DART molecule structure and mechanism of action is shown in **Figure 1**. Refer to the **MGD014 IB** for additional information.

2.3.2.1 MGD014 Clinical Experience

One clinical study of MGD014, Study CP-MGD014-01, is complete. This trial was a Phase 1, open-label, single-center study to evaluate the safety, immunologic, and virologic responses of MGD014. Refer to the **MGD014 IB** for additional information.

As of 26 September 2020, Study CP-MGD014-01 enrolled 21 PWH on ART and dosed with single-dose MGD014 as follows: 1 participant each at 0.1 and 0.3 mcg/kg; 4 participants at 1 mcg/kg; and 3 participants each at 3, 10, 30, 100, and 300 mcg/kg MGD014.

Treatment-related AEs were reported among 4 of 21 (19.0%) participants receiving MGD014. These included AEs of feeling hot (n = 1 at 3.0 mcg/kg), diarrhea (n = 1 at 10 mcg/kg), flushing (n = 1 at 100 mcg/kg), and electrocardiogram QT prolonged and sensory disturbance (both in the same participant at 100 mcg/kg). All AEs were Grade 1 in severity, possibly related to MGD014, and occurred on the day of study drug infusion. All treatment-related AEs resolved without intervention. No dose-limiting toxicity (DLT), serious adverse events (SAEs), deaths, or treatment-related AEs leading to study drug discontinuation were reported.

Eighteen participants were evaluable for preliminary PK analysis following single administration of 0.1, 0.3, 1, 3, 10, 30, or 100 mcg/kg of MGD014. Dose normalized values of C_{max} and area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$) are approximately constant for the 3 to 100 mcg/kg doses, indicating dose proportionality in MGD014 PK for this dose range. Estimates for $t_{1/2}$, volume of distribution in liters, and CL of MGD014 are 10-12.5 days, 11-22 L, and 0.04 L/hr, respectively.

There were no increases in serum cytokine (IFN-γ, TNF-α, interleukin [IL]-2, IL-5, IL-6, or IL-10) concentrations or increases in activation markers (CD25, CD69, CD134, or CD137) on circulating $CD4^+$ or $CD8^+$ T cells following MGD014 administration. Most circulating $CD4^+$ or $CD8^+$ T cells exhibited MGD014 binding at 24 hours following MGD014 administration at 100 or 300 mcg/kg.

2.3.2.2 MGD014 Non-Clinical Experience

Non-clinical studies necessary to support clinical studies with MGD014 have been performed and are summarized in the **MGD014 IB**.

2.4 Dose Selection

2.4.1 MGD020 Dose Selection

A first-in-human starting dose of 1 mcg/kg MGD020 is proposed. Rationale supporting this dose selection is based on nonclinical data with MGD020 and nonclinical and clinical data with MGD014. MGD014 is a DART molecule with a structure like MGD020 but with specificity for a different HIV-1 env epitope. The MGD020 MABEL of 7 ng/mL corresponds to the median EC_{50} for in vitro redirected T-cell cytolysis of human $CD4^+$ cells infected by HIV-1 IMCs. An MGD020 starting dose of 1 mcg/kg is projected to yield a C_{max} of ~24 ng/mL, which exceeds the MABEL by ~3-fold. The 1 mcg/kg dose is expected to be a safe starting dose for MGD020 based on the rarity of target cells (HIV-1-infected, env-expressing cells) in PWH on ART, and thus the risk of adverse effects due to cytokine release or T-cell activation resulting from MGD020-mediated activity is minimal. The starting dose is supported by a study conducted in SHIV-infected rhesus monkeys on ART in which MGD020 was well tolerated when administered at 1 mg/kg weekly for 6 weeks. The 1 mg/kg dose yielded mean C_{max} of 27,200 ng/mL with no increases in serum cytokines or activation of circulating T cells. The starting dose is also supported by clinical experience with MGD014. MGD014 was well tolerated in Study CP-MGD014-01 conducted in PWH on ART when administered at doses ranging from 0.1 to 300 mcg/kg with mean C_{max} of 23.7 ng/mL at 1 mcg/kg and 5108 ng/mL at 300 mcg/kg. No DLT or SAEs were observed. There were no increases in serum cytokines or activation of circulating T cells following MGD014 administration at all dose levels examined.

2.4.1.1 Rationale for Every 2 Week Administration

Part 2 uses multi-dose, sequential administration of the combination of a fixed dose of MGD020 and a fixed dose of MGD014 on a Q2W schedule. The Q2W dosing is based on simulation of PK data of the MGD014 dose escalation part of Study CP-MGD014-01. Because the PK of MGD020 and MGD014 were comparable in a study conducted in SHIV-infected rhesus monkeys on ART, PK of both MGD020 and MGD014 DART molecules is expected to be comparable in PWH on ART.

2.4.2 MGD020 and MGD014 Combination Dose Selection

In Part 1B, a single ascending dose of MGD020 will be combined with a fixed dose of MGD014. The 300 mcg/kg dose of MGD014 was selected on the basis of non-clinical studies and available clinical data from Study CP-MGD014-01 (see **Section 2.3.2.1**). In Study CP-MGD014-01, doses ranging from 0.1 to 300 mcg/kg were examined in the single ascending dose part of the study. MGD014 was well tolerated with no observed DLTs, SAEs, or treatment-related AEs leading to study drug discontinuation. A dose of 300 mcg/kg was selected for evaluation in the multiple-

ascending dose part of Study CP-MGD014-01, where MGD014 is administered by IV infusion Q2W for a total of 3 infusions over 4 weeks.

In Part 1B, the starting dose of MGD020 is the dose determined to be one dose level lower than the MTD/MAD determined in Part 1A. A dose de-escalation design is employed.

In Part 2, the MGD020 dose will be the MTD/MAD from Part 1B combined with 300 mcg/kg MGD014.

2.4.3 Post-Infusion Monitoring

Events of infusion related reaction (IRR) including cytokine release syndrome (CRS) typically occur within the first hours (up to 24 hours) after infusion of a biologic. These events generally appear in the dose finding phase of studies (**3**, **15**, **18**, **19**). No events of IRR or CRS have been observed in participants dosed with MGD014 in Study CP-MGD014-01 to date.

As a conservative measure, participants will be monitored on-site per **Section 6.5.1** following study drug infusion(s).

2.5 Risk Benefit Assessment

2.5.1 Risk Assessment

Details for information on risks of MGD020 and MGD014 are provided in their respective IBs.

One clinical study of MGD014 is ongoing (Study CP-MGD014-01) as described in **Section 2.3.2.1**. MGD014 infusions were well tolerated with no SAEs, DLTs, or increase in serum cytokine levels. No clinical studies of MGD020 have been conducted. It is expected MGD020 will have similar risks as MGD014, because MGD020 and MGD014 are based on the same DART molecule structure. Refer to the respective IBs for a summary of non-clinical information.

The combination of MGD020 and MGD014 is expected to have risks similar to administration of either study drug alone.

Infusion related reaction and CRS are potential risks of DART molecules. These risks typically occur within the first hours after infusion of the study drug. Management of CRS and IRR is based on the severity of reaction, including temporarily stopping the infusion, administering histamine blockers, corticosteroids, and resuming the infusion of study drug at a slower rate (see **Section 7.1**) (**15**, **18**).

2.5.2 Benefit Assessment

The addition of MGD020 as a single agent or in combination with MGD014 to a participant's ART regimen provides no direct benefit to participants. Participation contributes to ongoing HIV-1 research, potentially resulting in the development of new treatments for HIV-1 infection.

2.5.3 Overall Assessment

The protocol incorporates risk mitigation measures including eligibility criteria, monitoring of participants, and discontinuation criteria. An independent safety monitor will provide study oversight and evaluate cumulative safety and other clinical data at regular intervals. Anticipated AEs are expected to be managed using standard of care. The risk-benefit profile supports investigation of MGD020 as a single agent or in combination with MGD014 in the study population.

3 STUDY OBJECTIVES

3.1 Primary Objective

Primary Objective	Outcome or Endpoint
Characterize safety and tolerability of MGD020 as a single agent and in combination with MGD014	1. Incidence of treatment-emergent AEs, SAEs, and AEs leading to discontinuation

Abbreviations: AE: adverse event; SAE: serious adverse event.

3.2 Secondary Objectives

Secondary Objective	Outcome or Endpoint
Assess PK and immunogenicity (ADA) of MGD020	1. Serum MGD020 concentrations 2. Summary PK parameters for MGD020 3. Incidence of ADA to MGD020
Assess PK and immunogenicity (ADA) of MGD014	1. Serum MGD014 concentrations 2. Summary PK parameters for MGD014 3. Incidence of ADA to MGD014
Assess serum cytokine levels	1. Serum cytokine concentrations

Abbreviations: ADA: anti-drug antibody; PK: pharmacokinetics.

3.3 Exploratory Objectives

Results of exploratory objectives may not be included in the clinical study report (CSR) unless they represent meaningful findings.

Exploratory Objective	Outcome or Endpoint
Explore T-cell binding	1. Percentages of peripheral CD4 and CD8 T cells with study drug bound over time
Explore immunologic responses	1. Changes in markers of activation or exhaustion on peripheral CD4 and CD8 T cells over time
Explore markers of persistent HIV-1	1. Changes in frequency of resting CD4+ T-cell infection by QVOA and/or IPDA 2. Changes in levels of rca-RNA 3. Changes in levels of residual low-level HIV-1 viremia quantified by SCA
Explore correlations between virologic and immunologic markers	1. Association between changes in immunologic and virologic markers

Abbreviations: CD: cluster of differentiation; HIV-1: human immunodeficiency virus-1; IPDA: intact proviral DNA assay; QVOA: quantitative viral outgrowth assay; rca-RNA: resting CD4+ T-cell-associated HIV-1 gag RNA; RNA: ribonucleic acid; SCA: single copy assay.

4 STUDY DESIGN

4.1 Overall Study Design

Study CP-MGD020-01 is a phase 1, open-label, dose-escalation, and multi-dose expansion study of MGD020 as a single agent or in combination with MGD014 in PWH on ART. The study is designed to characterize the safety, tolerability, PK, immunogenicity, and PD of the study drugs. The study consists of 3 parts (Part 1A, Part 1B, and Part 2). In all parts, the participant's standard of care ART regimen is continued throughout the study period.

Part 1A evaluates single ascending doses of MGD020, Part 1B evaluates single ascending doses of MGD020 in combination with fixed-dose MGD014, and Part 2 is a multi-dose expansion cohort with sequential administration of combination MGD020 and MGD014 Q2W for 3 combination doses over 4 weeks.

The study consists of a screening phase of up to 8 weeks, and an approximately 6-week (Part 1A and Part 1B) or 11-week (Part 2) study period (dosing and follow-up), which concludes with an end of study visit (EOSV) approximately 6 weeks (Part 1A and Part 1B) or 7 weeks (Part 2) after the last dose of study drug. Thus, the total study duration for each participant is approximately 14 weeks (Part 1A and Part 1B) or 19 weeks (Part 2). If a participant is unable to complete the study, but has not withdrawn consent, the EOSV is conducted 30 days (+3 day window) after the last dose of study drug.

An independent safety monitor will provide study oversight and evaluate cumulative safety and other clinical data at regular intervals as described in **Section 14.9**.

4.1.1 Part 1A: Single Ascending Dose of MGD020

Part 1A evaluates single ascending doses of MGD020 with a 1+3 design for cohorts 1–3 and a 3+3 design for cohorts 4–6. A 2-week DLT period is observed prior to escalation to the next cohort level.

Part 1A has 6 cohorts (**Table 1**). For cohorts 1–3, each cohort consists of 1 participant, unless a DLT occurs, which prompts expansion of the cohort to add an additional 3 participants. For cohorts 4–6, each cohort consists of 3 participants, with at least 24 hours between dosing of each participant within the cohort. If a DLT is experienced in 1 of the 3 participants in the cohort, the cohort will be expanded to add 3 additional participants. If one or more of the additional 3 participants treated at any given dose level also experiences a DLT, then that dose level will be defined as exceeding the MTD. The MTD will then be defined as the next lower dose level of MGD020. Escalation proceeds according to the rules described in **Section 4.2** until either the MTD or MAD is determined.

Table 1 MGD020 Dose Escalation Scheme (Part 1A)

Cohort	MGD020 Dose (mcg/kg)	Design
1	1	1+3
2	3	1+3
3	10	1+3
4	30	3+3
5	100	3+3
6	300	3+3

4.1.2 Part 1B: Single Ascending Dose of MGD020 and Fixed-Dose of MGD014

Part 1B commences only after the MTD or MAD of single-agent MGD020 has been determined in Part 1A. During Part 1B, participants will be enrolled and treated with a single ascending dose of MGD020 in combination with a fixed dose of 300 mcg/kg MGD014.

MGD020 and MGD014 will be administered at the doses shown in **Table 2** using a 3+3 design, beginning with Cohort 1, with at least 72 hours between dosing of each participant within a cohort. The first cohort will be treated with a single dose of MGD020 at a dose determined to be one dose level lower than the MTD/MAD from Part 1A (i.e., one dose level lower than MTD_{1A}/MAD_{1A}). MGD014 is dosed at 300 mcg/kg, as determined from Study CP-MGD014-01.

In Part 1A, the MGD020 dose is increased in half-log increments from 1 to a maximum of 300 mcg/kg. In Part 1B, the maximum starting dose of MGD020 for Cohort 1 of Part 1B will thus be 100 mcg/kg (one dose level below the Cohort 6 dose of 300 mcg/kg). In combination with MGD014 at 300 mcg/kg, this would yield a maximum total DART dose of 400 mcg/kg for Cohort 1 of Part 1B, which is less than a half-log increment over the total DART dose that would have been tolerated in Part 1A.

Escalation to the next cohort follows the rules described in **Section 4.2**.

Table 2 MGD020 and MGD014 Combination Dose Escalation Scheme (Part 1B)

Cohort	MGD020 [a] (mcg/kg)	MGD014 (mcg/kg)	Design
-1 [b]	MGD020 MTD_{1A}/MAD_{1A} -2	300	3+3
1	MGD020 MTD_{1A}/MAD_{1A} -1	300	3+3
2	MGD020 MTD_{1A}/MAD_{1A}	300	3+3

a Dosing for Part 1B will begin with Cohort 1. The MGD020 dose in Cohort 1 will be one dose level below the single-agent MTD/MAD in Part 1A. For example, if the MTD/MAD in Part 1A for MGD020 is 300 mcg/kg, Cohort 1 of Part 1B would receive 100 mcg/kg MGD020 + 300 mcg/kg MGD014.

b If the dose level in Part 1B Cohort 1 exceeds the MTD, de-escalation to Cohort -1 may be considered. For example, if MTD is exceeded when the Part 1B Cohort 1 dose is 100 mcg/kg MGD020 + 300 mcg/kg MGD014, Cohort -1 of Part 1B would receive 30 mcg/kg MGD020 (MTD_{1A}/MAD_{1A} -2 dose from Part 1A) + 300 mcg/kg MGD014.

Participants who completed Part 1A may be considered for enrollment in Part 1B, provided they meet all eligibility criteria, did not experience DLT in Part 1A, and do not have detectable ADA against MGD014 and/or MGD020 at the completion of Part 1A.

4.1.3 Part 2: Multi-Dose Expansion Cohort: Fixed-Dose of MGD020 and Fixed-Dose of MGD014

Part 2 commences only after an MTD or MAD of MGD020 in combination with MGD014 has been determined in Part 1B. Part 2 is a multi-dose expansion cohort with sequential infusions of a fixed dose of MGD020 in combination with a fixed dose of MGD014 administered Q2W for 3 combination doses over 4 weeks (**Table 3**). MGD020 is dosed at the MTD/MAD determined in Part 1B (i.e., MTD_{1B}/MAD_{1B}). MGD014 is dosed at 300 mcg/kg, as determined from Study CP-MGD014-01.

Up to 6 participants may be enrolled in Part 2 using a conventional 3+3 design. If 2 or more participants in the cohort of 6 participants experience a DLT, enrollment and further dosing of ongoing participants will be suspended pending further assessment of safety data.

Table 3 MGD020 and MGD014 Combination Multi-Dose Expansion Cohort Scheme (Part 2)

Cohort	MGD020 [a] (mcg/kg)	MGD014 (mcg/kg)	Design
1	MGD020 MTD_{1B}/MAD_{1B}	300	3+3

a The MGD020 dose is determined by the combination MTD or MAD in Part 1B.

Participants who completed Part 1 may be considered for enrollment in Part 2, provided they meet all eligibility criteria, did not experience DLT in Part 1, and do not have detectable ADA against MGD014 and/or MGD020 at the completion of Part 1.

4.2 Dose Escalation Rules

Dose escalation from one dose cohort to the next higher dose cohort depends upon the clinical safety profile (e.g., evaluation of AEs, vital signs, ECGs, and clinical laboratory parameters) of the dose administered up to and including the preceding dose cohort. Dose escalation to the next dose level is permitted only after the participants enrolled in the current dose cohort have completed the DLT evaluation period and the safety data have been reviewed by the sponsor medical monitor and the study investigators. Evaluation of safety data from each cohort will include an assessment of the proportion of participants who receive planned doses, and the percentage of participants that require dose reductions or dose discontinuations for toxicity. Available data from participants both during and beyond the 2-week DLT evaluation period will be considered when making dose escalation decisions.

Dose escalation continues until all cohorts are enrolled, provided the MTD is not exceeded. If 2 or more of the participants in a dose cohort experience a DLT, the MTD will have been exceeded. If a DLT occurs in 1 participant in a dose cohort, the dose cohort will be expanded to an additional 3 participants. Prior to dosing any additional participants at the same dose, study drug safety and tolerability are evaluated over the entire 2-week DLT period for the first additional participant.

If the first additional participant does not experience a DLT during the DLT period, the 2 other additional participants can proceed to receive study drug at this dose with a minimum of 24 hours between dosing of each participant. If none of the 3 additional participants experience a DLT during the DLT period, dose escalation to the next dose cohort may proceed.

If any of the 3 additional participants experiences a DLT during the DLT period (≥ 2 DLTs within the same dose cohort), no further participants will receive a dose at this dose level, as the MTD will have been exceeded. Part 1B then proceeds at one dose level below the single-agent MTD_{1A}/MAD_{1A} of MGD020 determined in Part 1A. If only 1 participant was enrolled at the prior dose level in Part 1A, an additional 3 participants will be enrolled at the prior dose for evaluation of the MTD/MAD.

Participants who do not complete the DLT period for reasons other than study drug-related toxicity may be replaced in the same dose cohort. At the discretion of the sponsor, dose escalation may be stopped before an MTD is reached. In this case, the MAD may be chosen based on an assessment of PK, pharmacodynamics (PD), and safety data. For example, dose escalation may be stopped if study drug binding to $CD3^+$ T cells exceeds 95% within a dose cohort.

4.3 Dose-Limiting Toxicity

DLT is defined based on treatment-related AEs that occur during the DLT period following study drug administration. The DLT period is defined as the period from initial infusion of study drug(s) through 2 weeks following the last study drug infusion.

Severity of AEs is graded according to the National Institute of Allergy and Infectious Diseases (NIAID) Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1, July 2017 (see **Section 12.1.6**).

A DLT is any ≥ Grade 2 treatment-related AE, with the following exceptions, based on the medical judgement of the investigator (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.

4.4 Guidelines for Dose Modification

No dose modifications are allowed. A reduction of the infusion rate is allowed during re-challenge for an infusion reaction (**Section 7.1**).

4.4.1 Dose Delays

Hold study drug administration for toxicity, pending assessment, management, and resolution of the AE. If the AE is assessed as unrelated to study drug(s) or does not meet DLT criteria, study drug(s) may be restarted at the previous dose and schedule, after appropriate recovery.

In Part 2, a dose delay of up to 7 days is allowed for drug-related or non-drug related AEs. Refer to **Section 7.1** for specific guidance on restarting study therapy after infusion reactions. A dose delay > 7 days due to drug-related toxicity will prompt study drug discontinuation.

4.5 Study Drug Discontinuation

Administration of study drug(s) may continue as specified in the protocol until any of the following conditions are met:

- Adverse event requiring study drug discontinuation (including DLT)
- Completed dosing per protocol
- Death
- Lost to follow-up
- Investigator decision
- Pregnancy
- Major protocol deviation requiring study drug discontinuation
- Study terminated
- Participant decided to discontinue study drug

- Participant withdrew consent from study

4.6 Follow-Up

In Part 1A and Part 1B, after completion of study drug dosing, participants enter the follow-up period, i.e., visits 2 through 7, per the schedule in **Appendix 1**.

In Part 2, after study drug discontinuation or completion of all 3 combination doses, participants enter the follow-up period, i.e., visits 7 through 9, per the schedule in **Appendix 1**, if feasible. Visit 7 should be scheduled approximately 14 days after study drug discontinuation. Additional and/or more frequent safety laboratory tests may be performed as clinically indicated per the investigator's discretion.

In all study parts, if a participant is unable to complete the study but has not withdrawn consent, the EOSV (i.e., visit 8 in Part 1A and Part 1B, and visit 10 in Part 2) is conducted 30 days (+3 day window) after the last dose of study drug.

Participants may be classified as lost to follow-up after both of the following criteria are met:

- Failure of participant to respond or reply to 3 documented phone or electronic mail contact attempts.
- Failure of participant to respond to a certified letter.

4.7 Study Discontinuation

Participants who discontinue study drug(s) but are still on study in the follow-up period can be terminated from the study for the following reasons:

- Completed protocol-defined follow-up period
- Death
- Lost to follow-up
- Investigator decision
- Study terminated
- Participant withdrew consent from study

4.8 Study Duration

For individual participants, the study duration is approximately 14 weeks in Part 1A and Part 1B. The study duration is approximately 19 weeks in Part 2. The study duration includes screening, dosing, follow-up, and an end of study visit.

The overall study duration is approximately 24 months. This estimate may vary from that observed in the actual conduct of the study.

4.9 End of Study

The end of study for each participant occurs when study discontinuation criteria are met per **Section 4.7**.

The end of the overall study occurs at the time of study database lock. Database lock occurs when the last participant has met off-study criteria and the data collection process is complete.

5 ELIGIBILITY CRITERIA

All inclusion criteria and no exclusion criteria must be met to enroll. No exceptions to these criteria will be granted by the sponsor.

5.1 Inclusion Criteria

1. Ability to provide informed consent. Participants must be willing and able to comply with study procedures.
2. Aged ≥ 18 years and ≤ 70 years of age.
3. HIV-1 infection documented by rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test and confirmed by Western blot or a second antibody test (other than the initial rapid HIV test or E/CIA), HIV-1 antigen, or plasma HIV-1 RNA viral assay.
4. Plasma HIV-1 RNA viral load must meet the following conditions:
   a. < 50 copies/mL at 2 time points within 24 months prior to screening (1 time point within 12 months prior to screening).
   b. < 50 copies/mL at screening.
   c. Not ≥ 50 copies/mL on 2 consecutive time points within 24 months nor > 1000 copies/mL at any time within 6 months prior to screening.
5. On continuous ART for at least 24 months prior to screening and must continue ART throughout the study. Participant must not have missed > 9 total days or > 4 consecutive days in the 3 months prior to screening. No changes in ART medication or modifications of ART dosing are allowed within 30 days prior to screening. Permitted ART regimens include:
   a. At least 3 ART drugs (< 200 mg ritonavir [total daily dose] or cobicistat [any dose] are not considered as one of the 3 ART drugs). One of the ART drugs must include an integrase inhibitor, non-nucleoside reverse transcriptase inhibitor (NNRTI), or boosted protease inhibitor.

      or

   b. At least 2 ART drugs, in which one of the drugs is either a boosted protease inhibitor or an integrase inhibitor, that are Food and Drug Administration (FDA) approved or are recommended by Department of Health and Human Services Treatment Guidelines.
6. CD4 cell count > 350 cells/mm^3 at screening.
7. Hepatitis C virus (HCV) antibody negative or HCV RNA negative.
8. Hepatitis B surface antigen negative.
9. Adequate vascular access.

10. Clinical laboratory parameters obtained at screening as follows:
    a. Platelet count ≥ 125 × 10^3/μL.
    b. Absolute neutrophil count ≥ 1.5 × 10^3/μL.
    c. Hemoglobin ≥ 12 g/dL (male) and ≥ 11 g/dL (females)
    d. Prothrombin time or international normalized ratio (INR) ≤ 1.1 × upper limit of normal (ULN)
    e. Serum total bilirubin < 1.5 × ULN. If total bilirubin is elevated, direct bilirubin < 2 × ULN. If ART includes atazanavir, direct bilirubin must be ≤ 1.0 mg/dL.
    f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 1.5 × ULN
    g. Alkaline phosphatase (ALP) ≤ 1.5 × ULN
    h. Estimated glomerular filtration rate (eGFR) > 60 mL/min as determined by the Chronic Kidney Disease Epidemiology Collaboration equation.
    i. Negative serum pregnancy test for individuals of childbearing potential (IOCBP)
11. IOCBP, defined as assignment of female sex at birth, not surgically sterilized (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy), and between menarche and 1-year post menopause, must have a negative serum pregnancy test performed within 72 hours prior to initiation of study drug. IOCBP must agree to abstain from egg donation during the course of the study.
12. IOCBP and male participants with partners of IOCBP must agree to use highly effective methods of contraception according to **Section 8.1.3** from the time of consent through 6 months after discontinuation of study drug. Male participants must agree to abstain from sperm donation during the course of the study.
13. IOCBP is not pregnant, expecting to become pregnant, or breastfeeding or male participant is not expecting to father children within the projected duration of the study, starting with screening visit through 6 months after the last dose of study drug.

5.2 Exclusion Criteria

1. History or other evidence of severe illness, immunodeficiency other than HIV-1, or any other condition, such as known psychiatric or substance abuse disorder, that in the opinion of the investigator would impair the ability to receive, tolerate, or comply with study drug administration or study procedures.
2. History of any HIV-1 vaccine or HIV-1 immunotherapy, except MGD014 or MGD020, within 6 months prior to screening.
3. Clinically significant cardiovascular disease within 12 months prior to screening (unless otherwise stated) including but not limited to:
    a. Myocardial infarction or unstable angina within the past 6 months.

b. Cardiac arrhythmias.

c. Uncontrolled hypertension at screening: systolic blood pressure > 180 mmHg, diastolic blood pressure >100 mmHg that is sustained on repeat measurement (without intervention).

d. Deep vein thrombosis or pulmonary embolism within the past 6 months.

e. Cerebrovascular accident within the past 6 months.

f. QTc prolongation > 480 millisecond calculated from the average of 3 repeat electrocardiograms (ECGs) obtained at screening in approximately 1-minute intervals.

g. Congestive heart failure (New York Heart Association class III-IV).

h. Pericarditis.

i. Pericardial effusion.

j. Myocarditis.

4. Diabetes mellitus ≥ Grade 3 per DAIDS criteria (defined as uncontrolled despite treatment modification or hospitalization for immediate glucose control indicated).
5. 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 1 week prior to initiation of study drug.
6. Active coronavirus disease 19 (COVID-19)/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. While SARS-CoV-2 testing is not mandatory for study entry, testing should follow local clinical practice guidelines/standards. A positive test result for SARS-CoV-2 infection, known asymptomatic infection, or suspected infection is exclusionary.
7. Active, untreated syphilis (defined as rapid plasma reagin [RPR] positive at screening without history of treatment).
8. Known allergic hypersensitivity to recombinant proteins, or any excipient contained in the study drug or vehicle formulation for MGD020 or MGD014.
9. History of severe allergic reaction with generalized urticarial, angioedema, or anaphylaxis.
10. History of malignancy that may require systemic anti-cancer therapy or radiation therapy. A history of non-melanoma skin cancer with documentation of complete resection or resolution per licensed and board-certified dermatologist is not exclusionary.
11. History of uncontrolled seizure within the past 2 years. A seizure disorder controlled on anti-epileptic therapy is not exclusionary.

12. History of organ or tissue transplantation.
13. History of autoimmune disease, including type I diabetes mellitus, with the specific exceptions of:
    a. Vitiligo.
    b. Resolved childhood atopic dermatitis.
    c. Psoriasis (except psoriatic arthritis) not requiring systemic treatment (within the past 2 years).
    d. Euthyroid Graves' disease or non-autoimmune hypothyroidism.
14. History of unstable asthma, including any of the following events within the past 12 months:
    a. > 1 exacerbation of asthma symptoms treated with oral/parenteral corticosteroids.
    b. Emergency care, urgent care, hospitalization, or intubation for asthma.
15. History of coagulopathy or other bleeding disorder.
16. Participation in another investigational clinical research study within 60 days prior to screening. The following exceptions apply:
    a. Enrollment in an ART study using FDA-approved ART.
    b. Enrollment in the ACTG 5332 REPRIEVE study (NCT02344290) and using FDA-approved pitavastatin provided the participant has been on study for ≥ 4 months.
17. Use of any of the following within 90 days prior to planned first dose of study drug: any blood product, immune globulin, immunomodulatory therapy, cytokine therapy, or growth stimulating factors such as systemic corticosteroids, cyclosporine, methotrexate, azathioprine, anti-CD25 antibody, interferon, IL-2, systemic cytotoxic chemotherapy, or investigational therapy. Intent to use immunomodulators (e.g., IL-2, IL-12, interferons, or tumor necrosis factor [TNF] modifiers) during the study.
18. History of virologic failure on an ART regimen containing FDA-approved HIV-1 entry inhibitors (e.g., maraviroc, enfuvirtide, fostemsavir, and/or ibalizumab). Virologic failure is defined as a confirmed plasma HIV-1 RNA ≥ 150 copies/mL following assessment of drug adherence, repeat HIV-1 RNA testing with continued treatment, and/or resistance testing.
19. Current use of an FDA-approved HIV-1 entry inhibitor.
20. For participants with prior exposure to MGD020, positive ADA to MGD020.
21. For participants with prior exposure to MGD014, positive ADA to MGD014 (Part 1B or Part 2 only).
22. Prisoners or other individuals who are involuntarily detained.
23. Employees of the sponsor unless approved by the Institutional Review Board (IRB) of record.

24. Any investigative site personnel directly affiliated with this study.

6 STUDY DRUG DOSING

6.1 Description of Dosing Regimens

Study drug(s) are administered either as a single dose of MGD020 (Part 1A), a sequential infusion of MGD020 and MGD014 for a single combination dose (Part 1B), or sequential infusions of the MGD020 and MGD014 combination dosed Q2W for a total of 3 combination doses (Part 2).

MGD020 is infused first on days when both MGD020 and MGD014 are administered. Infusion of MGD014 will start at least 30 minutes after the end of MGD020 infusion. The infusions are not to be administered at the same time to ensure that rapid onset infusion reactions (e.g., anaphylaxis) can likely be attributed to a single study drug. The interval between infusions was selected empirically, based on the time required to set up a second infusion, the required post-infusion observation period, and a desire to keep the day as short as possible for the participant. Infusions may be administered into the same arm as local reactions with DART molecule administration are unlikely. Infusion reactions that are delayed (i.e., occur after the completion of study drug infusion) will by necessity be attributed to both drugs as it will not be possible to determine which drug (or both) caused the event.

Refer to **Sections 6.4.1**, **6.4.2**, and the pharmacy manual for further information on study drug dosing.

6.2 Method of Assigning Participants to Cohorts

Participants are assigned sequentially to the dose escalation and multi-dose expansion cohorts. Procedures for enrollment, registration, and cohort assignment are specified in **Section 9.4**.

6.3 Blinding

This is an open-label study.

6.4 Study Drugs and Supplies

6.4.1 MGD020

The concentration and function of each component in the DP are summarized in **Table 4**.

MGD020 is supplied as a sterile aqueous solution packaged in a United States Pharmacopeia (USP) and European Pharmacopoeia (Ph. Eur.) conforming Type I borosilicate, 10 cc clear flint glass vial with a 20 mm West 4023/50 gray butyl rubber serum stopper with B2-40® and FluroTec® coating on the plug. The vial is sealed with a 20 mm TruEdge® aluminum closure with a plastic overseal.

MGD020 will generally be administered over 60 minutes by IV infusion after dilution in Infusion may be slowed for IRR (see **Section 7.1**) but should be completed within 120 minutes. MGD020 must not be administered as an IV push or bolus.

6.4.1.1 Storage and Handling of MGD020

Vials containing MGD020 should be stored upright under refrigerated condition at 2–8°C (36–46°F) in an appropriate, locked room accessible only to pharmacy personnel, the study investigator, or duly designated personnel. MGD020 vials should be protected from light during storage and should not be shaken or frozen during storage. Standard laboratory practices should be used for avoidance of contact with MGD020.

Additional details regarding MGD020 storage, handling, and accountability can be found in the pharmacy manual.

6.4.2 MGD014

MGD014 is supplied as a sterile aqueous solution packaged in a USP and Ph. Eur. conforming Type I borosilicate, 10 cc clear flint glass vial with a 20 mm West 4023/50 gray butyl rubber stopper with B2-40® and FluroTec® coating on the plug. The vial is sealed with a 20 mm TruEdge® aluminum closure with a plastic overseal.

MGD014 will generally be administered over 60 minutes by IV infusion after dilution in Infusion may be slowed for IRR (see **Section 7.1**) but should be completed within 120 minutes. MGD014 must not be administered as an IV push or bolus.

6.4.2.1 Storage and Handling of MGD014

Vials containing MGD014 should be stored upright under refrigerated condition at 2–8°C (36–46°F) in an appropriate, locked room accessible only to pharmacy personnel, the study investigator, or duly designated personnel. MGD014 vials should be protected from light during storage and should not be shaken or frozen during storage. Standard laboratory practices should be used for avoidance of contact with MGD014.

Additional details regarding MGD014 storage, handling, and accountability can be found in the pharmacy manual.

6.4.3 Vehicle

MGD020 DP must be diluted in a Vehicle prior to administration. MGD014 DP must also be diluted in the Vehicle prior to administration.

Vehicle is supplied as a sterile aqueous solution packaged in a USP and Ph. Eur. conforming Type I borosilicate, 50 cc clear flint glass vial with a 20 mm West 4432/50 gray butyl rubber serum stopper with FluroTec® coating on the plug. The vial is sealed with a 20 mm TruEdge® aluminum closure with a plastic overseal.

6.4.3.1 Storage and Handling of Vehicle

Vials containing Vehicle should be stored upright under refrigerated condition at 2–8°C (36–46°F) in an appropriate, locked room accessible only to pharmacy personnel, the study investigator, or duly designated personnel. Vehicle vials should not be frozen and should be protected from light during storage. Standard laboratory practices should be used for avoidance of contact with Vehicle.

Additional details regarding Vehicle storage, handling, and accountability can be found in the pharmacy manual.

6.5 Study Drug Preparation and Administration

MGD020, MGD014, and Vehicle will be supplied by the sponsor.

Instructions on the preparation of the study drugs are each detailed separately in the respective pharmacy manuals.

6.5.1 Monitoring Post-administration

Infusion reactions (including CRS) may occur with administration of protein-based DART molecules such as MGD020 or MGD014. Precautions for anaphylaxis should be observed during study drug administration. Please refer to **Section 7.1.3** for specific guidelines regarding the management of infusion reactions. Supportive measures will be provided throughout the study according to institutional standards.

The duration of on-site monitoring following study drug infusion will vary from 2 to 12 hours post-infusion depending on the protocol stage:

- **Part 1A and Part 1B:** Each participant will be monitored for 12 hours post-infusion of study drug(s).
- **Part 2:** Each participant will be monitored for 6 hours following their first MGD020 and MGD014 sequential infusion. The duration of direct monitoring may be reduced to 2 hours for subsequent sequential infusions; participants may be requested to stay on site for an additional 2 hours to facilitate sample collection per **Appendix 2**.

During the monitoring period, participants are observed for clinical AEs. Vital signs, ECGs, and blood samples are obtained per the schedules in **Appendix 1** and **Appendix 2**. When indicated, PK, ADA, and serum cytokine samples may be obtained selectively at additional time points for participants experiencing IRR and/or CRS (**Appendix 2**).

6.6 Compliance

Study drug will be administered by qualified healthcare professionals under the supervision of the investigator. Records of dose calculation, administration, and dosing regimen will be

maintained by study staff. The sponsor or designated monitor will review the study site pharmacy and participant medical records according to the clinical monitoring plan.

6.7 Accountability

Accounting of all study drugs must be maintained. The investigator agrees to keep an inventory of study drugs using the institution's drug accountability logs or logs provided by sponsor. The investigator will maintain records of temperature monitoring of study drugs. Drug disposition records must be kept in compliance with applicable guidelines and regulations.

A pharmacy manual will be provided to the investigator or designee. When the study is completed, copies of all study drug accountability records must be provided to the sponsor. Original accountability records for study drugs must be maintained with the rest of the documentation for inspection by the study monitors.

6.8 Disposition of Study Drug at End of Study

All unopened vials of study drug will be destroyed on site unless return to depot is authorized by the sponsor or its representative. Additional details regarding storage, handling, and accountability can be found in the pharmacy manual.

7 ADVERSE EVENTS AND SUPPORTIVE CARE MEASURES

7.1 Infusion Related Reactions Including Cytokine Release Syndrome

Infusion reactions including CRS may occur with MGD020 and/or 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, and/or bronchospasm. These reactions should be managed according to the standard practice of medicine. General guidelines for the management of such reactions are provided in this section. Severe reactions may require intensive interventions including, but not limited to, hospitalization, steroids, anti-TNF-α antibodies, and/or IL-6 inhibitors.

The infusion room/area must have immediate access to medications and supportive measures for the treatment of severe hypersensitivity reactions, inclusive of resuscitation equipment and necessary supplies for emergency management of an allergic/toxic reaction.

7.1.1 Grading and Management of Infusion Reactions

Infusion reactions and CRS will be graded according to the criteria in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1, July 2017.

7.1.2 Premedication

The following are guidelines for the investigator to be followed to mitigate potential infusion reactions. Equivalent medications may be substituted based on the local practice of medicine and availability.

Approximately 60 minutes prior to infusion of study drug, premedicate as follows:

- Acetaminophen 650 mg oral administration (PO)
- H_1-antagonist: Diphenhydramine 50 mg PO or IV or equivalent
- H_2-antagonist: Famotidine 40 mg PO or 20 mg IV or equivalent

Hydrocortisone (50 to 100 mg IV) or dexamethasone (10 to 20 mg IV), may be added to the infusion prophylaxis regimen if ≥ Grade 2 IRR occurs with the first infusion.

7.1.3 Management of Observed Infusion Reactions

The following are suggested guidelines regarding management of infusion reactions including CRS. These guidelines may be modified as needed by the investigator or designee according to institutional standards. Equivalent medications may be substituted based on the local practice of medicine and availability.

Record modifications of the infusion of study drug(s) including interruption, reduction in infusion rate, and duration of interruption.

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 infusion rate 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 applicable, consider beginning all subsequent infusions at 50% rate and increasing as tolerated.
- If symptoms persist but do not worsen, completion of the infusion will be at the discretion of the site investigator or designee, with careful monitoring.

Grade 2:

- Stop the infusion.
- Administer diphenhydramine hydrochloride 25–50 mg IV.
- Acetaminophen (or equivalent) 650–1000 mg PO or ibuprofen 400 mg PO for fever.
- Oxygen and bronchodilators as needed.
- Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to Grade 1. The rate may then be escalated to the original rate after 30 minutes, as tolerated. If applicable, consider beginning all subsequent infusions at 50% rate and increasing as tolerated.
- Monitor for worsening condition. If symptoms recur, discontinue the infusion; no further study drug will be administered at that visit.

Grade 3:

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PARTICIPANT. NO FURTHER STUDY DRUG SHOULD BE ADMINISTERED AT THIS VISIT.
- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING – ASPIRATE RESIDUAL DRUG FROM THE VASCULAR ACCESS DEVICE.
- Administer diphenhydramine hydrochloride 25–50 mg IV, dexamethasone 10–20 mg IV (or equivalent), and other medications/treatment as medically indicated. Higher doses of corticosteroids (e.g., methylprednisolone 2–4 mg/kg IV or equivalent) may also be considered for acute management.
- Consider administering tocilizumab (an IL-6 receptor inhibitor) 4–8 mg/kg IV, in the absence of colitis.

- Consider IV fluids, supplemental oxygen, and bronchodilators as appropriate.
- The participant may restart study drug(s) at the next scheduled dose if symptoms have completely resolved within 12 hours. A 50% infusion rate reduction is required.

Grade 4:

- STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PARTICIPANT. NO FURTHER STUDY DRUG SHOULD BE ADMINISTERED.
- TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING – ASPIRATE RESIDUAL DRUG FROM THE VASCULAR ACCESS DEVICE.
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 20 mg IV (or higher doses of steroids, e.g., methylprednisolone 2–4 mg/kg IV or equivalent, as appropriate) and other medications/treatment as medically indicated.
- Consider administering tocilizumab (an IL-6 receptor inhibitor) 4–8 mg/kg IV, in the absence of colitis.
- Give epinephrine or bronchodilators as indicated.
- Support ventilation and blood pressure as indicated.
- Permanently discontinue study drug(s).

7.2 COVID-19/SARS-CoV-2 Infection or Vaccination

Symptoms of COVID-19 will be carefully assessed and treated based on the assessment of the investigator (or designee). An evaluation for infection, including COVID-19, should be performed.

Participants with confirmed (positive by regulatory authority approved/authorized test) or presumed (test pending/clinical suspicion) COVID-19/SARS-CoV-2 infection will be discontinued from study drug.

At the discretion of the investigator, SARS-CoV-2 vaccine may be administered per local practice (refer to **Section 8.1.1** for further guidance on vaccination).

8 CONCOMITANT THERAPY AND RESTRICTIONS

8.1 Concomitant Therapy

Concomitant medications administered from within 4 weeks prior to first dose of study drug, during the participation in the study, and until the end of study visit must be recorded in the source document and on the electronic case report form (eCRF).

The ART regimen is a concomitant therapy and recorded in the source document and eCRF. Participants are required to continue their baseline ART throughout the study. ART will not be provided by the study.

8.1.1 Prohibited Therapy

Refer to the respective IBs for information on special warnings, precautions for use, interaction with other medicinal products, other forms of interaction, and undesirable effects associated with study drug(s).

The following rules apply during study participation:

- Participants may not receive other investigational drugs.
- Participants may not be switched to another ART regimen.
- Use of other immune-suppressive agents including corticosteroids is prohibited, unless used to treat an AE.
- Vaccinations are prohibited within 14 days prior to first administration of study drug through 14 days after the last dose of study drug(s).

8.1.2 Permitted Therapy

Participants may receive the following concurrent therapy after consultation with the sponsor:

- Antipyretics, analgesics, antidepressants, sleep medications, megestrol acetate, testosterone, and other medications for chronic conditions that do not interact with ART regimen, MGD020, or MGD014.
- Oral and topical antibiotics for bacterial infection.
- Intermittent inhaled (e.g., for chronic pulmonary disease or asthma), otic, ophthalmic, and topical corticosteroids (e.g., creams) to small areas of the skin (approximately 15 cm^2) are permitted only if not receiving ritonavir or cobicistat as part of their current ART regimen.
- Non-steroidal anti-inflammatory drugs for treatment of IRR (Grade 1 and Grade 2).

8.1.3 Contraception

Highly effective contraceptive measures are specified below. Male participants are required to use a condom regardless of their IOCBP partner's method of contraception.

Note: If IOCBP is receiving ritonavir or cobicistat, estrogen-based contraceptives are not reliable, and an alternative method must be used.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner is a highly effective birth control method provided that the vasectomized partner is the sole sexual partner of the IOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug(s). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

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**. All data will be recorded in source documents and entered into the eCRF.

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 regulations, i.e., Health Insurance Portability and Accountability Act).
- 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 is used, results and laboratory accreditation will be documented in study records.

9.2 Informed Consent

The investigator is responsible for ensuring informed consent is obtained prior to performing any study-related assessments, evaluations, or procedures that are not part of standard of care. Informed consent for this study must be provided by signing an IRB -approved informed consent document. A copy of the relevant signed informed consent document must be provided to the participant or participant's legal representative, included in medical records, and the original maintained according to institutional procedures.

9.3 Screening Period

The first dose of study drug(s) may be administered within 8 weeks of signing the informed consent. This period is defined as the screening period. Participants will enter the study upon signing the informed consent document. No screening activities outside of usual standard of care will be performed prior to obtaining informed consent.

Participants who sign the informed consent form but fail to meet the eligibility criteria are defined as screen failures. Demographic information, reason for screen failure, and serious adverse events (SAEs) related to study procedures must be recorded on the eCRF.

9.4 Enrollment and Registration

The participant must be registered with the sponsor after eligibility is confirmed. The following information is provided during registration:

- Year of birth
- Date of signed informed consent
- Planned date of first dose of study drug

The sponsor will assign a dose cohort after informed consent is obtained and necessary baseline assessments are completed. The investigator or site staff will complete a participant registration form (PRF) and send it to the designated sponsor study team member. The sponsor will assign a participant identification number, which is used on all eCRF pages and other study-related documentation or relevant correspondence.

9.5 Medical History

Obtain a complete medical history. Record all concurrent medical conditions in the last 60 days and any significant medical conditions noted in medical records (e.g., hospitalizations, surgeries, prior medical history). Medical history obtained at screening includes demographic information (e.g., date of birth, gender, race, and ethnicity), HIV-1 testing history (CD4 and viral load), and HIV-1 genotypes if available.

Any untoward event that occurs prior to the first dose of study drug(s) should be recorded as medical history and not as an AE (unless due to a protocol-related procedure).

9.6 Concomitant Medications and Procedures

9.6.1 Concomitant Medications

Record all prescription and non-prescription medications taken within 30 days prior to screening. Record all medications, HIV-1 ART regimen, and blood product transfusions from screening through the end of study visit.

During the study, record all modifications to the participant's ART regimen since the last study visit or at the study visit including change in medication(s), interruptions, dose modifications, formulation modifications, and permanent discontinuations.

9.6.2 Concomitant Procedures

Record all non-protocol specified medical or surgical procedures from screening through the end of study visit.

9.7 Antiretroviral Therapy

Adherence to ART is required to remain on study and is reviewed according to the schedule in **Appendix 1**. Record any missed doses while on study. Continuance on study will be contingent on ART adherence.

9.8 Physical Examination

The complete physical examination includes skin, head, eyes, ears, nose, throat, lymph nodes, heart, chest, lungs, abdomen, genitourinary, musculoskeletal/extremities, and neurologic system according to schedule in **Appendix 1**. A directed physical exam will be performed at the visits indicated in **Appendix 1** which includes vital signs. The targeted or directed physical examination addresses any previously identified or new event experienced since the last study visit or any unresolved signs or symptoms previously experienced.

Weight is recorded per the schedule in **Appendix 1**. Height is required at screening only.

9.9 Vital Signs

Vital signs include temperature, pulse, blood pressure, and respiratory rate. It is recommended vital signs are obtained in a seated, semi-recumbent, or supine position after appropriate rest.

9.10 Optional Leukapheresis

Leukapheresis is optional and performed in Part 2 only. The leukapheresis procedure occurs at baseline and at approximately 2 weeks after last dose of study drug administration (+2 week window) as specified in **Appendix 1**.

9.11 Laboratory Tests

9.11.1 Clinical Laboratory Tests

Clinical laboratory tests on blood and urine samples collected are described in **Table 6**. Hematology, chemistry, pregnancy, urinalysis, coagulation, and other specified tests are performed locally. Clinical laboratory tests scheduled for Day 1 of study drug infusion can be performed up to 7 days prior to infusion and must be reviewed before dosing.

Depending on site capability, human leukocyte antigen (HLA) typing may be performed in a central laboratory designated by the sponsor.

Table 6 Clinical Laboratory Tests

Pregnancy test: Serum or urine human chorionic gonadotropin **Hematology:** Hemoglobin Hematocrit Platelets Leukocytes Absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils **Serum chemistry:** Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Bilirubin: total and direct (indirect is required if participant on atazanavir) Blood urea nitrogen Calcium Chloride Creatinine Glucose Magnesium Phosphate Potassium Sodium	**Coagulation:** Prothrombin time Activated partial thromboplastin time Prothrombin international normalized ratio **Urinalysis:** Protein Occult blood If abnormal protein or occult blood, reflex test for microscopic evaluation **Other tests:** CD4, CD8, and CD4/CD8 HIV-1 PCR viral load Human leukocyte antigen typing Rapid plasma reagin Hepatitis B virus surface antigen Hepatitis C virus antibody or RNA (reflex PCR viral load test performed only if positive to antibody) Follicle stimulating hormone (optional for proof of menopause)

9.11.2 Central Laboratory Tests

Samples for PK, ADA, cytokine, and PD assays are collected per **Appendix 2**. These assays are performed in a central laboratory designated by the sponsor.

9.11.3 Sample Collection, Storage, and Shipping

Details on laboratory specimen processing, storage, and shipping are provided in the laboratory manual.

9.12 Electrocardiography

Twelve-lead ECGs including QTc interval are assessed per **Appendix 1**. To account for intrinsic variability, ECGs are obtained in triplicate (3 ECGs per time point at approximately 1-minute intervals).

9.13 End of Study

The EOSV occurs after the last dose of study drug(s) and completion of the follow-up period per **Appendix 1**. If a participant is unable to complete the study, but has not withdrawn consent, the EOSV is conducted 30 days (+3 day window) after the last dose of study drug.

10 ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

10.1 Pharmacokinetic Assessments

Serum concentrations of study drug(s) will be assessed using quantitative validated bioanalytical methods. Single-dose and multiple-dose PK parameters will be derived from serum concentration versus time data. These parameters may include maximum concentration (C_{max}), time to maximal concentration (T_{max}), area under the concentration-time curve for a dosing interval (AUC_{tau}), trough concentration (C_{trough}), clearance (CL), volume at steady state (V_{ss}), and terminal half-life ($t_{1/2}$).

Analysis of PK data will be performed using industry standard software. Population PK analyses may be conducted using data from this study alone or combined with data from other sponsor-conducted studies.

10.2 Immunogenicity Assessments

Incidence of ADA to study drug(s) will be assessed using validated bioanalytical methods.

10.3 Pharmacodynamic Assessments

The PD samples are prospectively collected and retrospectively analyzed.

10.3.1 Serum Cytokines

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

10.3.2 T-Cell Binding

Peripheral blood samples will be analyzed using flow cytometry to determine the percentage of study drug bound to CD4 and CD8 T cells.

10.3.3 T-Cell Phenotype and Function

Peripheral blood samples will be analyzed using flow cytometry to determine the expression of cell surface markers of T-cell activation and exhaustion. Functional changes in circulating CD8 T cells may also be assessed.

10.3.4 Persistent Human Immunodeficiency Virus-1

Measurements of persistent HIV-1 may include the following:

- Changes in pre- and post-dose measurements of the frequency of resting CD4+ T-cell infection by quantitative viral outgrowth assay (QVOA) in participants who complete the optional leukapheresis.
- Changes in pre- and post-dose measurements of the frequency of resting CD4+ T-cell infection by intact proviral DNA assay (IPDA).
- Changes in pre- and post-dose measurements of the level of resting CD4+ T-cell-associated HIV-1 gag RNA (rca-RNA).
- Changes in pre- and post-dose measurements of levels of residual low-level HIV-1 viremia quantified by single copy assay (SCA).

Although exposure to DART molecules in this study is brief, and latency reversing agents are not included in the experimental intervention at this time, there is a possibility that some persistently infected cells may be depleted. Exploratory assays are limited by blood volumes and the practical considerations of apheresis, but sufficient samples will be available to assess changes in IPDA, rca-RNA, and SCA. When possible, QVOA will be measured. In our experience, performing multiple assays, when possible, is desirable, given the biological and assay variations of these assessments.

11 ASSESSMENT OF EFFICACY

Not applicable.

12 ADVERSE EVENT REPORTING AND ASSESSMENT OF SAFETY

The safety assessment is based on evaluation of AEs occurring from the first administration of study drug(s) through the EOSV or 30 days after the last dose of study drug(s), whichever is later. The safety assessment is based on signs, symptoms, physical examination findings, and laboratory test results.

12.1 Definitions

12.1.1 Adverse Event

An AE means any untoward medical occurrence associated with the use of a drug in humans. AEs may or may not be drug related. An AE is:

- Any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal product.
- Any medical occurrence that is new or has increased in severity or frequency from the baseline condition.
- Any abnormal results of diagnostic procedures, including laboratory test abnormalities.

12.1.2 Adverse Drug Reaction

An adverse drug reaction is a noxious and unintended response to the medicinal product related to any dose. The phrase “response to a medicinal product” means that a causal relationship between a drug and an AE is at least a reasonable possibility.

12.1.3 Adverse Event of Special Interest

An adverse event of special interest (AESI) is a noteworthy event that a sponsor may wish to monitor carefully. It could be serious or non-serious and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals.

Currently, there are no protocol-specified AESIs for MGD020 or MGD014 in this study.

12.1.4 Serious Adverse Event

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

12.1.5 Assessment of Causality

Assessment of causality is a determination that describes the relationship or association of the drug with an AE.

This assessment of causality is made by the investigator based on 1) temporal relationship of the event to the administration of study drug; 2) whether an alternative etiology has been identified, and 3) biological plausibility.

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

- *None:* The event is related to an etiology other than the study treatment. An alternative etiology should be documented in the participant's medical record.
- *Unlikely:* The event is unlikely to be related to the study treatment and likely to be related to factors other than study treatment. An alternative explanation is more likely (e.g., concomitant drugs, concomitant disease), or the relationship in time suggests that a causal relationship is unlikely.

If an SAE causality assessment is "unlikely" or "none", the investigator should document the likely causative mechanism for the event.

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

- *Possible:* There is a temporal association of the event with the administration of the study drug. There is a plausible mechanism for relationship to the study drug. However, there is an alternative explanation, such as the participant's clinical status or underlying disease.
- *Probable:* There is a temporal association of the event with the administration of the study drug. There is a plausible mechanism for relationship to the study drug. There is no other reasonable explanation.
- *Definite:* There is a temporal association of the event with the administration of the study drug. There is a plausible mechanism for relationship to the study drug. Causes other than the study drug are ruled out, or the event re-appeared on re-exposure to the study drug.

12.1.6 Severity Criteria

Severity of AEs is assigned per investigator assessment using the DAIDS grading table, corrected version 2.1: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

Severity Grade for Adverse Events 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 DAIDS version 2.1 grading table.

ADVERSE EVENT	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING	GRADE 5 FATAL
Clinical adverse event not identified in the DAIDS version 2.1 grading table	Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated	Severe symptoms causing inability to perform usual social and 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	Death

12.2 Adverse Event Collection and Documentation

12.2.1 Adverse Events

AEs and SAEs will be collected from the time the participant consents to study participation. AEs and SAEs reported between the time the participant signs the informed consent form and administration of the first dose of study drug will be captured as concurrent medical history unless the events are attributed to protocol-specified procedures.

Events attributed to protocol-specified procedures will be collected on the AE eCRFs and SAE Report Form, as appropriate.

AEs, regardless of seriousness, severity, or relationship to study drug(s), are documented in the source and the eCRF, including:

- Duration, severity, and seriousness of each AE.
- Action taken with respect to the study drug(s).
- Investigator’s attribution/causality assessment.

- Any medications used to treat the AE.
- Outcome of the event.

A diagnosis should be recorded 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 for AE management will be recorded. All non-serious AEs should be entered into the eCRFs within 10 days of study site awareness.

Clinical Laboratory Changes: Clinical laboratory test results are evaluated by the investigator for clinical significance. The investigator is responsible for reviewing the results of all laboratory tests in a timely manner. The investigator may repeat the laboratory test or request additional tests to verify the results of laboratory tests.

Clinically significant laboratory abnormalities are reported as AEs. A laboratory abnormality is considered clinically significant if it is associated with study drug discontinuation, study drug dose reduction or delay, requires an intervention, or it is suggestive of disease or organ toxicity.

Laboratory abnormalities associated with a diagnosed AE are not reported as separate AEs. For example, report renal failure or hematuria, not the laboratory abnormality (e.g., elevated creatinine or urine red blood cells increased).

The sponsor reports all suspected unexpected serious adverse reactions (SUSARs) to the regulatory authorities and the investigator. The investigator must report SUSARs to the IRB of record as required by the site's institutional policy.

If reporting to the regulatory authorities such as FDA or IRB is required, a copy of the report will also be sent to the NIAID Program Officer or Contracting Officer's Representative, per the NIAID Clinical Terms of Award (https://www.niaid.nih.gov/grants-contracts/niaid-clinical-terms-award).

For this study, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating at least the following:

- Study number
- Statement that the participant is participating in a clinical study
- Investigator name and 24-hour contact telephone number
- Participant number

12.2.2 Serious Adverse Events

All SAEs, regardless of causality, occurring from first administration of study drug through 30 days after the last dose of study drug must be reported to the sponsor. SAEs related to study drug(s) may be reported at any time. The investigator must report the SAE to the sponsor.

- **Within 24 hours** of becoming aware of an SAE, the investigator should send the sponsor a completed SAE Report form by email, or fax, The SAE Report Form and Completion Guidelines, and Contact Information for Reporting SAEs, are provided by the sponsor. Upon receipt of SAE follow-up information, a follow-up SAE Report form should be submitted within 24 hours of becoming aware of the follow-up information. SAEs should be entered into the eCRFs within 5 calendar days of the site's awareness.
- The investigator must follow all SAEs until resolution and record the date of resolution. 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. Unresolved SAEs must be followed until:
    - 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 study must be reported as a SAE, except:
    - A standard hospitalization for administration of the study drug.
    - A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic or biomarker blood sampling).
    - Hospitalizations not intended to treat an acute illness or AE (e.g., social reasons such as pending placement in long-term care or hospice facility).
    - Surgery or procedure planned before entry into the study (must be documented in the eCRF).
- Any SAE of suspected transmission of an infectious agent via a medicinal product will be reported.

12.2.3 Pregnancy

All pregnancies in IOCBP participants or IOCBP partners of male participants must be reported to the sponsor. The pregnancy exposure form is sent to the sponsor within 24 hours of study site awareness. The reporting period is from consent through 24 weeks after the last dose of study drug. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth,

congenital anomalies, ectopic pregnancy) are considered SAEs, and reported according to the method in **Section 12.2.2**. Participants with a positive pregnancy test result at any time during the study must discontinue study drug(s).

The investigator must attempt to follow the pregnancy to term or termination and report the outcome and health status of the mother and child. The investigator should discuss with and encourage the pregnant partner to allow collection of follow up information. The pregnant partner information release form must be signed prior to collecting follow-up information. Follow-up information will be collected for all live newborns at birth and 6 months after birth. Information will be collected to assess study drug effects on the newborn. If appropriate, follow-up will be extended.

12.2.4 Other Reporting Situations

12.2.4.1 Adverse Events of Special Interest

Currently, there are no protocol-specified AESIs for MGD020 or MGD014 in this study.

12.2.4.2 Study Drug Overdose

Overdose is administration of a dose of study drug ≥ 20% above the assigned dose. An AE related to study drug overdose must be reported to sponsor within 24 hours of awareness.

12.2.4.3 Product Quality

Any suspected transmission of an infectious agent via a medicinal product or other product quality issue that results in an event of clinical consequence are AEs. The product quality issue must be reported within 24 hours of awareness of the event. See **Section 13** for product quality complaint handling.

12.2.4.4 Discontinuation of Study Drug Due to an Adverse Event

Any AE resulting in the study drug discontinuation must be reported to the sponsor within 24 hours. Follow up of AEs resulting in study drug discontinuation will continue until resolution or stabilization of the AE, unless the participant withdraws consent for further follow up, or until the EOSV. For SAEs, refer to **Section 12.2.2** for follow-up requirements.

13 PRODUCT QUALITY COMPLAINT 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.

All PQCs must be reported to the sponsor within 24 hours of awareness of the event.

If the product defect results in an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to **Section 12.2.2**, SAEs). A sample of the suspected product should be maintained under correct storage conditions for further investigation if requested by the sponsor.

The name(s) and corresponding telephone numbers of the individuals who should be contacted regarding PQC issues are listed on the contact information page, which is provided as a separate document.

14 STATISTICAL ANALYSIS

This section outlines the statistical methodology and principles which will be used for data analysis in this study. A statistical analysis plan and statistical programming plan will describe the statistical methods and govern the analysis.

14.1 Determination of Sample Size

The study plans to enroll up to approximately 54 participants in total, including up to 30 in Part 1A, 18 in Part 1B, and 6 in Part 2. The exact number of participants cannot be determined precisely in advance but depends upon the occurrence of DLTs and potential need for expanded cohorts.

The sample size in Part 1A is based on a 1+3 design with 3 planned cohorts (12 participants) and 3+3 design for 3 cohorts (18 participants). The sample size in Part 1B is based on a 3+3 design with 3 planned cohorts (18 participants). Part 2 of the study may enroll up to 6 participants based on a 3+3 design with 1 cohort.

The number of participants is not based on statistical power calculations. No inferential statistics will be calculated. The sample size is considered sufficient to evaluate the primary objective of this study (characterize safety and tolerability of the study drugs).

14.2 Analysis Populations

Study analyses will be performed on the following population:

- **Safety population:** All participants who received at least one dose of either study drug. This population will be used to summarize safety data. This population will also be used to summarize baseline data for PK, PD, and immunogenicity analyses.

14.3 Demographics and Baseline Characteristics

Participant disposition, demographics, baseline characteristics, disease history, and medical history will be summarized using descriptive statistics.

14.4 Study Drug Exposure and Concomitant Medications

Study drug exposure and concomitant medications will be summarized by descriptive statistics. The summary of study drug exposure will include descriptive statistics as well as frequency counts for the number of doses received, the total dose actually administered as well as the total dose intended, and the dose intensity which is calculated as percentage of total dose actually administered divided by total dose intended during whole treatment period.

Concomitant medications are coded using the World Health Organization Drug Dictionary.

14.5 Pharmacokinetic and Pharmacodynamic Analysis

14.5.1 Pharmacokinetic Analysis

Summary statistics will be tabulated for PK parameters by dose. Geometric means and percent coefficients of variation may be reported for C_{max}, AUC_{tau}, and C_{trough}; arithmetic means and standard deviations may be reported for $t_{1/2}$, CL, and V_{ss}; and medians, minimum, and maximum may be reported for T_{max}. Population PK analyses may be conducted using data from this study alone or combined with data from other sponsor-conducted studies.

14.5.2 Immunogenicity Analysis

The proportions of participants negative for ADA at baseline with a positive ADA result on study, negative at baseline and remain negative, and positive ADA at baseline that increases or decreases in titer on study will be summarized. Samples with a positive ADA result may be evaluated for further immunogenicity including but not limited to neutralizing capacity. The incidence of neutralizing antibodies may be summarized if available.

14.5.3 Pharmacodynamic Analysis

Summary statistics for PD parameters listed in **Section 10.3** and changes from baseline will be summarized. Analyses may be presented graphically with possible associations between changes in PD measures of interest and study drug dose and exposure.

14.5.3.1 Serum Cytokines

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

14.5.3.2 T-Cell Binding

Percentages of $CD4^+$ or $CD8^+$ cells in blood with bound MGD020 (Part 1A) or bound with both MGD020 and MGD014 (Part 1B and Part 2) will be calculated.

14.5.3.3 T-Cell Phenotype and Function

Percentages of $CD4^+$ or $CD8^+$ cells in blood with expression of markers of activation (e.g., CD25, CD69, CD134, CD137) or exhaustion (e.g., PD-1, LAG-3, TIM-3, TIGIT, CTLA-4) will be calculated.

14.5.3.4 Quantitative Viral Outgrowth Assay

In Part 2 only, for participants who complete the optional leukapheresis, changes in pre- and post-dose measurements of the frequency of resting CD4+ T-cell infection by QVOA (**2**) will be

assessed. Data will be reported as infectious units per million (IUPM) and 95% CI values will be determined from the maximum likelihood method. Statistical significance of changes in QVOA values following dosing will be evaluated by a nonparametric 2-sided exact sign test. The exact sign test used for this analysis makes minimal statistical assumptions and is based solely upon whether IUPM values decrease following dosing. As QVOA is a robust and reproducible assay, declines of more than 50% in QVOA values from serial measurements are infrequently seen and would be suggestive evidence for HIV-1 reservoir depletion (**11**, **14**).

14.5.3.5 Intact Proviral Deoxyribonucleic Acid Assay

In Parts 1A, 1B and 2, pre- and post-dose measurements of the frequencies of resting CD4+ T-cell infection by IPDA (**4**) will be analyzed. Data will be reported as intact HIV-1 provirus per million CD4+ T-cells. 95% CIs for IPDA values will be determined and the statistical significance of changes following dosing will be evaluated by a nonparametric 2-sided exact sign test. Like QVOA, declines of more than 50% in IPDA values from serial measurements would be suggestive evidence for HIV-1 reservoir depletion.

14.5.3.6 Resting CD4+ T-Cell-Associated HIV-1 gag RNA

In Part 2 only, changes in pre- and post-dose measurements of rca-RNA will be assessed. TATA binding protein RNA will be used as the reference to normalize HIV gene expression given its reported stability across treatment conditions (**7**). Data will be log-transformed and Wilcoxon Two-Sample test will be used for statistical analysis of rca-RNA of pre- and post-DART treatment as previously reported (**13**).

14.5.3.7 Plasma Viremia by Single Copy Assay

In Part 2 only, changes in pre- and post-dose measurements of levels of residual low-level HIV-1 viremia quantified by SCA will be assessed. Data will be reported as HIV-1 copies per mL plasma. 95% CIs for the SCA values will be determined and the statistical significance of changes following dosing will be evaluated by a nonparametric 2-sided exact sign test.

14.6 Efficacy Endpoints and Analyses

Not applicable.

14.7 Safety Endpoints and Analyses

14.7.1 Adverse Events

Treatment-emergent AEs will be summarized in tables and listings. All AEs prior to treatment (e.g., due to study-related procedures) will be presented in listings only. Tables will display the number and percent of participants that experience the given event.

AEs will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. AEs will be summarized by system organ class, preferred term, relationship to study drug, and highest severity.

14.7.2 Laboratory Values

Summaries of laboratory values will display descriptive statistics for numerically quantified laboratory assessments. Summaries will be grouped by laboratory panel (hematology, blood chemistry, and urinalysis) and will be displayed by study visit for each laboratory parameter. Shift tables may be produced.

14.7.3 Other Safety Endpoints

ECGs will be collected and analyzed. Vital signs will be summarized with descriptive statistics at each study visit and time point collected. Shift tables may be produced.

14.8 Other Assessments or Analyses

Any additional analyses will be defined in the statistical analysis plan.

14.9 Cohort Analyses and Monitoring

As described in **Section 4.2**, the decision to escalate doses from cohort to cohort will only occur based on consensus supporting escalation by the investigator (or designee) and medical monitor. The review will include aggregate safety data through the DLT period for all dosed participants from the prior dose cohort.

An independent safety monitor 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. Safety data will be reviewed to assess the relationship of reported toxicities and AEs to study drug(s).

If at any time during the study, 2 or more participants (in any part of the study) experience a toxicity that is Grade 3 or higher and considered related to study drug (per investigator assessment) or 2 or more participants experience the same toxicity that is Grade 2 or higher and considered related to study drug (per investigator) then enrollment and further dosing of ongoing participants will be suspended and the independent safety monitor will be asked to review all safety data, review study drug attribution to the event(s), and recommend how the study should proceed with respect to resuming enrollment and continuing study drug.

15 QUALITY CONTROL AND ASSURANCE

Quality review activities will be undertaken to ensure accurate, complete, and reliable data. The sponsor and/or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Conduct a start-up training session (investigator meeting or study initiation visit) to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site to monitor protocol compliance and general GCP compliance.
- Be available for consultation and stay in contact with the study site personnel by mail, e-mail, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer checks to detect and query errors in data collection.
- Conduct a quality review of the database.

15.1 Monitoring, Auditing, and Inspections

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

The sponsor or its designee will monitor the study on a regular basis throughout the study period. The investigator will allocate adequate time for such monitoring activities. The study monitor periodically will conduct a cross-check of participant data recorded on eCRFs against source documents at the study site. The sponsor or designated monitor will review study pharmacy and medical records according to the clinical monitoring plan. The investigator will also ensure that the designated study 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 data are unclear or contradictory. The investigator and study site personnel must address all queries.

Participation as an investigator in this study implies acceptance of the potential for inspection by the study sponsor or representatives, US or non-US government regulatory authorities, IRB of record, 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., pharmacy, diagnostic laboratory, etc.).

15.2 Data Collection and Management

Site personnel will record all data through eCRFs using an electronic data capture (EDC) system provided and approved by the sponsor. Additional information, if any, regarding eCRFs used as source documentation will be provided by the sponsor. Study sites must complete eCRFs after each participant visit per the eCRF completion guidelines. The investigator must sign the investigator statement in each eCRF.

The EDC system automatically generates queries resulting from the computer edit checks embedded into the system to ensure data accuracy, quality, consistency, and completeness. Manual queries resulting from review by study and medical monitors, medical coders, and data management staff are also generated from within the EDC system. Study sites are expected to resolve the queries and correct the entered data accordingly. Every change to data is captured in the EDC system audit trail. Upon completion of the study, or after reaching a pre-specified point in the study, data management will lock the database and generate the SAS datasets necessary for analysis and reporting. Each study site will receive the eCRFs for each of their participants.

16 ADMINISTRATIVE CONSIDERATIONS

16.1 Institutional Review Board

The study protocol, any related documents, and participant-facing materials will be submitted to the IRB of record for review and approval. Written approval of the study protocol and the informed consent forms (ICFs) will be in the possession of the investigator and the sponsor before the study drug is shipped to the investigator's site. This approval must include the date of review, the protocol title and/or study number and version number, and ICF version number or date. A stamped version of the IRB of record-approved consent is acceptable. If the IRB of record 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 investigator should provide the sponsor with a statement of compliance from the IRB of record indicating compliance with the applicable regulations in the region and ICH.

Protocol modifications or changes may not be initiated without approval from the sponsor and prior written IRB of record approval (when required), except when necessary to eliminate immediate hazards to participants. Such modifications will be submitted to the IRB of record; and written verification that the modification was submitted should be obtained. The investigator must submit all changes and updates to required documents to the IRB of record.

16.2 Ethical Conduct of the Study

The investigational study will be conducted according to the Protection of Human Subjects (21 CFR [Code of Federal Regulations] 50), Institutional Review Boards (21 CFR 56), Obligations of Clinical Investigators (21 CFR 312.60 – 312.69), the current ICH Guideline for Good Clinical Practice (ICH E6), Office for Human Research Protections (45 CFR 46), and all other applicable regulations.

16.3 Participant Information and Consent

The investigator will obtain, document, and retain IRB or record-approved written informed consent from the participant, as specified in **Section 9.2**. Where required, the investigator will use an appropriately translated and IRB of record-approved version. The sponsor reserves the right to delay initiation of the study at a site where 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 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 sponsor personnel.

16.4 Participant Confidentiality

To maintain participant confidentiality, all 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 the participant's legally authorized representation, except as necessary for monitoring by the relevant regulatory authorities, the sponsor, or the sponsor's representative. The investigator must comply with all local applicable privacy regulations regarding the protection of participant data.

16.5 Source Documents

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 into the eCRFs.

16.6 Retention of Data

All essential documents, including eCRFs, source documents (regardless of media), and signed ICFs, should be retained by the investigator, per the guidance in ICH E6 or other regulatory retention requirements. There may be other circumstances for which the sponsor is required to maintain study records for longer periods; therefore, the sponsor should be contacted before study records are removed from the control of the study site for any reason. The investigator must obtain written permission from the sponsor prior to destruction of study documents.

16.7 Sample Retention and Secondary Research

Samples acquired for protocol-specified assays are retained according to local and regional regulatory requirements. If the participant consents, or the participant's legal representative consents, to the use of their study samples for secondary research purposes, samples may be used for exploratory testing and retained up to 15 years from the end of study.

16.8 Financial Disclosure

The investigator and sub-investigators are required to disclose in writing any applicable financial arrangement as defined in US regulation. The investigator's disclosure will be signed and dated prior to participating in the study.

The information, as defined in 21 CFR 54, will be collected about the investigators, their spouses and each dependent child. Investigators must update the sponsor with any changes in reported information up to 1 year following the end of the study.

In accordance with US Securities and Exchange Commission regulation (17 CFR 229.404), investigators and sub-investigators must disclose if they are employees of the sponsor, or if an immediate family member of a sponsor employee, officer, or board director.

16.9 Publication and Disclosure Policy

Data collected in this clinical study belong to the study sponsor. The publication terms regarding use of study data are noted in the clinical trial agreement. This includes authorship; scheduling and prioritizing analyses for reports, publications, and presentations; and developing a review and approval process.

16.10 Discontinuation of the Study or Study Sites

Site participation may be discontinued by the sponsor, the investigator, a regulatory authority, or the IRB of record. The study may be discontinued by a regulatory authority or at the discretion of the sponsor.

16.11 Identification of the Coordinating Principal Investigator

is the coordinating principal investigator for this study.

The coordinating investigator's responsibilities include review of the final CSR. Agreement with the final CSR is documented by the dated signature of the coordinating principal investigator.

17 REFERENCE LIST

***Note**: Newly added literature references are in colored text. Previously cited submitted literature references are in black text.*

1. **Archin NM, Sung JM, Garrido C, Soriano-Sarabia N, and Margolis DM**, Eradicating HIV-1 infection: seeking to clear a persistent pathogen. Nat Rev Microbiol, 2014. 12(11): p. 750-64.
2. **Archin NM, Liberty AL, Kashuba AD, Choudhary SK, Kuruc JD, Crooks AM, et al.**, Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. Nature, 2012. 487(7408): p. 482-5.
3. **Baldo BA**, Adverse events to monoclonal antibodies used for cancer therapy: Focus on hypersensitivity responses. Oncoimmunology, 2013. 2(10): p. e26333.
4. **Bruner KM, Wang Z, Simonetti FR, Bender AM, Kwon KJ, Sengupta S, et al.**, A quantitative approach for measuring the reservoir of latent HIV-1 proviruses. Nature, 2019. 566(7742): p. 120-125.
5. **CDC**. Estimated HIV incidence and prevalence in the United States, 2014–2018. 2020; Available from: **http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html**.
6. **CDC**. Monitoring Selected National HIV Prevention and Care Objectives by Using HIV Surveillance Data United States and 6 Dependent Areas, 2018. 2020 May 2020; Available from: **http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html**.
7. **Ceriani C, Streeter GS, Lemu KJ, James KS, Ghofrani S, Allard B, et al.**, Defining stable reference genes in HIV latency reversal experiments. J Virol, 2021.
8. **Chawla A, Wang C, Patton C, Murray M, Punekar Y, de Ruiter A, et al.**, A Review of Long-Term Toxicity of Antiretroviral Treatment Regimens and Implications for an Aging Population. Infect Dis Ther, 2018. 7(2): p. 183-195.
9. **Chun TW, Davey RT, Jr., Engel D, Lane HC, and Fauci AS**, Re-emergence of HIV after stopping therapy. Nature, 1999. 401(6756): p. 874-5.
10. **Chun TW, Carruth L, Finzi D, Shen X, DiGiuseppe JA, Taylor H, et al.**, Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection. Nature, 1997. 387(6629): p. 183-8.
11. **Crooks AM, Bateson R, Cope AB, Dahl NP, Griggs MK, Kuruc JD, et al.**, Precise Quantitation of the Latent HIV-1 Reservoir: Implications for Eradication Strategies. J Infect Dis, 2015. 212(9): p. 1361-5.
12. **DHHS**. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. 2019; Available from: **https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf**.
13. **Gay CL, Kuruc JD, Falcinelli SD, Warren JA, Reifeis SA, Kirchherr JL, et al.**, Assessing the impact of AGS-004, a dendritic cell-based immunotherapy, and vorinostat on persistent HIV-1 Infection. Sci Rep, 2020. 10(1): p. 5134.
14. **Gay CL, James KS, Tuyishime M, Falcinelli SD, Joseph SB, Moeser MJ, et al.**, Stable Latent HIV Infection and Low-level Viremia Despite Treatment With the Broadly Neutralizing Antibody VRC07-523LS and the Latency Reversal Agent Vorinostat. J Infect Dis, 2022. 225(5): p. 856-861.

15. **Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al.**, Current concepts in the diagnosis and management of cytokine release syndrome. Blood, 2014. 124(2): p. 188-195.
16. **Li J, Piskol R, Ybarra R, Chen YJ, Li J, Slaga D, et al.**, CD3 bispecific antibody-induced cytokine release is dispensable for cytotoxic T cell activity. Sci Transl Med, 2019. 11(508).
17. **Moore PL, Crooks ET, Porter L, Zhu P, Cayanan CS, Grise H, et al.**, Nature of nonfunctional envelope proteins on the surface of human immunodeficiency virus type 1. J. Virol, 2006. 80(5): p. 2515-2528.
18. **Vogel WH**, Infusion reactions: diagnosis, assessment, and management. Clin J Oncol Nurs, 2010. 14(2): p. E10-21.
19. **Winkler U, Jensen M, Manzke O, Schulz H, Diehl V, and 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(7): p. 2217-24.

Appendix 1 Time and Events Schedules

Table 7 Time and Events Schedule (Part 1A and Part 1B)

Procedure	Screening [a]	Dosing	Follow-up Period						End of Study [b]
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day	**Day -56 to -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8 (± 2 days)**	**Day 15 (± 2 days)**	**Day 22 (± 2 days)**	**Day 29 (± 2 days)**	**Day 43 (± 3 days)**
Study Drug Administration									
MGD020 infusion (Part 1A and Part 1B) [c]		X							
MGD014 infusion (Part 1B only)		X							
Clinical Procedures									
Informed consent	X								
Inclusion/exclusion criteria	X								
Enrollment	X								
Medical history	X								
Demographics	X								
Physical examination [d]	X	X	X	X	X	X	X	X	X
Vital signs [e]	X	X	X	X	X	X	X	X	X
Weight	X	X							
Height	X								
ART adherence	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
ECG [f]	X	X							X
Adverse events [g]	X	X	X	X	X	X	X	X	X
Clinical Laboratory Collection [h]									
Hematology	X	X [i]	X		X		X		X
Chemistry	X	X [i]	X		X		X		X
Coagulation	X								X
Urinalysis	X								X
Pregnancy test [j]	X	X [j]						X	X
Optional FSH	X								
CD4/CD8	X								X
HIV-1 PCR viral load	X								X

Table 7 Time and Events Schedule (Part 1A and Part 1B)

Procedure	Screening [a]	Dosing	Follow-up Period						End of Study [b]
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day	**Day -56 to -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8 (± 2 days)**	**Day 15 (± 2 days)**	**Day 22 (± 2 days)**	**Day 29 (± 2 days)**	**Day 43 (± 3 days)**
Rapid plasma reagin	X								
Hepatitis B surface antigen	X								
HCV antibody or RNA [k]	X								
Research Laboratory Sample Collection									
PK/ADA/PD/cytokines/HLA	See **Table 9** (Part 1A) or **Table 10** (Part 1B) in **Appendix 2**								

a Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the 56 day window may be used for screening.

b If a participant is unable to complete the study, but has not withdrawn consent, the end of study visit (EOSV) is conducted 30 days (+3 day window) after the last dose of study drug(s).

c MGD020 is infused first on days when both MGD020 and MGD014 are administered (Part 1B only).

d Full physical exams are performed at screening and EOSV. All other physical exams are directed physical exams based on signs and symptoms, and as clinically indicated.

e At the dosing visit, vital signs are measured pre-infusion; at 15 and 30 min after start of infusion (± 5 min); at end of infusion (EOI) of all study drug(s) (± 5 min); at 15, 30, 45, and 60 min post-infusion of last study drug (± 5 min); then every 60 min (± 10 min) until 6 hours after EOI or until the end of the monitoring period (see **Section 6.5.1**), whichever comes first. For participants on Parts 1A and 1B, vital signs are also measured at 10 hours (± 10 min) after the EOI. At non-dosing in-person visits, vital signs are assessed once.

f ECGs are performed in triplicate (approximately 1 min apart). At screening and EOSV, ECGs will be taken at one time point. At the dosing visit (Day 1), ECG is recorded pre-infusion, at EOI of all study drug(s), at 30 and 60 min after EOI of last study drug, and as clinically indicated. ECGs after EOI have a ± 10 min window.

g Assess participants for adverse events. Participants are also instructed to contact the study coordinator or investigator if any signs or symptoms of an AE occur at any time during the study.

h Additional and/or more frequent safety laboratory tests may be performed as clinically indicated per the investigator's discretion.

i Clinical laboratory assessments scheduled for Day 1 can be obtained within 7 days prior to infusion. See **Section 9.11** for detailed list of assessments. Indirect bilirubin is required if participant on atazanavir.

j Participants of childbearing potential only. Serum pregnancy test is required at screening. Subsequent pregnancy tests may use serum or urine. Results must be reviewed before study drug infusion. If screening test is performed within 72 hours of study drug infusion, repeat testing on Day 1 may be deferred.

k Reflex HCV PCR viral load test is performed only if positive for HCV antibody.

Abbreviations: ADA: anti-drug antibody; ART: antiretroviral therapy; CD: cluster of differentiation; ECG: electrocardiogram; EOI: end of infusion; EOSV: end of study visit; FSH: follicle stimulating hormone; HCV: hepatitis C virus; HIV-1: human immunodeficiency virus-1; HLA: human leukocyte antigen; PCR: polymerase chain reaction; PD: pharmacodynamics; PK: pharmacokinetics.

Table 8 Time and Events Schedule (Part 2)

Procedure	Screening [a]	Dosing Period						Follow-up Period			End of Study [b]
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Study Day	**Day -56 to -1**	**Day 1**	**Day 2**	**Day 4**	**Day 8 (± 1 day)**	**Day 15 (± 1 day)**	**Day 29 (± 1 day)**	**Day 43 (± 2 days)**	**Day 50 (± 2 days)**	**Day 64 (± 3 days)**	**Day 78 (± 3 days)**
Study Drug Administration											
MGD020 infusion [c]		X				X	X				
MGD014 infusion		X				X	X				
Clinical Procedures											
Informed consent	X										
Inclusion/exclusion criteria	X										
Enrollment	X										
Medical history	X										
Demographics	X										
Physical exam [d]	X	X	X	X	X	X	X	X	X	X	X
Vital signs [e]	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X				X	X				
Height	X										
ART adherence	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
ECG [f]	X	X				X	X				X
Adverse events [g]	X	X	X	X	X	X	X	X	X	X	X
Optional leukapheresis [h]	X [h]							X [h]			
Clinical Laboratory Collection [i]											
Hematology	X	X [j]				X	X	X [k]			X
Chemistry	X	X [j]				X	X				X
Coagulation	X										X
Urinalysis	X										X
Pregnancy test [l]	X	X [l]				X	X			X	X
Optional FSH	X										
CD4/CD8	X										X
HIV-1 PCR viral load	X										X
Rapid plasma reagin	X										
Hepatitis B surface antigen	X										

Table 8 Time and Events Schedule (Part 2)

Procedure	Screening [a]	Dosing Period						Follow-up Period			End of Study [b]
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Study Day	**Day -56 to -1**	**Day 1**	**Day 2**	**Day 4**	**Day 8 (± 1 day)**	**Day 15 (± 1 day)**	**Day 29 (± 1 day)**	**Day 43 (± 2 days)**	**Day 50 (± 2 days)**	**Day 64 (± 3 days)**	**Day 78 (± 3 days)**
HCV antibody or RNA [m]	X										
Research Laboratory Sample Collection											
PK/ADA/PD/cytokines/HLA	See **Table 11** in **Appendix 2**										

a Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the 56 day window may be used for screening.

b If a participant is unable to complete the study, but has not withdrawn consent, the end of study visit (EOSV) is conducted 30 days (+3 day window) after the last dose of study drug(s).

c MGD020 is infused first on days when both MGD020 and MGD014 are administered.

d Full physical exams are performed at screening and EOSV. All other physical exams are directed physical exams based on signs and symptoms, and as clinically indicated.

e On dosing visits (Day 1, 15, and 29), vital signs are measured pre-infusion; at 15 and 30 min after start of infusion (± 5 min); at end of infusion (EOI) of all study drug(s) (± 5 min); at 15, 30, 45, and 60 min post-infusion of last study drug (± 5 min); then every 60 min (± 10 min) until 6 hours after EOI or until the end of the monitoring period (see **Section 6.5.1**), whichever comes first (until 2 hours after EOI on Day 15 and 29). During non-dosing in-person visits, vital signs are assessed once.

f ECGs are performed in triplicate (approximately 1 min apart). At screening and EOSV, ECGs will be taken at one time point. On dosing visits (Day 1, 15, and 29), ECG is recorded pre-infusion, at EOI of all study drug(s), at 30 and 60 min after EOI of last study drug, and as clinically indicated. ECGs after EOI have ± 10 min window.

g Assess participants for adverse events. Participants are also instructed to contact the study coordinator or investigator if any signs or symptoms of an AE occur at any time during the study.

h Optional leukapheresis is performed only after the participant is enrolled in the study. If the participant consents to this optional procedure, a baseline leukapheresis is completed. If a baseline leukapheresis was performed, a second leukapheresis procedure is completed 2 weeks (+2 week window) following the final study drug infusion.

i Additional and/or more frequent safety laboratory tests may be performed as clinically indicated per the investigator's discretion.

j Clinical laboratory assessments scheduled for Day 1 can be obtained within 7 days prior to infusion. See **Section 9.11** for detailed list of assessments. Indirect bilirubin is required if participant on atazanavir.

k Day 43 hematology is assessed only for participants undergoing leukapheresis. This hematology assessment is performed within the window for the scheduled leukapheresis.

l Participants of childbearing potential only. Serum pregnancy test is required at screening. Subsequent pregnancy tests may use serum or urine. Results must be reviewed before study drug infusion on Day 1, Day 15, and Day 29. If screening test is performed within 72 hours of first infusion, repeat testing on Day 1 may be deferred.

m Reflex HCV PCR viral load test is performed only if positive for HCV antibody.

Abbreviations: ADA: anti-drug antibody; ART: antiretroviral therapy; CD: cluster of differentiation; ECG: electrocardiogram; EOI: end of infusion; EOSV: end of study visit; FSH: follicle stimulating hormone; HCV: hepatitis C virus; HIV-1: human immunodeficiency virus-1; HLA: human leukocyte antigen; PCR: polymerase chain reaction; PD: pharmacodynamics; PK: pharmacokinetics.

Appendix 2 Pharmacokinetics, Immunogenicity, and Pharmacodynamic Sample Collection Schedule

Table 9 Pharmacokinetic, Immunogenicity, and Pharmacodynamic Sampling Schedule: Part 1A

Study Day	Time Point	Window	PK (Serum) [a]	ADA to MGD020 (Serum)	Cytokines (Serum)	PD: T-cell Binding & Phenotype (Whole Blood)	PD: IPDA (PBMCs)	HLA Typing (Whole Blood)
-56 to -1	Screening	N/A		X				
1	Pre-MGD020 infusion	N/A	X		X	X	X	X
1	EOI MGD020	+ 10 min	X					
1	1 h after EOI MGD020	± 5 min	X		X	X		
1	4 h after EOI MGD020	± 5 min	X		X	X		
2	No specific time	N/A	X		X	X		
3	No specific time	N/A	X					
8	No specific time	± 2 days	X		X	X		
15	No specific time	± 2 days	X	X				
22	No specific time	± 2 days	X					
29	No specific time	± 2 days	X	X				
IRR-CRS [b]	No specific time [b]	N/A	X	X	X			
43/EOS	EOS	± 3 days	X	X			X	

a Obtain pre-infusion PK samples before start of infusion on visit day (dosing day) or day before. When collecting multiple samples, collect PK sample first.

b PK, ADA, and cytokine samples may be obtained selectively at additional time points in participants who experience signs and symptoms of IRR or CRS.

Abbreviations: ADA: anti-drug antibody; CRS: cytokine release syndrome; EOI: end of infusion; EOS: end of study; HLA: human leukocyte antigen; IPDA: intact proviral DNA assay; IRR: infusion related reaction; N/A: not applicable; PBMC: peripheral blood mononuclear cell; PD: pharmacodynamic; PK: pharmacokinetic.

Table 10 Pharmacokinetic, Immunogenicity, and Pharmacodynamic Sampling Schedule: Part 1B

Study Day	Time Point	Window	PK [a] (Serum)		ADA (Serum)		Cytokines (Serum)	PD: T-cell Binding & Phenotype (Whole Blood)	PD: IPDA (PBMCs)	HLA Typing (Whole Blood)
			MGD020	MGD014	MGD020	MGD014				
-56 to -1	Screening	N/A			X [b]	X [b]				
1	Pre-MGD020 infusion	N/A	X	X			X	X	X	X
1	EOI MGD020	+ 10 min	X							
1	EOI MGD014	+ 10 min		X						
1	1 h after EOI MGD014	± 5 min	X	X			X	X		
1	4 h after EOI MGD014	± 5 min	X	X			X	X		
2	No specific time	N/A	X	X			X	X		
3	No specific time	N/A	X	X						
8	No specific time	± 2 days	X	X			X	X		
15	No specific time	± 2 days	X	X	X	X				
22	No specific time	± 2 days	X	X						
29	No specific time	± 2 days	X	X	X	X				
IRR-CRS [c]	No specific time [c]	N/A	X	X	X	X	X			
43/EOS	End of study	± 3 days	X	X	X	X			X	

a Obtain pre-infusion PK samples before start of infusion on visit day (dosing day) or day before. When collecting multiple samples, collect PK sample first.

b For participants who have been previously exposed to MGD014 or MGD020, obtain screening samples for ADA (MGD014 and MGD020) at least 21 days prior to enrollment to allow for results to be reported before enrollment.

c PK, ADA and cytokine samples may be obtained selectively at additional time points in participants who experience signs and symptoms of IRR or CRS.

Abbreviations: ADA: anti-drug antibody; CRS: CRS: cytokine release syndrome; EOI: end of infusion; EOS: end of study; HLA: human leukocyte antigen; IPDA: intact proviral DNA assay; IRR: infusion related reaction; N/A: not applicable; PBMC: peripheral blood mononuclear cell; PD: pharmacodynamic; PK: pharmacokinetic.

Table 11 Pharmacokinetic, Immunogenicity, and Pharmacodynamic Sampling Schedule: Part 2

Study Day	Time Point	Window	PK [a] (Serum)		ADA (Serum)		Cytokines (Serum)	PD: T-cell Binding & Phenotype (Whole Blood)	PD: IPDA & rca-RNA (PBMCs)	HLA Typing (Whole Blood)	PD: QVOA (Leuka-pheresis)	PD: SCA (Plasma)
			MGD020	MGD014	MGD020	MGD014						
-56 to -1	Screening	N/A			X [b]	X [b]					X [c]	
1	Pre-MGD020 infusion	N/A	X	X			X	X	X	X		X
1	EOI MGD020	+ 10 min	X									
1	EOI MGD014	+ 10 min		X								
1	1 h after EOI MGD014	± 5 min	X	X			X	X				
1	4 h after EOI MGD014	± 5 min	X	X			X	X				
2	No specific time	N/A	X	X			X	X				
4	No specific time	N/A	X	X								
8	No specific time	± 1 day	X	X			X	X				
15	Pre-MGD020 infusion	N/A	X	X	X	X	X	X				
15	EOI MGD020	+ 10 min	X									
15	EOI MGD014	+ 10 min		X								
15	4 h after EOI MGD014	± 5 min	X	X			X	X				
29	Pre-MGD020 infusion	N/A	X	X	X	X	X	X				
29	EOI MGD020	+ 10 min	X									
29	EOI MGD014	+ 10 min		X								
29	4 h after EOI MGD014	± 5 min	X	X			X	X				
43	No specific time	± 2 days	X	X					X		X [c]	X
50	No specific time	± 2 days	X	X								
64	No specific time	± 3 days	X	X								
IRR-CRS [d]	No specific time [d]	N/A	X	X	X	X	X					
78/EOS	EOS	± 3 days	X	X	X	X						X

a Obtain pre-infusion PK samples before start of infusion on visit day (dosing day) or day before. When collecting multiple samples, collect PK sample first.

b For participants who have been previously exposed to MGD014 or MGD020, obtain screening samples for ADA (MGD014 and MGD020) at least 21 days prior to enrollment to allow for results to be reported before enrollment.

c Optional leukapheresis is performed only after the participant is enrolled in the study. If the participant consents to this optional procedure, a baseline leukapheresis is completed. If a baseline leukapheresis was performed, a second leukapheresis procedure is completed 2 weeks (+2 week window) following the final study drug infusion.

d PK, ADA, and cytokine samples may be obtained selectively at additional time points in participants who experience signs and symptoms of IRR or CRS.

Abbreviations: ADA: anti-drug antibody; CRS: cytokine release syndrome; EOI: end of infusion; EOS: end of study; HLA: human leukocyte antigen; IPDA: intact proviral DNA assay; IRR: infusion related reaction; N/A: not applicable; PBMC: peripheral blood mononuclear cell; PD: pharmacodynamic; PK: pharmacokinetic; QVOA: quantitative viral outgrowth assay; rca-RNA: resting CD4+ T-cell-associated HIV-1 gag RNA; SCA: single copy assay.

Appendix 3 Principal Investigator's Agreement

Study Title:	A Phase 1 Study of MGD020 as a Single Agent or in Combination with MGD014 in Persons with HIV-1 on Antiretroviral Therapy
Study Number:	CP-MGD020-01
DAIDS Document ID:	38879

I have read the protocol described above.

I have fully discussed the objectives of this study 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 the sponsor. It is, however, permissible to provide information to a participant in order to obtain consent.

I understand that the sponsor may decide to suspend or prematurely terminate the study 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 study, I will communicate my intention immediately in writing to the sponsor.

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 study in accordance with ICH guidelines on GCP and with the applicable regulatory requirements.

Signed: _____ Date: _____

Printed name: _____

Title: _____

Affiliation: _____

Address: _____

Phone number: _____

CP-MGD020-01 Protocol Amendment 1 (12-Jan-2023)

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

User Task: eSignatories Approval	Data Management/Statistics Approval (Intended or Designee) 12-Jan-2023 20:01:46 GMT+0000

User Task: eSignatories Approval	search Approval (Intended or Designee) 13-Jan-2023 19:13:42 GMT+0000