STATISTICAL ANALYSIS PLAN
VERSION 1.0

CLINICAL STUDY PROCOTOL: CP-MGD014-01

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

REVISION HISTORY

Version	Date
1.0	17 March 2021

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LIST OF ABBEVIATIONS

ACTG	AIDS clinical trials group
ADA	anti-drug antibody
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
AUC	area under the curve
CI	confidence interval
CL	clearance
CLIA	clinical laboratory improvement amendments
Cmax	maximum serum concentration
CRS	cytokine release syndrome
CSR	clinical study report
DLT	dose limiting toxicity
EC_{50}	half maximal effective concentration
HIV-1	human immunodeficiency virus-1
IRE	immediately reportable event
IUPM	infectious units per million
IV	intravenous(ly)
LCA	latency clearance assay
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
OBD	optimal biologic dose
PD	pharmacodynamics
PK	pharmacokinetics
PLWH	people living with HIV-1
QVOA	quantitative viral outgrowth assay
SAE	serious adverse event
SAP	statistical analysis plan
SCA	single copy assay
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure

SPP	statistical programming plan
TLFs	tables, listings, and figures
T_{max}	time to maximal concentration
V_{ss}	steady-state volume of distribution

1 INTRODUCTION

This statistical analysis plan (SAP) provides a detailed and comprehensive description for the analysis of the study CP-MGD014-01 entitled "A Phase 1 Study to Evaluate the Safety, Immunologic, and Virologic Responses of MGD014 Therapy in HIV-Infected Individuals on Suppressive Antiretroviral Therapy". This SAP Version 1.0 applies to the Protocol [redacted] of this study and describes in detail the statistical methods to be used for analysis of the primary, secondary, and exploratory objectives to be collected from this study.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The objective of this study is to characterize the safety and tolerability of MGD014 administered IV to persons living with human immunodeficiency virus-1 (HIV-1) (PLWH) maintained on suppressive antiretroviral therapy (ART).

2.2 Secondary Objectives

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

2.3 Exploratory Objectives

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

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

3 STUDY DESIGN AND PLAN

3.1 Overall Study Design and Plan

This is a Phase 1, single-center, open-label study of MGD014 in PLWH infection on stable ART. PLWH who began ART during either chronic HIV-1 infection or acute HIV-1 infection with plasma HIV-1 RNA < 50 copies/mL for 24 months prior to screening will be consented to the study. The screening procedures and initial evaluations that follow the consent determine eligibility for study entry. Eligible participants continue their baseline ART regimens throughout the study and receive either one infusion (Part 1) or an IV infusion once every 2 weeks (Q2W) for a total of three infusions of 300 mcg/kg of MGD014 for 4 weeks (Part 2), as briefly described below. See **CP-MGD014-01 Protocol Section 4.2** and **4.3** for further details.

3.2 Part 1 – Dose Escalation Phase

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

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

3.3 Part 2 – Multi-Dose Cohort Expansion Phase

Part 2 is a multi-dose expansion cohort with repeat administrations of MGD014 at 300 mcg/kg. Up to 6 patients will be enrolled in Part 2.

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

In Part 2, additional optional assessments on the effects of MGD014 on HIV-1 latent infection parameters include measurements of resting cell infection (frequency of persistent infection of resting CD4 T cells) by quantitative viral outgrowth assay (QVOA), latency clearance assay (LCA) to assess the impact of MGD014 administration on MGD014-mediated clearance activity in vitro, SCA, and T-cell phenotype and functional properties.

4 STATISTICAL METHODOLOGY

4.1 General Considerations

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

All data summaries and tabulations will be conducted using SAS® software Version 9.4 or higher.

4.2 Missing Data

Data that are reported as missing will be treated as missing in all data summaries. Imputation rules for partially recorded dates, in case that the complete dates are required to carry out an analysis, will be provided in the Statistical Programming Plan (SPP). In descriptive summaries for safety, observations that are spurious (extreme relative to the majority of the data) will not be altered or removed from the summary.

4.3 Determination of Sample Size

The number of participants is not based on statistical power calculations. A 1+3 design is utilized in the first two dose levels of Part 1 because the starting dose is considered biologically conservative and the anticipated risk of DLT is low. A 3+3 design is used for dose cohorts 3-8. The total sample size of Part 1 is at least 20, but will depend upon the occurrence of DLTs and potential need for expanded dose level cohorts (see **CP-MGD014-01 Protocol Section 4.2.1**). Part 2 of the study will have up to six (n=6) participants. This study overall plans to have approximately 26 HIV-1 infected, ART suppressed participants in total (Part 1 + Part 2). No inferential statistics will be calculated in Part 1. This sample size is considered biologically sufficient to evaluate the primary objective of this study (first in human evaluation of safety and tolerability of MGD014).

4.4 Analysis Populations

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

4.5 Demographics and Baseline Characteristics

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

4.6 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 study treatment period.

Duration of study treatment (months) will be calculated as:

- (date decided to discontinue treatment – date of first dose + 1)/(365.25/12) for patients who have discontinued treatment.
- (date of data cutoff – date of first dose + 1)/(365.25/12) for patients whose treatment is ongoing.

The summary of concomitant medications will include the number and percentage of patients who receive any concomitant medications as well as each concomitant medication by drug class.

4.7 Protocol Deviations

Major protocol deviations will be identified prior to database lock for final analysis and will be listed and summarized.

4.8 Safety Endpoints and Analyses

4.8.1 Adverse Events

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

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

- All AEs
- All study drug-related AEs
- Study drug related AEs by severity grade
- AEs by severity grade
- All SAEs (this may be a listing if there are few events)
- Study drug-related SAEs
- Fatal AEs (this may be a listing if there are few events)

- AEs that result in study discontinuation
- AEs that lead to withdrawal of study drug
- AEs categorized as AESI and/or IREs
- AEs with severity grade 3 or greater
- Study drug-related AEs with severity grade 3 or greater

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

4.8.2 Laboratory Values and Analyses

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

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

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

4.8.3 Other Safety Endpoints and Analyses

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

4.9 Efficacy Endpoints and Analyses

The following efficacy endpoints are exploratory and only apply to Part 2 patients. The described analyses of these endpoints below are optional and may not be performed if less than 6 patients is eventually enrolled to Part 2.

4.9.1 Quantitative Viral Outgrowth Assay

For participants who completed the optional leukapheresis, a comparison of pre-MGD014 and post-MGD014 frequency of HIV infection per million resting CD4 T cells will be

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

Table 1 Precision calculations for QVOA analysis

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

IUPM=infectious units per million CI=confidence interval

4.9.2 Single Copy Assay

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

4.9.3 Exploratory Endpoints and Analyses

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

assessed graphically (e.g., scatter plots, correlate heat map) and estimated with a non-parametric rank based correlation method. Additionally, association between antiviral impact of MGD014 and baseline participant clinical characteristics, such as stage of HIV infection (acute vs. chronic) at initiation of ART, will also be described and examined. Correlation including one or more measures from the same participant may be assessed using Kendall's tau for clustered data [1]. Exploratory analyses will be conducted using a two-sided 0.05 significance level with no adjustment for multiplicity.

4.10 Pharmacokinetic Endpoints and Analyses

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

4.11 Pharmacodynamic Endpoints and Analyses

Summary statistics for biomarkers, such as but not limited to those listed under **CP-MGD014-01 Protocol Section 10.3** and corresponding changes from baseline, will be summarized and may also be presented graphically as will possible associations between changes in PD measures of interest and MGD014 dose and exposure.

4.11.1 Serum Cytokines

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

4.12 Immunogenicity Endpoints and Analyses

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

5 LIST OF TABLES, LISTINGS AND FIGURES

The list of tables, listings, and figures (TLFs) and associated shells planned for the clinical study report based on the analyses described in **Section 4.1 - 4.3** of this SAP will be provided in a SPP, which will also include data reporting conventions and programming specifications for the development of these TLFs. The analyses described in **Section 4.4 - 4.6** of this SAP will be performed and presented separately by MG's research group.

6 REFERENCES

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