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STATISTICAL ANALYSIS PLAN
VERSION 2.0

CLINICAL STUDY PROCOTOL: CP-MGD020-01

A Phase 1 Study of MGD020 as a Single Agent or in Combination with MGD014 in Persons with HIV-1 on Antiretroviral Therapy

REVISION HISTORY

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LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ART	antiretroviral therapy
AUC	area under the curve
CD	Cluster of differentiation
CI	confidence interval
CL	clearance
C_{max}	maximum serum concentration
C_{trough}	trough concentration
CSR	clinical study report
DLT	dose-limiting toxicity
ECG	electrocardiogram
HIV-1	human immunodeficiency virus, in this document the virus denotes specifically HIV-1
Ig	immunoglobulin
IPDA	intact proviral DNA assay
IUPM	infectious units per million
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
PD	pharmacodynamics
PK	pharmacokinetics
PT	preferred term
PWH	persons with HIV-1
QVOA	quantitative viral outgrowth assay
rca-RNA	resting CD4+ T-cell-associated HIV-1 gag RNA
SAE	serious adverse event
SAP	statistical analysis plan
SCA	single copy assay
SD	standard deviation
SOC	system organ class
SPP	statistical programming plan
TLFs	tables, listings, and figures
$t_{1/2}$	terminal half-life

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-MGD020-01 titled “A Phase 1 Study of MGD020 as a Single Agent or in combination with MGD014 in Persons with HIV-1 on Antiretroviral Therapy”. This SAP Version 2.0 incorporates changes made in CP-MGD020-01 Protocol Amendment 1 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 safety and tolerability of MGD020 as a single agent and in combination with MGD014.

2.2 Secondary Objectives

- Assess pharmacokinetics (PK) and immunogenicity (anti-drug antibody [ADA]) of MGD020.
- Assess PK and immunogenicity (ADA) of MGD014.
- Assess serum cytokine levels.

2.3 Exploratory Objectives

- Explore T-cell binding.
- Explore immunologic responses.
- Explore markers of persistent HIV-1.
- Explore correlations between virologic and immunologic markers.

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

3 STUDY DESIGN AND PLAN

3.1 Overall Study Design and Plan

This is a Phase 1, open-label 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.

3.2 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 3+3 design for cohorts 4–6. A 2-week dose-limiting toxicity (DLT) period is observed prior to escalation to the next cohort level.

Part 1A has 6 cohorts. 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 maximum tolerated dose (MTD). The MTD will then be defined as the next lower dose level of MGD020. Escalation proceeds until either the MTD or maximum administered dose (MAD) is determined.

3.3 Part 1B – Single Ascending Dose of MGD020 and Fixed-dose of MGD014

Part 1B commences only after 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 of MGD014.

MGD020 and MGD014 will be administered at the doses shown in the table below 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 1 dose level lower than MTD/MAD from Part 1A. MGD014 is dosed at 300 mcg/kg. Escalation to the next cohort follows the prespecified escalation rules.

MGD020 and MGD014 Combination Dose Escalation Scheme

Cohort	MGD020 [a] (mcg/kg)	MGD014 (mcg/kg)	Design
-1 [b]	MGD020 MTD/MAD -2	300	3+3
1	MGD020 MTD/MAD -1	300	3+3
2	MGD020 MTD/MAD	300	3+3

a The MGD020 dose is determined by the single-agent MTD or MAD in Part 1A; the MGD020 dose in Cohort 1 will be one dose below the single-agent MTD/MAD (i.e., MTD/MAD -1).

b If the dose level in Cohort 1 exceeds the MTD, de-escalation to Cohort -1 dose levels (MTD/MAD -2) may be considered.

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.

3.4 Part 2 – Multi-Dose Expansion Cohort

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. MGD014 is dosed at 300 mcg/kg.

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

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 STATISTICAL METHODOLOGY

4.1 General Considerations

The majority of the statistical summaries for this Phase 1 study 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 perform 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 study plans to enroll up to 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 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.

4.4 Analysis Populations

All participants who receive at least one dose of either study drug will be included in the safety population. This population will be used to summarize safety data. This population will also be used to summarize baseline data and for PK, PD, and immunogenicity analyses.

4.5 Demographics and Baseline Characteristics

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

4.6 Study Drug Exposure and Concomitant Medications

Study drug exposure, ART, 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 or cycles 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 participants who have discontinued treatment.
- (date of data cutoff – date of first dose + 1)/(365.25/12) for participants whose treatment is ongoing.

The summary of concomitant medications will include the number and percentage of participants who receive any concomitant medications as well as each concomitant medication by drug class. Concomitant medications are coded using the World Health Organization Drug Dictionary.

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

Treatment-emergent adverse events (AEs) will be summarized in tables and listings. All AEs prior to treatment (e.g., due to study-related procedure) 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). Events will be summarized by system organ class, preferred term, relationship to study drug, and highest severity.

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
- Study drug-related AEs
- Study drug-related AEs by severity grade

- AEs by severity grade
- All severe AEs (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 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 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.

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 value normality between baseline and each post-baseline visit.

4.8.3 Other Safety Endpoints and Analyses

Electrocardiograms (ECGs) will be collected and analyzed for evidence of cardiac toxicity, especially prolongation of QT interval. Summary statistics will be tabulated for ECGs parameters. The following categories for QTc interval and maximum post dose change from baseline QTc will be used in summary:

QTc: $\leq$ 450 msec, > 450 to 480 msec, > 480 to 500 msec, and > 500 msec

Vital signs will be summarized with descriptive statistics at each visit and time point where they are collected. Shift tables may be produced to display percent of participants who have a shift from normal between baseline and each post-baseline visit.

4.9 Exploratory Endpoints and Analyses

The endpoints described in Sections 4.12.2-4.12.7 below are exploratory and only include participants from one or multiple parts of the study. The described analyses of these endpoints are optional and may not be performed if sample size does not permit.

4.10 Pharmacokinetic Endpoints and Analyses

Summary statistics will be tabulated for PK parameters by dose. Geometric means and percent coefficients of variation may be reported for maximum concentration (C_{max}), lowest concentration (C_{min}) observed at the last study point, area under the curve (AUC) for Parts 1A and 1B, area under the curve for 2 week interval (AUC_{tau}) for Part 2, and trough concentration (C_{trough}) for Part 2; arithmetic means and standard deviations (SD) may be reported for terminal half-life ($t_{1/2}$), clearance (CL), and steady-state volume of distribution (V_{ss}); and medians, minimum, and maximum will be reported for time to maximal concentration (T_{max}).

4.11 Immunogenicity Endpoints and Analyses

The proportion of participants who are 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. The impact of immunogenicity on safety, PK, and PD may be summarized and explored graphically.

4.12 Pharmacodynamic Endpoints and Analyses

Summary statistics for biomarkers, such as but not limited to those listed in CP-MGD020-01 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 MGD020 alone or MGD020 and MGD014 dose and exposure.

4.12.1 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 MGD020 alone or MGD020 and MGD014 serum concentrations and serum cytokines (e.g., an exposure-response analysis), if deemed appropriate.

4.12.2 T-cell Binding

The percentages of cluster of differential $CD4^+$ and $CD8^+$ cells in blood with bound MGD020 (Part 1A) or bound with both MGD020 and MGD014 (Part 1B and Part 2) will be summarized over time. Values may also be presented graphically where appropriate.

4.12.3 T-cell Phenotype and Function

The percentages of $CD4^+$ and $CD8^+$ cells in blood with expression of activation markers (e.g., CD25, CD69, CD134, CD137), cytolytic markers (granzyme B, perforin), regulatory T cell marker (FoxP3), proliferation marker (Ki67), or memory subsets (naïve, central memory, effector memory, effector memory re-expressing CD45RA) will be summarized over time. Values may also be presented graphically where appropriate. Note that some biomarkers mentioned in the protocol amendment 1 have been removed and new biomarkers have been added here to reflect the change in terms of planned biomarker analyses.

4.12.4 Quantitative Viral Outgrowth Assay (QVOA)

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 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.

4.12.5 Intact Proviral Deoxyribonucleic Acid Assay (IPDA)

In Parts 1A, 1B and 2, pre- and post-dose measurements of the frequencies of resting CD4+ T-cell infection by IPDA 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.

4.12.6 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. 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.

4.12.7 Plasma Viremia by Single Copy Assay (SCA)

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.

5 LIST OF TABLES, LISTINGS, AND FIGURES

The list of tables, listings, and figures (TLFs) and associated shells planned for the CSR based on the analyses described in this SAP will be provided in a separate SPP, which will also include data reporting conventions and programming specifications for the development of these TLFs. Note that the SPP will not include TLF shells for the exploratory analyses described in Sections 4.12.2-4.12.7 as they will be performed and reported separately.