STATISTICAL ANALYSIS PLAN

Protocol HVTN 140/HPTN 101

Version 1.0

A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, and pharmacokinetics of PGDM1400LS alone and in combination with VRC07-523LS and PGT121.414.LS in healthy, HIV-uninfected adult participants

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Approval Signature Page

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I have read this Statistical Analysis Plan and approve its contents.

See appended email signature

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SAP Modification History

The version history of, and modifications to, this statistical analysis plan are described below.

SAP Version	Date	Modification
0.0	05 Nov 2021	First draft concerning only the analysis of safety endpoints.
1.0	16 Nov 2021	Incorporated review comments

Table of Contents

1 OVERVIEW

The following describes the Statistical Analysis Plan (SAP) for the analysis of data from HVTN 140 for Safety Monitoring Board (SMB) reports, the Final Study Report (FSR) for Safety, Protocol Team (PT) reports for immunogenicity data, and the FSR for Immunogenicity. As detailed in SCHARP SOP-0013, Revision 5 (effective date: August 15, 2016), this SAP is required prior to the first analysis and must be approved by the lead protocol statistician. SMB reporting begins shortly after enrollment opens, and subsequent revisions are expected to describe analysis of immunogenicity data. The SAP will be reviewed prior to the first SMB report and before the final analysis with all major revisions of the plan archived.

2 PROTOCOL SUMMARY

A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, and pharmacokinetics of PGDM1400LS alone and in combination with VRC07-523LS and PGT121.414.LS in healthy, HIV-uninfected adult participants

Study Products

- PGDM1400LS: a human mAb that targets the HIV-1 V2 glycan, centered on N160. It is a derivative of PGDM1400 that was engineered to improve in vivo elimination half-life. It has been developed by the Vaccine Research Program (VRP) of the National Institute of Allergy and Infectious Diseases (NIAID). PGDM1400LS was manufactured under current Good Manufacturing Practice (cGMP) standards at Just-Evotec (Seattle, Washington) under contract to DAIDS's Vaccine Translational Research Branch (VTRB). The drug product was filled and released at the VRC Pilot Plant, operated under contract by Vaccine Clinical Materials Program (VCMP), Leidos Biomedical Research, Inc., Frederick, MD. The drug product is provided at 100 mg/mL as 10 mL glass vials with a 4.75 mL fill volume.

- PGT121. 414.LS: is a human mAb that targets the HIV-1 V3 glycan, centered on N332. It is a derivative of PGT121 that was engineered for improved manufacturing, stability and in vivo elimination half-life by Just Biotherapeutics in collaboration with Dan Barouch and Collaboration for AIDS Vaccine Discovery (CAVD) investigators. The drug substance was manufactured under cGMP standards at Just Biotherapeutics under contract to DAIDS's VTRB. The drug product was filled and released by the VRC and VCMP, Leidos Biomedical Research, Inc., Frederick, MD. Product is provided at 100 mg/mL as 10 mL glass vials with a 4.75 mL fill volume.

- VRC-HIVMAB075-00-AB (VRC07-523LS): is a human mAb that targets the HIV-1 CD4 binding site. It was developed by the VRC/NIAID/NIH and manufactured under cGMP standards at the VRC Pilot Plant operated under contract by the VCMP, Leidos Biomedical Research, Inc., Frederick, MD. Product is provided at 100 ± 10 mg/mL as 10 mL glass vials with a 6.25 ± 0.1 mL fill volume and 3 mL glass vials with a 2.25 mL ± 0.1 mL fill volume.

Participants

- About 95 healthy, HIV-1–uninfected volunteers aged 18 through 50 years

Study arm	N*	Dose	Route	Month 0	Month 4
Part A					
Group 1	3	5 mg/kg	IV	PGDM1400 LS	-
Group 2[1]	3	20 mg/kg	IV	PGDM1400 LS	-
Group 3[1]	3	20 mg/kg	SC	PGDM1400 LS	-
Group 4[2]	3	40 mg/kg	IV	PGDM1400 LS	-
Group 5[2]	3	40 mg/kg	SC	PGDM1400 LS	-
Part B**					
Group 6[3]	16	20 mg/kg + 20 mg/kg + 20 mg/kg	IV	PGDM1400 LS + VRC07-523LS + PGT121.414. LS	PGDM1400 LS + VRC07-523LS + PGT121.414. LS
Group 7[3]	16	20 mg/kg + 20 mg/kg + 20 mg/kg	SC	PGDM1400 LS + VRC07-523LS + PGT121.414. LS	PGDM1400 LS + VRC07-523LS + PGT121.414. LS
Group 8[3]	16	1.4 g + 1.4 g + 1.4 g	IV	PGDM1400 LS + VRC07-523LS + PGT121.414. LS	PGDM1400 LS + VRC07-523LS + PGT121.414. LS
Group 9[3]	16	1.4 g + 1.4 g + 1.4 g	SC	PGDM1400 LS + VRC07-523LS + PGT121.414. LS	PGDM1400 LS + VRC07-523LS + PGT121.414. LS
Group 10[4]	16	40 mg/kg + 40 mg/kg + 40 mg/kg	IV	PGDM1400 LS + VRC07-523LS + PGT121.414. LS	PGDM1400 LS + VRC07-523LS + PGT121.414. LS
Total			**95**		

IV = intravenous infusion; SC = subcutaneous infusion; *additional participants may be enrolled to ensure the availability of safety data from at least 3 participants in each group;**antibodies will be administered sequentially as 3 separate infusions; + sign = "and".

[1]Opening enrollment in Groups 2 & 3 follows review of safety data for participants in Group 1. Details are described in Section 11.3.1.

[2]Opening enrollment in Group 4 & 5 follows review of safety data for participants in Groups 1- 3.

[3]Opening enrollment in Groups 6, 7, 8, and 9 follows review of safety data for participants in Part A.

[4]Opening enrollment in Group 10 follows review of safety data for participants from Groups 1-9.

3 OBJECTIVES AND ENDPOINTS

3.1. Primary objective:

Primary objective 1:

To evaluate the safety and tolerability of PGDM1400LS when administered via intravenous (IV) or subcutaneous (SC) routes (Part A) and of PGDM1400LS, VRC07-523LS and PGT121.414.LS when administered in sequence IV or SC (Part B)

Primary endpoints 1:

- Local and systemic Solicited AEs, laboratory measures of safety, Unsolicited AEs, and SAEs
- Early discontinuation of administration and reason(s) for discontinuation and early study termination

Primary objective 2:

To evaluate the serum concentrations and pharmacokinetics of PGDM1400LS after a single administration (Part A) and of PGDM1400LS, VRC07-523LS, and PGT121.414.LS after each three-mAb administration (Part B)

Primary endpoint 2:

Serum concentrations of PGDM1400LS, VRC07-523LS and PGT121.414.LS at prespecified timepoints among participants who received all scheduled product administrations

Primary objective 3:

To evaluate the individual mAb-specific serum neutralizing activity after single product administration of PGDM1400LS (Part A) and after each three-mAb administration of PGDM1400LS, VRC07-523LS and PGT121.414.LS (Part B)

Primary endpoint 3:

Magnitude and breadth of neutralizing activity measured with Env pseudotyped viruses specific for either PGDM1400LS, VRC07-523LS or PGT121.414LS in TZM-bl cells at prespecified timepoints among participants who received all scheduled product administrations

3.2. Secondary objective:

Secondary objective 1:

To correlate serum concentrations of PGDM1400LS, VRC07-523LS and PGT121.414.LS with corresponding virus neutralization titers in serum

Secondary endpoints 1:

- Serum concentrations of PGDM1400LS, VRC07-523LS and PGT121.414.LS at prespecified timepoints for all participants in all groups regardless of how many product administrations and how much product they received

- Magnitude of serum neutralizing activity measured with mAb-specific Env-pseudotyped viruses in TZM-bl cells at prespecified timepoints for all participants in all groups regardless of how many product administrations and how much product they received

Secondary objective 2:

To determine whether the mAbs maintain their expected combined magnitude and breadth of serum neutralizing activity after each PGDM1400LS, VRC07-523LS and PGT121.414.LS three-mAb administration (Part B) as predicted by the known magnitude and breadth of neutralization of the corresponding mAb combinations as non-infused clinical products

Secondary endpoint 2:

Magnitude of neutralizing activity against a panel of Env-pseudotyped reference viruses that are sensitive to all three bnAbs in TZM-bl cells at selected timepoints for all participants in all groups regardless of how many product administrations and how much product they received

Secondary objective 3:

To determine whether anti-drug antibodies (ADA) are present

Secondary endpoint 3:

ADA titers in each group measured at prespecified timepoints for all participants in all groups regardless of how many product administrations and how much product they received

Secondary objective 4:

To evaluate the impact of body weight and other baseline covariates on the pharmacokinetics of PGDM1400LS, VRC07-523LS and PGT121.414.LS in both the weight-based and fixed-dose groups.

Secondary endpoint 4:

Serum concentrations of PGDM1400LS, VRC07-523LS and PGT121.414.LS at prespecified timepoints

3.3. Exploratory objective:

Exploratory objective 1:

To determine whether any confirmed positive ADA samples have functional activity that impacts the neutralizing activity of PGDM1400LS, VRC07-523LS and PGT121.414.LS

Exploratory objective 2:

To further evaluate non-neutralizing anti-viral activities, additional assays (eg, ADCC, ADCP, virion capture) may be performed for activities that the PGDM1400LS, VRC07-523LS and PGT121.414.LS are shown to exhibit in vitro

Exploratory objective 3:

To conduct analyses related to predicting serum neutralization over time against a set of potentially exposing viruses in a future efficacy trial for ranking and down-selecting bnAb regimens

Exploratory objective 4:

To conduct analyses related to furthering the understanding of HIV, passive immunity, immunology, vaccines, and clinical trial conduct.

4 COHORT DEFINITION

Participants

About 95 healthy, HIV-1–uninfected volunteers aged 18 through 50 years

Design

Multicenter, randomized, open-label study

Duration per participant

6 months per participant in Part A and 10 months per participant in Part B of scheduled clinic visits

Estimated total study duration

14 months (includes enrollment, planned safety holds, and follow-up)

5 POTENTIAL CONFOUNDERS

Characterization of the safety of the vaccine is susceptible to confounding by adverse events not related to the vaccine that by chance occur more often in one arm of the trial than another. Therefore analyses involving adverse events will incorporate the reported relationship to product as assessed by HVTN staff.

6 RANDOMIZATION

There will be no randomization for Group 1 as they will be enrolled first. Contingent on safety data from Group 1, Groups 2 and 3 will be randomized and enrolled simultaneously. Contingent on safety data from Groups 2 and 3, Groups 4 and 5 will be randomized and enrolled simultaneously. Contingent on data from Part A, Groups 6, 7, 8, and 9 will be randomized in blocks to ensure balance across groups for simultaneous enrollment. There will be no randomization for Group 10. A participant's randomization assignment will be computer generated and provided to the CRS pharmacist through a web-based randomization system.

7 BLINDING

Participants and CRS staff will be unblinded to participant treatment arm assignments. Laboratory Center staff will be unblinded to whether a sample is from Part A or Part B, but will remain blinded to treatment assignment within Part A or Part B during sample analysis.

8 STATISTICAL ANALYSIS

All safety data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many study product administrations and how much study product they received. Analyses of safety data are modified intent-to-treat (MITT) in that individuals who are randomized but not enrolled do not contribute data and hence are excluded. Because of the brief length of time between randomization and enrollment—typically no more than 4 working days—very few such individuals are expected.

The primary analysis of mAb concentration and anti-viral functional activity data are per-protocol (PP) in that only individuals who receive the expected mAb at the expected dose level within the expected visit window contribute data. Secondary analysis will also involve the MITT cohort, and when necessary account for the actual specimen collection time, and the actual time and dose amount of each product administration.

Analyses for primary endpoints will be performed using SAS and R. Additional software may be used to perform non-compartmental PK and population PK analyses (eg, Monolix). All other descriptive and inferential statistical analyses will be performed using SAS, StatXact, or R statistical software.

No formal multiple comparison adjustments will be employed for multiple primary or secondary endpoints. However, multiplicity adjustments will be made for certain primary or secondary endpoint assays, as discussed below, when the assay endpoint is viewed as a collection of hypotheses (eg, testing multiple pseudo-viruses to determine a positive antiviral functional activity response). Unless otherwise noted, all statistical tests will be 2-sided and will be considered statistically significant if $p < 0.05$.

8.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, mAb concentration, mAb functionality, and ADA for primary- and secondary-objective analyses.

8.2 Analysis tools

Analyses for primary endpoints will be performed in SAS (v9.4). All other descriptive and inferential statistical analyses will be performed using SAS, Monolix, and/or R statistical software.

8.3 Baseline comparability

Treatment arms will be compared for baseline participant characteristics using descriptive statistics.

8.4 Safety/tolerability analysis

Since enrollment is concurrent with receiving the first study product administration, all participants will have received at least 1 product administration and therefore will provide some safety data.

8.4.1 Solicited AEs

The number and percentage of participants experiencing each type of Solicited AE sign or symptom (see Section 11.2.2) will be tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given sign or symptom, each participant's Solicited AEs will be counted once under the maximum severity for all injection visits. In addition, to the individual types of events, the maximum severity of local pain or tenderness, induration or erythema, and of systemic symptoms will be calculated. Kruskal-Wallis tests will be used to test for differences in severity between arms.

8.4.2 SAEs and Unsolicited AEs

Unsolicited AEs (see Section 11.2.2) will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an Unsolicited AE within a System Organ Class or within preferred term category by severity or by relationship to study product. For the calculations in these tables, a participant with multiple Unsolicited AEs within a category will be counted once under the maximum severity or the strongest recorded causal relationship to study product. Formal statistical testing comparing arms is not planned since interpretation of differences must rely heavily upon clinical judgment.

A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events including severity, relationship to study product, time between onset and last study product administration, and number of study product administrations received.

8.4.3 Local laboratory values

Box plots of local laboratory values will be generated for baseline values and for values measured during the course of the study by treatment arm and visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers (values outside the box plot) will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

For each local laboratory measure, summary statistics will be presented by treatment arm and timepoint, as well as changes from baseline for postenrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 1 AE criteria or above as specified in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (see Section 9.8) will be tabulated by treatment arm for each poststudy product administration timepoint. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

8.4.4 Reasons for study product administration discontinuation and early study termination

The number and percentage of participants who discontinue study product administration and who terminate the study early will be tabulated by reason and treatment arm.

8.5 Analyses prior to end of scheduled follow-up visits

Any analyses conducted prior to the end of the scheduled follow-up visits should not compromise the integrity of the trial in terms of participant retention or other study endpoint assessments.

8.5.1 Safety

During the course of the trial, unblinded analyses of safety data will be prepared approximately every 4 months for review by the SMB. Ad hoc safety reports may also be prepared for SMB review at the request of the HVTN 140/HPTN 101 PSRT.

9 SAFETY TABLES AND FIGURES

9.1 List of Tables

- Enrollment Report
- Demographics and Study Product Administration Frequencies
- Overall Protocol Status
- Discontinuation Status
- Study Product Administration Errors
- Maximum Local and Systemic Solicited AE Summaries
- Severe or Life-threatening Local Solicited AE's
- Moderate, Severe, and Life-threatening Erythema / Induration
- Adverse Experiences by Body System and Severity – By Decreasing Frequency
- Adverse Experiences by Preferred Term and Severity – By Decreasing Frequency – Includes Severe, Life-threatening or Fatal Events Only
- Adverse Experiences by Preferred Term and Severity – By Decreasing Frequency – Includes Events of All Severities
- Adverse Experiences by Preferred Term and Relationship to Study Product – By Decreasing Frequency – Includes Related Events Only
- Adverse Experiences by Preferred Term and Relationship to Study Product – By Decreasing Frequency – Includes Events of Any Relationship
- Severe, Life-Threatening, or Fatal Adverse Events
- Related Events

9.2 Participant Listings

The following listings of participant-level data are included in the SMB reports.

- Discontinuations
- Pregnancies
- Severe or Life-Threatening Local and Systemic Solicited AEs
- Moderate or Severe Erythema and Induration
- Expedited Adverse Experiences (EAEs)
- Severe, Life-Threatening, or Fatal Adverse Experiences
- Adverse Experiences with Relationship to Study Product (Grade 2 or higher)
- Study Product Administration Errors
- HIV Infection Results from Lab and Reported by Site
- mAb Reactions

9.3 List of Graphs

- Maximum Local Solicited AEs
- Maximum Systemic Solicited AEs
- Boxplots for Alkaline Phosphatase, AST, ALT, Creatinine, WBC, Hemoglobin, Platelets, Lymphocyte Count, Neutrophil Count

10 REFERENCES

1. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat 1998;52:119-26.