STATISTICAL ANALYSIS PLAN

Protocol HVTN 136/HPTN 092

Protocol version 1.0

A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of the monoclonal antibody PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous or subcutaneous infusions in healthy, HIV-uninfected adult participants

Date: 12 January 2022

Version 1.0

Prepared by

Protocol Statisticians **Zonglin He, PhD**

Approval Signature Page

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

See email signature attached_____ 10/27/2021_____

Yunda Huang, PhD Date

Principle Staff Scientist

Vaccine and Infectious Disease Division

Fred Hutchinson Cancer Research Center

See email signature attached_____ 10/27/2021_____

Brett Hanscom, PhD Date

Staff Scientist

Vaccine and Infectious Disease Division

Fred Hutchinson Cancer Research Center

See email signature attached_____ 10/27/2021_____

Zonglin He, PhD Date

Statistical Research Associate

Fred Hutchinson Cancer Research Center, SCHARP

SAP Modification History

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

Date: 27 October 2021
SAP version: Version *0.0*
Modifications: First draft concerning only the analysis of safety endpoints.
Date: 12 January 2022
SAP version: Version *1.0*
Modifications: Finalized in PDF and certified.

SAP Version	Date	Modification
0.0	27 October 2021	Initial
1.0	12 January 2022	Finalized in PDF and certified

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1 OVERVIEW

The following describes the Statistical Analysis Plan (SAP) for the analysis of data from HVTN 136/HPTN092 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

Title

A phase 1 dose-escalation clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of the monoclonal antibody PGT121.414.LS administered alone and in combination with VRC07-523LS via intravenous or subcutaneous infusions in healthy, HIV-uninfected adult participants

Study products and routes of administration

- PGT121.414.LS: PGT121.BIJ414.LS (referenced and labeled as PGT121.414.LS) was a human mAb produced by Just Biotherapeutics in collaboration with Dan Barouch (Beth Israel Deaconess Medical Center), and collaborative engagement of CAVD investigators. The drug substance was manufactured under cGMP standards at Just Biotherapeutics under contract to DAIDS's Vaccine Translational Research Branch (VTRB). The drug product was filled and released for the Dale and Betty Bumpers Vaccine Research Center (VRC) by the Vaccine Clinical Materials Program (VCMP), Leidos Biomedical Research, Inc., Frederick, MD. Product will be supplied as 10 mL single-use glass vials with a 4.75 mL fill volume, at a concentration of 100 mg/mL. Each vial contains a clear, colorless to yellow, preservative free, sterile solution for injection. The formulation buffer is composed of acetate, sucrose, polysorbate 80 at pH of 5.2. Product will be administered with and without VRC07-523LS by both the intravenous infusion (IV) and subcutaneous injection (SC) routes.

- VRC07-523LS (VRC-HIVMAB075-00-AB): a human mAb targeting the HIV-1 CD4 binding site, developed by NIAID-NIH at the VRC. Product will be supplied as 10 mL single-use glass vials with a 6.25 ± 0.1 mL fill volume and 3 mL single-use glass vials with a 2.25 mL ± 0.1 mL fill volume, at a concentration of 100 ± 10 mg/mL. Each vial contains a clear, colorless to yellow isotonic, preservative free, sterile solution essentially free of visible particles; some opaque or translucent particles may be present. The formulation buffer is composed of histidine, sodium chloride, sucrose, and sorbitol at pH 6.8. Vials do not contain a preservative. Product will be administered with PGT121.414.LS by both the IV and SC routes.

Participants

- 32 healthy, HIV-1–uninfected volunteers aged 18 to 50 years

Schema

Study arm	Number	Dose	Route	Month 0 (Day 0)	Month 4 (Day 112)	Month 8 (Day 224)
Part A						
Group 1*	3	3 mg/kg	IV	PGT121.414.LS	—	—
Group 2[a*]	3	10 mg/kg	IV	PGT121.414.LS	—	—
Group 3[b*]	3	30 mg/kg	IV	PGT121.414.LS	—	—
Group 4[b*]	3	5 mg/kg	SC	PGT121.414.LS	—	—
Part B						
Group 5[c]	10	20 mg/kg + 20 mg/kg	IV	PGT121.414.LS + VRC07-523LS	PGT121.414.LS + VRC07-523LS	PGT121.414.LS + VRC07-523LS
Group 6[c]	10	5 mg/kg + 5 mg/kg	SC	PGT121.414.LS + VRC07-523LS	PGT121.414.LS + VRC07-523LS	PGT121.414.LS + VRC07-523LS
Total	32					

Notes

IV = intravenous infusion; SC = subcutaneous infusion. Infusions are given sequentially in the order shown.

[a] Enrollment in Group 2 begins following review of safety data for participants in Group 1.

[b] Enrollment in Groups 3 and 4 begins concurrently following review of safety data for participants in Groups 1 and 2.

[c] Enrollment in Groups 5 and 6 begins concurrently following review of safety data for participants in Part A. Details described in Protocol Version 1.0 Section 11.3

*Additional participants may be enrolled to ensure the availability of 2-week safety data from at least 3 participants

3 OBJECTIVES AND ENDPOINTS

3.1 Primary objectives and endpoints

Primary objective 1

- To evaluate the safety and tolerability of the PGT121.414.LS monoclonal antibody (mAb) when administered alone via intravenous (IV) or subcutaneous (SC) infusion (Part A) and of PGT121.414.LS and VRC07-523LS administered consecutively via IV or SC routes at and after each product administration visit (Part B)

Primary endpoints 1

- Local and systemic solicited AEs, laboratory measures of safety, and 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 pharmacokinetic (PK) properties of PGT121.414.LS after a single administration (Part A) and of PGT121.414.LS and VRC07-523LS after consecutive administration of the pair of mAbs at and after each of 3 quarterly visits (Part B)

Primary endpoint 2

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

Primary objective 3

- To evaluate the individual mAb-specific serum neutralizing activity of PGT121.414.LS after a single administration (Part A) and of PGT121.414.LS and VRC07-523LS after consecutive administration of the pair of mAbs at and after each of 3 quarterly visits (Part B).

Primary endpoint 3

- Magnitude of serum neutralizing activity measured with mAb-specific Env-pseudotyped viruses in TZM-bl cells from samples obtained at prespecified timepoints among participants who received all scheduled product administrations

3.2 Secondary objectives and endpoints

Secondary objective 1

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

Secondary endpoints 1

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

- Magnitude of neutralizing activity against a panel of Env-pseudotyped reference viruses 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 2

- To determine whether the mAbs maintain their expected combined magnitude and breadth of serum neutralizing activity as predicted by the known magnitude and

breadth of neutralization of the corresponding mAb combinations as non-infused clinical products in vitro

Secondary endpoint 2

- Magnitude of neutralizing activity against a panel of Env pseudotyped reference viruses 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, and for the clinical product assayed at the same time.

Secondary objective 3

- To determine whether ADA are present and whether there is a correlation between PGT121.414.LS and VRC07-523LS concentrations and ADA titers in serum samples

Secondary endpoint 3

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

3.3 Exploratory objectives

Exploratory objective 1:
To determine whether any confirmed positive ADA samples have functional activity that impacts the neutralizing activity of PGT121.414.LS and
VRC07-523LS

Exploratory objective 2
To further evaluate non-neutralizing antiviral activities, additional assays (eg, antibody dependent cell mediated cytotoxicity [ADCC], antibody dependent cellular phagocytosis [ADCP], virion capture) may be performed for activities that PGT121.414.LS and VRC07-523LS are shown to exhibit in vitro

Exploratory objective 3
To develop predictive population PK models and to assess PK, drug-drug interaction, and neutralization drug-drug interaction among PGT121.414.LS and VRC07-523LS

Exploratory objective 4

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 5
To conduct analyses related to furthering the understanding of HIV, monoclonal antibodies, immunology, vaccines, and clinical trial conduct

4 COHORT DEFINITION

Participants
32 healthy, HIV-1–uninfected volunteers aged 18 to 50 years

Multicenter design
Part A: dose escalation, first in human, open-label IV or SC product administration with randomization into Groups 3 and 4

Part B: randomized, open-label IV or SC product administration

Duration per participant
Part A: 8 months per participant in Groups 1, 2 and 3; 6 months per participant in Group 4; 16 months per participant in Part B.

Estimated total study duration
24 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

Participants
32 healthy, HIV-1–uninfected volunteers aged 18 to 50 years

Multicenter design
Part A: dose escalation, first in human, open-label IV or SC product administration with randomization into Groups 3 and 4

Part B: randomized, open-label IV or SC product administration

Duration per participant
Part A: 8 months per participant in Groups 1, 2 and 3; 6 months per participant in Group 4; 16 months per participant in Part B.

Estimated total study duration
24 months (includes enrollment, planned safety holds, and follow-up)

7 BLINDING

Participants and CRS staff will be unblinded to participant group assignments. Laboratory program 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 they received. In the rare instance that a participant receives the wrong treatment at a specific study product administration time, the Statistical Analysis Plan (SAP) will address how to analyze the participant's safety data. 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

neutralizing activity data are per-protocol (PP) in that only individuals who receive the expected mAb combination at the expect 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, NONMEM). 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 (e.g., testing multiple pseudoviruses to determine a positive antiviral activity response). Unless otherwise noted, all statistical tests will be two-sided and will be considered statistically significant if $p < 0.05$.

8.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, serum mAb concentrations, neutralization, 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 will be tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given sign or symptom reported more than once, each participant's Solicited AEs will be counted once under the maximum severity for all infusion 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 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 (version specified in Study Specific Procedures [SSP]/Statistical Analysis Plan [SAP]) 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 safety or laboratory endpoint assessments.

8.5.1 Safety

During the course of the trial, 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 136/HPTN 092 PSRT.

9 SAFETY TABLES AND FIGURES

9.1 List of Tables

SMB reports and Safety FSRs include the following tables.

- Enrollment Report
- Demographics and Study Product Administration Frequencies
- Overall Protocol Status
- Discontinuation Status
- Study Product Administration Errors
- Maximum Local and Systemic Solicited Adverse Event Summaries
- 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 Events of Any Relationship
- Expedited Adverse Experiences (EAEs) Reported to the Regulatory Support Center (RSC)
- Study Product Related Events
- Pregnancy Listing
- HIV Infections
- Monoclonal Antibody Solicited Adverse Events

Safety FSRs include the following additional tables.

- Social Impact Summary
- End of Study Diagnostic ELISA Testing Results
- Local Laboratory Values Meeting Grade 1 AE Criteria or Above
- Local Lab Value Summary Statistics

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 Adverse Events
- 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

9.3 List of Graphs

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

10 REFERENCES

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4. Rotnitzky A, Robins J. Analysis of semi-parametric regression models with non-ignorable non-response. Stat Med 1997;16:81-102.

5. Huang Y, Gilbert P, Montefiori D, Self S. Simultaneous evaluation of the magnitude and breadth of a left- and right-censored multivariate response, with application to HIV vaccine development. Statistics in Biopharmaceutical Research 2009;1:81-91.

6. Liu W. On sample size determination of Dunnett's procedure for comparing several treatments with a control. Journal of Statistical Planning and Inference 1997;62:255-261.