STATISTICAL ANALYSIS PLAN

HVTN 128

Version 2.0

A phase 1 clinical trial to evaluate the safety and pharmacokinetics of VRC-HIVMAB075-00-AB (VRC07-523LS) in the sera and mucosae of healthy, HIV-1–uninfected adult participants

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Version 2.0

Prepared by

Protocol Statisticians **Ollivier Hyrien**
Xue Han

SAP Modification History

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

Date: 4 November 2020
SAP version: Version *1.0*
Modifications: Second draft concerning only the analysis of safety endpoints.

Date: 16 August 2021
SAP version: Version *2.0*
Modifications: Third draft concerning only the analysis of safety endpoints.

- Randomization section has been updated according to the protocol.
- Blinding section has been updated according to the protocol.
- Statistical analyses section has been updated according to the protocol.
- Updated list of tables.

Table of Contents

1 OVERVIEW

The following describes the Statistical Analysis Plan (SAP) for the analysis of safety and tolerability data from HVTN 128. The analysis plan for other trial endpoints will be described in a future version of the SAP. As detailed in SCHARP SOP-0013, Version 7.0 (issue date: October 1, 2019), this SAP is required prior to the first analysis and must be approved by the protocol team chair and the lead protocol statistician. The plan will be reviewed and updated prior to any interim analyses and before the final analysis with all major revisions of the plan archived.

2 PROTOCOL SUMMARY

Title

A phase 1 clinical trial to evaluate the safety and pharmacokinetics of VRC-HIVMAB075-00-AB (VRC07-523LS) in the sera and mucosae of healthy, HIV-1–uninfected adult participants

Study products and routes of administration

- VRC07-523LS: a human monoclonal antibody (mAb) targeted to the HIV-1 CD4 binding site. It was developed by the VRC/NIAID/NIH and manufactured under current Good Manufacturing Practice regulations at the VRC Pilot Plant operated under contract by the Vaccine Clinical Materials Program, Leidos Biomedical Research, Inc., Frederick, MD. Product is provided at 100 ± 10 mg/mL in a volume of 6.25 ± 0.10 mL filled into 10 mL glass vials. Administered IV in 100 mL of normal saline (Sodium Chloride for Injection 0.9%, USP).

Participants

24 healthy, HIV–uninfected volunteers aged 18 to 50 years.

Schema

Group	N*	Route	VRC07-523LS Dose	Product administration Schedule		
				D0	D112	D224
				W0	W16	W32
1	12	IV	10 mg/kg	X	X	X
2	12	IV	30 mg/kg	X	X	X
Total	24					

Design

Multicenter, randomized, unblinded trial

Safety monitoring

HVTN 128 PSRT; HVTN Safety Monitoring Board (SMB)

3 OBJECTIVES AND ENDPOINTS

3.1 PRIMARY

Primary objective 1:

- To evaluate the safety and tolerability of VRC07-523LS administered at 10 mg/kg IV infusion every 4 months
- To evaluate the safety and tolerability of VRC07-523LS administered at 30 mg/kg IV infusion every 4 months

Primary endpoint 1:

- Local and systemic Solicited AE signs and symptoms, laboratory measures of safety, Unsolicited AEs, SAEs, AEs of special interest (AESI) and rates of discontinuation

Primary objective 2:

- To determine whether multiple infusions of VRC07-523LS reach and maintain detectable levels in the mucosa
- To correlate levels of VRC07-523LS in serum and the mucosa

Primary endpoint 2:

- Levels of VRC07-523LS in genital and rectal secretions, as well as cervical, vaginal, and rectal tissues at the collection timepoints
- Levels of VRC07-523LS in serum out to Week 48, 16 weeks after the last product administration

3.2 SECONDARY

Secondary objective 1:

- To compare dose regimens of VRC07-523LS delivery for their ability to sustain mucosal mAb levels at serial timepoints post repeat administration

Secondary endpoint 1:

- Levels of VRC07-523LS in genital and rectal secretions and tissue at specified timepoints

Secondary objective 2:

- To determine whether ADA can be detected in serum

Secondary endpoint 2:

- Serum concentration of ADA in each group measured at multiple timepoints from baseline through the final study visit

3.3 EXPLORATORY

Exploratory objective 1:
To assess the acceptability and tolerability of repeat mucosal sampling, including secretions and biopsies, for application in future studies

Exploratory objective 2:
To develop predictive mucosal population pharmacokinetic models of VRC07-523LS administered IV

Exploratory objective 3:
To conduct analyses related to furthering the understanding of HIV, monoclonal antibodies, immunology, vaccines, and clinical trial conduct

4 COHORT DEFINITION

Participants will enroll in the study at the first biopsy collection. Only participants who remain in the trial after completion of the first biopsy visit will be randomized. Since randomization is concurrent with receiving the first study product administration, all randomized participants will provide some safety data. All safety data from randomized participants will be analyzed according to the initial randomization assignment regardless of how many infusions they received. The analysis is a modified intent-to-treat analysis in that individuals who are enrolled but not randomized do not contribute safety data about the study product and hence are excluded. Since enrollment is concurrent with the first biopsy sample collection, all participants will provide some data regarding tolerability of mucosal sample collections.

5 POTENTIAL CONFOUNDERS

Characterization of the safety of the study product is susceptible to confounding by adverse events not related to the study product 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 will enroll in the study at the first biopsy collection. Only participants who remain in the trial after the completion of the first biopsy visit will be randomized.

Accrual will continue until 24 participants have received first product administration.

The randomization sequence will be obtained by computer-generated random numbers and provided to each HVTN CRS through the SDMC via a Web-based randomization system.

Groups 1 and 2 will be randomized simultaneously.

The randomization will be stratified by assigned sex at birth and done in blocks to ensure balance across both groups.

7 BLINDING

Participants and site staff will be unblinded as to participant treatment group assignments. VRC07-523LS concentration and ADA assessments will be performed in a blinded fashion.

8 STATISTICAL ANALYSIS

This section describes the final study analyses, unblinded as to treatment arm assignment. All analyses pertaining to safety and drug levels objectives of the study will be conducted with an intent-to-treat analysis that includes all randomized individuals per their randomization allocation. Additional analyses will be performed that account for the actual infusions and dose levels that each participant received. Analyses will be performed using SAS and R. Other software may be used to perform additional exploratory analyses. Unless otherwise stated, all tests will be two-sided and performed at a 5% significant level. In particular, no formal multiple comparison adjustments will be employed for multiple safety endpoints.

8.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, VRC07-523LS concentrations, and laboratory measurements for primary, secondary, and exploratory objective analyses

8.2 Baseline comparability

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

8.3 Safety/tolerability analysis

All participants who received at least 1 partial or complete administration of VRC07-523LS will provide some safety data.

8.3.1 Solicited AEs

The number and percentage of participants experiencing each type of Solicited AE sign or symptom will be tabulated by severity, attribution 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 infusion/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.

8.3.2 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. A separate listing will do the same for AESI. A list of AESI to be reported for this protocol is provided in Appendix H.

8.3.3 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 9.10) will be tabulated by treatment arm for each postadministration timepoint. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will be included in the tabulation of AEs described above.

8.3.4 Reasons for discontinuation of study product administration 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.

8.3.5 Acceptability of study product or procedure

Acceptability of study product administration and injection procedures will be tabulated by reason and treatment arm.

8.3.6 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, drug level or functional endpoint assessments.

8.3.7 Safety Analysis Schedule

During the course of the trial, analyses of safety data will be prepared approximately every 4 months during the main study for review by the SMB. Ad hoc safety reports may also be prepared for SMB review at the request of the HVTN 128 PSRT. The HVTN leadership must approve any other requests for safety data prior to the end of the scheduled follow-up visits.

9 SAFETY TABLES AND FIGURES

9.1.1 List of Tables

- Enrollment Report
- Demographics and Study Product Administration Frequencies
- Overall Protocol Status
- Study Product Discontinuation Status
- Study Product Administration Errors
- Maximum Local Solicited AE Summary
- Maximum Systemic Solicited AE Summaries
- Severe or Potential Life-Threatening Local Reactogenicities Listing
- Severe or Potential Life-Threatening Systemic Reactogenicities Listing
- Moderate, Severe, or Potential Life-Threatening Erythema/Induration Listing
- Mucosal Sampling Related Adverse Events
- Adverse Experiences by Treatment – Listed by Body System and Severity – By Decreasing Frequency
- Adverse Experiences by Preferred Term and Severity – By Decreasing Frequency – Includes Severe, Potential 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
- Expedited Adverse Experiences (EAEs) Reported to the Regulatory Support Center (RSC)
- Severe, Potentially Life-threatening, or Fatal Adverse Events Safety Population
- Listing of Adverse Events of Special Interest
- Related Events
- Pregnancy Listing
- HIV infections
- Listing of Pre-Infusion Procedure - Only Participants
- Listing of Pre-Infusion Procedure - Only Participants Adverse Events
- Mab Solicited Adverse Events
- Social Impact Summary by treatment
- Mucosal Sampling Acceptability Questionnaire - Participant Experience Safety Population
- Mucosal Sampling Acceptability Questionnaire - Participant Willingness to Undergo Safety Population

- Local Lab Values Meeting Grade 1 AE criteria or Above
- Local Lab Value Summary Statistics

9.1.2 List of Graphs

- Maximum Local Solicited AE
- Maximum Systemic Solicited AE
- Boxplots for ALT, Creatinine, WBC, Hemoglobin, Platelets, Lymphocyte Count, Neutrophil Count

10 ASSAY SPECIFIC TABLES AND FIGURES FOR PROTOCOL TEAM REPORTS

11 REFERENCES

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