STATISTICAL ANALYSIS PLAN

Protocol HVTN 123

Protocol Version 1.0

A phase 1 double-blind, randomized, controlled clinical trial in healthy, HIV-1-uninfected adult participants to compare the safety, tolerability and immunogenicity of CH505TF gp120 produced from stably transfected cells to CH505TF gp120 produced from transiently transfected cells

23 July 2019

SAP Version 1.0

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Approval Signature Page

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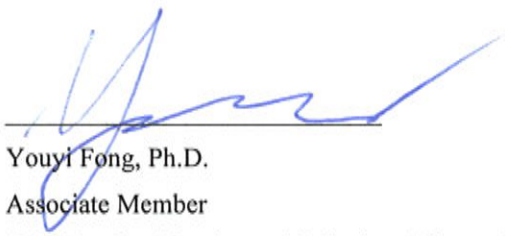
I have read this Statistical Analysis Plan and approve its contents.



7/24/2019

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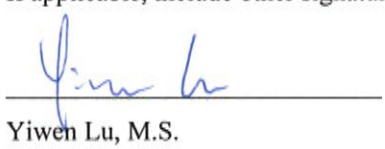
If applicable, include other signatures:



07/24/2019

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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
1.0	23 July 2019	First draft concerning only the analysis of safety endpoints.

Table of Contents

1 OVERVIEW

The following describes the Statistical Analysis Plan (SAP) for the analysis of data from HVTN 123 for Safety Monitoring Board (SMB) reports, the Final Study Report (FSR) for Safety. 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 double-blind, randomized, controlled clinical trial in healthy, HIV-1– uninfected adult participants to compare the safety, tolerability and immunogenicity of CH505TF gp120 produced from stably transfected cells to CH505TF gp120 produced from transiently transfected cells

Study products and routes of administration

- **Stable**: CH505TF gp120 developed via upstream stable transfection of CHO- DG44 cell line, mixed with GLA-SE (glucopyranosyl lipid A in a stable emulsion [oil-in-water emulsion containing squalene])
- **Transient**: CH505TF gp120 developed via upstream transient transfection of CHO-S cell line, mixed with GLA-SE

Schema

Study arm	n	Month 0	Month 2	Month 6
Group 1	15	100 mcg CH505TF gp120 **Stable**	100 mcg CH505TF gp120 **Stable**	100 mcg CH505TF gp120 **Stable**
Group 2	15	100 mcg CH505TF gp120 **Transient**	100 mcg CH505TF gp120 **Transient**	100 mcg CH505TF gp120 **Transient**
Total	30			

Notes

GLA-SE will be admixed with all proteins. The total dose of GLA-SE will be 10 mcg at all timepoints. The total volume for protein plus adjuvant for injection is 1 mL, mixed 1:1 by volume. All injections will be administered intramuscularly (IM) by needle and syringe.

Participants

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

Design

Multicenter, randomized, controlled, double-blind trial

Duration per participant

12 months of scheduled clinic visits (main study) followed by an Adverse Events of Special Interest (AESI) health contact at month 18

Estimated total study duration

21 months (includes enrollment, follow-up, and AESI health contact)

Investigational New Drug (IND) sponsor

DAIDS, NIAID, NIH, DHHS (Bethesda, Maryland, USA)

Study product providers

- Stable CH505TF gp120: DAIDS, NIAID, NIH, DHHS (Bethesda, Maryland, USA)
- Transient CH505TF gp120: DAIDS, NIAID, NIH, DHHS (Bethesda, Maryland, USA)
- GLA-SE adjuvant: DAIDS, NIAID, NIH, DHHS (Bethesda, Maryland, USA)

Core operations

HVTN Vaccine Leadership Group/Core Operations Center, Fred Hutchinson Cancer Research Center (Fred Hutch) (Seattle, Washington, USA)

Statistical and data management center (SDMC)

Statistical Center for HIV/AIDS Research and Prevention (SCHARP), Fred Hutch (Seattle, Washington, USA)

HIV diagnostic laboratory

University of Washington Virology Specialty Laboratory (UW-VSL) (Seattle, Washington, USA)

Endpoint assay laboratories

- Duke University Medical Center (Durham, North Carolina, USA)
- Fred Hutch/University of Washington (Seattle, Washington, USA)

Study sites

HVTN Clinical Research Sites (HVTN CRSs) to be specified in the Site Announcement Memo

Safety monitoring

HVTN 123 PSRT; HVTN SMB

3 OBJECTIVES AND ENDPOINTS

3.1 Primary objectives and endpoints

Primary objective 1:

To evaluate and compare the safety and tolerability of the CH505TF gp120 proteins produced by transient and stable transfection in HIV-1–uninfected, healthy adults

Primary endpoint 1:

Local and systemic reactogenicity signs and symptoms, laboratory measures of safety, and AEs and SAEs

Primary objective 2:

To evaluate and compare the magnitude of binding antibody responses elicited by the CH505TF gp120 proteins produced via transient and stable transfection methods

Primary endpoint 2:

HIV-specific total IgG binding antibody responses against the homologous proteins, as assessed by BAMA at peak timepoint (2 weeks after 3rd vaccination)

3.2 Secondary objectives and endpoints

Secondary objective 1:

To evaluate and compare the breadth and kinetics of binding antibody responses elicited by the CH505TF gp120 proteins produced via transient and stable transfection methods

Secondary endpoint 1:

HIV-specific total IgG binding antibody responses against the homologous proteins and magnitude-breadth (M-B) measures against panels of cross-clade Env proteins and of cross-clade V2 proteins, as assessed by BAMA at peak timepoints (2 weeks after the 2nd and 3rd vaccinations) and late timepoints (3 and 6 months after the 3rd vaccination)

Secondary objective 2:

To evaluate and compare the IgG subclass and IgA binding antibody responses elicited by the CH505TF gp120 proteins produced via transient and stable transfection methods

Secondary endpoint 2:

HIV-specific IgG subclass and IgA binding antibody response rates and magnitudes against homologous Env and V2 proteins, as assessed by BAMA at 2 weeks after the 2nd vaccination, 2 weeks after the 3rd vaccinations, and 3 and 6 months after the 3rd vaccination

Secondary objective 3:

To evaluate the ability of the two CH505TF gp120 proteins to elicit HIV-specific neutralizing antibodies (nAbs)

Secondary endpoint 3:

Magnitude and breadth of nAb responses against a panel of viral isolates as assessed by area under the M-B curves 2 weeks after the 2nd and 3rd vaccinations

Secondary objective 4:

To evaluate the avidity of antibody responses elicited by the CH505TF gp120 proteins

Secondary endpoint 4

Avidity of Env-specific IgG antibodies at baseline and 2 weeks after the 3rd vaccination

Secondary objective 5:

To evaluate HIV-specific T-cell responses induced by the two CH505TF gp120 proteins

Secondary endpoint 5:

Response rate, magnitude, and polyfunctionality of CD4+ T-cell responses as assessed by intracellular cytokine staining (ICS) assays 2 weeks after the 2^{nd} and 3^{rd} vaccinations

3.3 Exploratory objectives

Exploratory objective 1:

To evaluate the ability of the two CH505TF gp120 proteins to elicit memory B cells that differentially bind wildtype CH505 gp120Env vs mutant CH505 Env IΔ371 gp120

Exploratory objective 3:

To characterize the BCR repertoire of HIV-specific B cells

Exploratory objective 4:

To further evaluate vaccine immunogenicity, additional immunogenicity assays may be performed, including on samples from other timepoints, based on the HVTN Laboratory Assay Algorithm

Exploratory objective 5:

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

4 COHORT DEFINITION

All safety data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many vaccinations they received. In the rare instance that a participant receives the wrong treatment at a specific vaccination time, the Statistical Analysis Plan (SAP) will address how to analyze the participant's safety data. Analyses are modified intent-to-treat in that individuals who are randomized but not enrolled do not contribute data and hence are excluded. Because of blinding and the brief length of time between randomization and enrollment – typically no more than 4 working days – very few such individuals are expected.

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

A participant's randomization assignment will be computer-generated and provided to the HVTN CRS pharmacist through a Web-based randomization system. At each institution, the pharmacist with primary responsibility for dispensing study products is charged with maintaining security of the treatment assignments (except in emergency situations as specified in the HVTN MOP).

7 BLINDING

Participants and site staff (except for site pharmacists) will be blinded as to participant treatment arm assignments. Study product assignments are accessible to those HVTN CRS pharmacists, DAIDS protocol pharmacists and contract monitors, and SDMC staff who are required to know this information in order to ensure proper trial conduct. Any discussion of study product assignment between pharmacy staff and any other HVTN CRS staff is prohibited. The HVTN SMB members also are unblinded to treatment assignment in order to conduct review of trial safety.

When a participant leaves the trial prior to study completion, the participant will be told he or she must wait until all participants are unblinded to learn his or her treatment assignment.

In some cases, the CRS, PSRT, or study sponsor may believe unblinding of the site PI and participant would be appropriate to facilitate the clinical management of an AE or SAE. The HVTN Unblinding MOP specifies procedures for emergency unblinding, and for early unblinding for medical reasons.

8 STATISTICAL ANALYSIS

All safety data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many vaccinations they received.

Analyses are modified intent-to-treat in that individuals who are randomized but not enrolled do not contribute data and hence are excluded. Because of blinding and the brief length of time between randomization and enrollment – typically no more than 4 working days – very few such individuals are expected.

Analyses for primary endpoints will be performed using SAS and R. All other descriptive and inferential statistical analyses will be performed using SAS, StatXact, or R statistical software.

8.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, and immunogenicity for primary- and secondary-objective analyses.

8.2 Baseline comparability

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

8.3 Safety/tolerability analysis

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

8.3.1 Reactogenicity

The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given sign or symptom, each participant's reactogenicity 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.

8.3.2 AEs and SAEs

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 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 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 vaccination, and number of vaccinations received.

8.3.3 Reasons for vaccination discontinuation and early study termination

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

8.4 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 immunogenicity endpoint assessments. In particular, early unblinded analyses by treatment assignment require careful consideration and should be made available on a need to know basis only.

8.4.1 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 123 PSRT. Refer to the process described in the HVTN Unblinding MOP for any requests for unblinded safety data prior to the end of the scheduled follow-up visits.

9 SAFETY TABLES AND FIGURES

9.1 List of Tables

SMB reports and Safety FSRs include the following tables.

- Enrollment Report
- Demographics and Vaccination Frequencies
- Overall Protocol Status
- Maximum Local and Systemic Reactogenicity 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)
- Pregnancy Listing
- AEs of Special Interest (AESI)

Safety FSRs include the following additional tables.

- Social Impact Summary
- Local Lab Value Summary Statistics
- Local Laboratory Values Meeting Grade 1 AE Criteria or Above

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 Reactogenicities
- Moderate or Severe Erythema and Induration
- Expedited Adverse Experiences (EAEs)
- Adverse Experiences of Special Interest (AESIs)
- 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 Reactogenicities
- Maximum Systemic Reactogenicities
- Boxplots for white blood cells (WBC), neutrophils, lymphocytes, hemoglobin, platelets, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphaste (ALP) and creatinine at baseline and following vaccinations.

10 REFERENCES

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