SCHARP
Statistical Center for HIV/AIDS Research and Prevention

# STATISTICAL ANALYSIS PLAN FOR HVTN SAFETY

## Protocol HVTN 302 (v3.0)

***A phase 1, randomized, open-label clinical trial to evaluate the safety and immunogenicity of BG505 MD39.3, BG505 MD39.3 gp151, and BG505 MD39.3 gp151 CD4KO HIV trimer mRNA vaccines in healthy, HIV-uninfected adult participants.***

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**SAP version: 3.0**

# Statistical Analysis Plan for Safety

## Protocol: HVTN 302 (v3.0)

*Document will become effective on date of last signature.*

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# SAP Modification History

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

| SAP Version | Modification |
|---|---|
| 1.0 | Initial |
| 2.0 | Added the safety/tolerability and urticaria analysis to section 10.1 and 10.2. Added the tables in the FSR in section 11.1. |
| 3.0 | To correct the version typo in the version 2.0, the SAP was up version to 3.0. No other content has been changed. |

# Table of Contents

# 1 LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| AE | Adverse Experience |
| EAE | Expedited Adverse Experience |
| FSR | Final Study Report |
| RSC | Regulatory Support Center |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SMB | Safety Monitoring Board |

# 2 OVERVIEW

The following describes the Statistical Analysis Plan (SAP) for the analysis of safety data from HVTN 302 for Safety Monitoring Board (SMB) reports and the Final Study Report (FSR) for Safety.

# 3 PROTOCOL SUMMARY

Participants will receive BG505 MD39.3 mRNA, BG505 MD39.3 gp151 mRNA or BG505 MD39.3 gp151 CD4KO mRNA, at doses of 100 mcg or 250mcg, administered via intramuscular (IM) injections into the deltoid muscle. Participants will be evaluated for safety and immune responses through blood and lymph node fine-needle aspiration collection at specified timepoints throughout the study. The study schema is below:

**Table 1-1 Schema**

| Study Arm | N | Dose (mcg) | Month 0 | Month 2 | Month 6 |
|---|---|---|---|---|---|
| **Part A** | | | | | |
| **Group 1** | 18 | 100 | BG505 MD39.3 mRNA | BG505 MD39.3 mRNA | BG505 MD39.3 mRNA |
| **Group 2** | 18 | 100 | BG505 MD39.3 gp151 mRNA | BG505 MD39.3 gp151 mRNA | BG505 MD39.3 gp151 mRNA |
| **Group 3** | 18 | 100 | BG505 MD39.3 gp151 CD4KO mRNA | BG505 MD39.3 gp151 CD4KO mRNA | BG505 MD39.3 gp151 CD4KO mRNA |
| **Part B** | | | | | |
| **Group 4** | 18 | 250 | BG505 MD39.3 mRNA | BG505 MD39.3 mRNA | BG505 MD39.3 mRNA |
| **Group 5** | 18 | 250 | BG505 MD39.3 gp151 mRNA | BG505 MD39.3 gp151 mRNA | BG505 MD39.3 gp151 mRNA |
| **Group 6** | 18 | 250 | BG505 MD39.3 gp151 CD4KO mRNA | BG505 MD39.3 gp151 CD4KO mRNA | BG505 MD39.3 gp151 CD4KO mRNA |
| **Total** | **108** | | | | |

**Study Design**

This is a multicenter, randomized, open-label, Phase 1 study to evaluate the safety and immunogenicity of BG505 MD39.3, BG505 MD39.3 gp151, and BG505 MD39.3 gp151 CD4KO HIV trimer mRNA in healthy adults. The primary hypothesis is BG505 MD39.3 soluble and membrane-bound trimer mRNA vaccines will be safe and well-tolerated among HIV-uninfected individuals and will elicit autologous neutralizing antibodies.

**Study Population**

All inclusion and exclusion criteria must be met for eligibility. Screening procedures to determine eligibility must be performed within 56 days prior to enrollment.

Investigators should always use good clinical judgment in considering a volunteer's overall fitness for trial participation. Some volunteers may not be appropriate for enrollment even if they meet all inclusion/exclusion criteria. Medical, psychiatric, occupational, or other conditions may make evaluation of safety and/or immunogenicity difficult, and some volunteers may be poor candidates for retention.

**Vaccine Regimen**

**Group 1**

100 mcg of BG505 MD39.3 mRNA (labeled as mRNA-1574v1-GP140) to be administered as 0.5 mL doses intramuscularly (IM) at months 0, 2, and 6

**Group 2**

100 mcg of BG505 MD39.3 gp151 mRNA (labeled as mRNA-1574v2-GP151) to be administered as 0.5 mL doses intramuscularly (IM) at months 0, 2, and 6

**Group 3**

100 mcg of BG505 MD39.3 gp151 CD4KO mRNA (labeled as mRNA-1574v3-CD4KO-GP151) to be administered as 0.5 mL doses intramuscularly (IM) at months 0, 2, and 6

**Group 4**

250 mcg of BG505 MD39.3 mRNA (labeled as mRNA-1574v1-GP140) to be administered as 0.5 mL doses intramuscularly (IM) at months 0, 2, and 6

**Group 5**

250 mcg of BG505 MD39.3 gp151 mRNA (labeled as mRNA-1574v2-GP151) to be administered as 0.5 mL doses intramuscularly (IM) at months 0, 2, and 6

**Group 6**

250 mcg of BG505 MD39.3 gp151 CD4KO mRNA (labeled as mRNA-1574v3-CD4KO-GP151) to be administered as 0.5 mL doses intramuscularly (IM) at months 0, 2, and 6

# 4 SAFETY OBJECTIVES AND ENDPOINTS

**Primary Objectives and Endpoints**

*Primary objective 1:*

To evaluate the safety and tolerability of BG505 MD39.3 trimer mRNA vaccines in healthy, HIV-uninfected adults

*Primary endpoint 1:*

Local and systemic reactogenicity signs and symptoms for a minimum of seven days following receipt of any study product. Laboratory measures of safety. All adverse events (AEs) for thirty days after receipt of study vaccination

All serious adverse events (SAEs), medically attended adverse events (MAAEs), adverse events of special interest (AESIs), and AEs leading to early participant withdrawal or permanent discontinuation will be collected throughout the study

## 5 COHORT DEFINITION

Recruitment will target enrolling 108 healthy, HIV-uninfected adult participants from 18-55 years old.

Since enrollment is concurrent with receiving the first study vaccination, all participants will provide some safety data.

## 6 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.

## 7 RANDOMIZATION

Participants will first be randomized in a 1:1:1 ratio into the Part A sentinel safety cohort. If safety criteria are met, enrollment will proceed with Part B sentinel group of n=12 with 1:1:1 randomization and the remainder of Part A (n=42) with 1:1:1 randomization, with some sites enrolling into the Part B sentinel cohort while other sites are enrolling the remainder of Part A. Once the safety criteria for the Part B sentinel safety cohort have been met, the remaining Part B participants (n=42) will be enrolled with 1:1:1 randomization.

Randomization to Groups 1-3 will be stratified by willingness to consent to FNA and/or leukapheresis. A maximum of 27 participants in total that do NOT consent to either FNA and leukapheresis collection will be enrolled.

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 Manual of Operations [MOP]).

## 8 BLINDING

This study is open-label.

## 9 SAMPLE SIZE

Recruitment will target enrolling 108 healthy, HIV-uninfected adult participants.

108 healthy, HIV-uninfected adult participants will be enrolled into three 100 mcg vaccine dose groups in Part A and into three 250 mcg vaccine dose groups in Part B (n=18 per group). The study will begin by enrolling a Part A sentinel safety cohort with 1:1:1 randomization into Groups 1-3 (of n=12) to be evaluated for safety two weeks after the first vaccination. Participants that are randomized but not enrolled will be replaced to ensure that at least 12 participants are enrolled before initiation of the planned enrollment pause.

The PSRT will convene after the 12th participant in the Part A sentinel safety cohort has received their first vaccination and completed the 2 week post vaccination safety visit to determine if further participants should be enrolled. If safety criteria are met, enrollment will proceed with Part B sentinel group of n=12 with 1:1:1 randomization and the remainder of Part A (n=42) with 1:1:1 randomization. Once the safety criteria for the Part B sentinel safety cohort have been met, the remaining Part B participants (n=42) will be enrolled with 1:1:1 randomization. Figure 9-1 illustrates this plan.

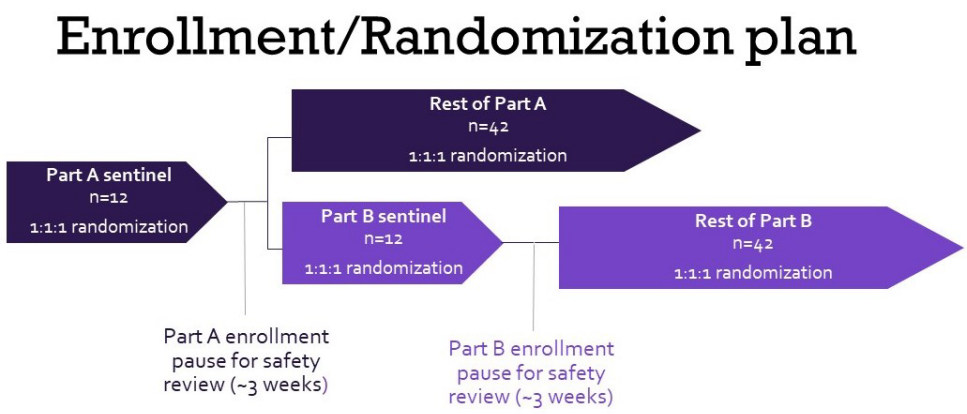


***Figure 9-1 Schema of enrollment strategy***

Since enrollment is concurrent with receiving the first study vaccination, all participants will provide some safety data. However, for immunogenicity analyses, it is possible that data may be missing for various reasons, such as participants terminating from the study early, problems in shipping specimens, low cell viability of processed peripheral blood mononuclear cells (PBMCs), or high assay background. Immunogenicity data from 17 phase 1 and 2 phase 2a HVTN vaccine trials, which began enrolling after June 2005 (data as of September 2014), indicate that 15% is a reasonable estimate for the rate of missing data at Month 6.5. For this reason, the sample size calculations below account for 15% enrolled participants having missing data for the primary immunogenicity endpoints.

## 10 STATISTICAL ANALYSIS

This section describes the final study analysis, unblinded as to treatment arm assignment. All data from enrolled participants will be analyzed 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.

No formal multiple comparison adjustments will be employed for multiple safety endpoints, multiple primary immunogenicity endpoints, or secondary endpoints. However, multiplicity adjustments will be made for certain immunogenicity assays, as discussed below, when the assay endpoint is viewed as a collection of hypotheses (eg, testing multiple peptide pools to determine a positive response).

## 10.1 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.

### 10.1.1 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 test will be used to test for differences in severity between arms.

### 10.1.2 AEs and SAEs

AEs will be summarized using Medical Dictionary for Regulatory Activities (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 the magnitude 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.

### 10.1.3 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 for changes between baseline and post-enrollment. 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 will be tabulated by treatment arm for each postvaccination timepoint. Reportable clinical laboratory abnormalities without an

associated clinical diagnosis will also be included in the tabulation of AEs described above.

### 10.1.4 Reason 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.

## 10.2 Analyses to investigate related urticaria adverse events

The following analyses will be conducted to generate potential explanations of the related urticaria adverse events observed in HVTN 302.

Urticaria cases are defined as participants who report any adverse event of urticaria (medDRA preferred term) of any duration deemed related to study product. Urticaria non-cases are defined as participants who do not report any such event.

Differences in baseline variables identified by the HVTN 302 protocol team leadership will be formally compared between urticaria cases and non-cases by Barnard's exact test for the following 15 binary variables at enrollment: female sex at birth, Hispanic or Latino ethnicity, race = White given data sparsity, history of eczema, history of seasonal and environmental allergies, history of food allergies, history of drug allergies, history of other and non-specified allergies, and use of antihistamine/asthma inhaler/steroid medications, COVID-19 infection, mRNA COVID-19 vaccination (Moderna or Pfizer), any Moderna COVID-19 vaccination, any Pfizer COVID-19 vaccination, Moderna received as last COVID-19 vaccination, Pfizer received as last COVID-19 vaccination. The Wilcoxon rank sum test will used to evaluate differences in distribution of age in years at enrollment between urticaria cases and non-cases. Multiplicity adjustment of the p-values for comparing each of these 16 demographic characteristics and prior histories between participants with and without urticaria will be done to control the family-wise error rate at 0.05 using Holm, 1979 adjustment. For covariates where the unadjusted p-value was less than 0.05 for the association with urticaria, odds ratios (OR) and nominal 95% CIs were calculated by median-unbiased estimation (mid-p) method [1] with Haldane-Anscombe correction for 0 counts [2].

Tables

- Demographics (sex at birth, ethnicity, race, age in years), prior conditions and use of allergy medications (history of eczema, history of seasonal and environmental allergies, history of food allergies, history of drug allergies, history of other and non-specified allergies, use of antihistamine/asthma inhaler/steroid mediations at enrollment), Covid-19 infection prior to enrollment, receipt of any Covid-19 mRNA vaccination prior to enrollment, receipt of any Moderna Covid-19 mRNA vaccination prior to enrollment, receipt of Moderna as last Covid-19 mRNA vaccination prior to enrollment. Stratified by urticaria case/non-case status, summarized by n/N, % for binary/categorical variables and by 25%, median, 75% for age in years.
- Covid-19 vaccination post-enrollment stratified by urticaria case/non-case status, summarized by n/N (%).

Figures

- Timeline of vaccination times (grey open circles), blood draws (red points), and urticaria AE onset and resolution (salmon line segments or arrows if no resolution) for urticaria cases where x-axis denotes study weeks from enrollment and y-axis denotes ptid (study group).
- Boxplots of days from last mRNA Covid-19 vaccination to enrollment for urticaria cases and non-cases, with different point types denoting Pfizer (triangle) vs. Moderna (filled circle) vaccine.
- Boxplots of days from last Moderna Covid-19 vaccination to enrollment for urticaria cases and non-cases.

- Spaghetti plots of eosinophil and basophil counts over time with red lines denoting urticaria cases and grey dashed lines indicating non-cases.

# 11 SAFETY TABLES, PARTICIPANT LISTINGS, AND FIGURES

## 11.1 List of Tables

The following tables are included in the SMB reports and FSR for Safety:

- 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 Experiences Only
- Adverse Experiences by Preferred Term and Severity – By Decreasing Frequency – Includes Experiences of All Severities
- Adverse Experiences by Preferred Term and Relationship to Study Product – By Decreasing Frequency – Includes Related Experiences Only
- Adverse Experiences by Preferred Term and Relationship to Study Product – By Decreasing Frequency – Includes Experiences of Any Relationship
- Expedited Adverse Experiences (EAEs) Reported to the Regulatory Support Center (RSC)
- Pregnancy Listing

Additional tables included in the FSR for Safety:

- Social Impact Summary
- FNA/Leukapheresis Related Events
- Listing of Urticaria Adverse Events
- End of Study Diagnostic Testing Results for Vaccinees
- Local Lab Value Summary Statistics
- Local Laboratory Values Meeting Grade 1 AE Criteria or Above

### 11.2 List of Participant Listings

These participant listings are included in the SMB reports:

- Discontinuation Status
- Pregnancies
- Severe or Life-Threatening Local and Systemic Reactogenicities
- Moderate 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
- HIV Infection Results from Lab and Reported by Site

### 11.3 List of Figures

These graphs are included in the SMB reports and FSR for Safety:

- Maximum Local Reactogenicities
- Maximum Systemic Reactogenicities
- Boxplots for CBC, ALT, Creatinine, Hemoglobin, WBC, Platelets

## 12 REFERENCES

1. Kenneth J. Rothman and Sander Greenland (1998), Modern Epidemiology, Lippincott-Raven Publishers

2. Haldane J. The estimation and significance of the logarithm of a ratio of frequencies. Annals of human genetics 1956;20(4):309–311 Anscombe FJ. On estimating binomial response relations. Biometrika 1956;43(3/4):461– 464