This is ACTG A5379 Primary SAP Version 3.1 with names of authors, names of publication writing team members and analysis timeline redacted.

A5379

B-ENHANCEMENT OF HBV VACCINATION IN PERSONS LIVING WITH HIV (BEe-HIVe): Evaluation of HEPLISAV-B

Protocol Version 3.0

ClinicalTrials.gov Identifier: NCT04193189

Primary Statistical Analysis Plan

Version 3.1

January 6, 2023

Created by: ACTG A5379 Study Statisticians

SDAC/Harvard T.H. Chan School of Public Health

Table of Contents

Version History

Version	Changes Made	Date Finalized (mm/dd/yyyy)
1.0	Original Version	11/18/2019
1.1	Protocol amendment review (V1.0, LOA #1)	02/05/2020
2.0	Protocol Version 2.0 • "Post-injection reactions" was changed to "Grade ≥2 adverse events" throughout to reflect updates to protocol secondary objectives (#7 in Group A, #4 in Group B below). • Subset analyses were added as Report Content 11. • Minor text edits were made throughout for clarity.	08/19/2020
3.0	• Protocol amendment review (V2.0, LOA #1): No changes related to the LOA. • A new section was added to include descriptions of primary and key secondary estimands, guided by ICH E9(R1). Text edits were made in sections following the new section for clarification. Additional missing data considerations for sensitivity analyses were added. Additional details about the statistical analyses were added.	04/29/2022
3.1	Protocol amendment review (V3.0)	01/06/2023

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the A5379 primary and secondary outcome measures that will be included in the primary manuscript. They address the major primary and secondary objectives of the study. The Primary SAP outlines the general statistical approaches for the analysis of the study, including the interim analyses of the primary outcome. It has been developed to facilitate discussion of the statistical analysis components and to provide agreement among the study team members regarding the statistical analyses to be performed and presented in the Primary Analysis Report.

Detailed outlines of tables, figures, and coding descriptions that will be included in the Primary Analysis Report are provided in the Analysis Implementation Plan (AIP).

The Primary Analysis Report will be generated separately for Groups A and B in A5379, and the primary analysis timelines will be derived separately for Groups A and B. Analyses for the Primary Analysis Report for each Group will be finalized once the last participant in the Group has completed the Week 28 study visit (prior to study completion at Week 72), all queries have been resolved, and the study database closure/data lock has been completed.

Results from the primary analysis may be presented publicly, for example at a conference, upon completion of relevant data prior to the entire study database finalization.

The final analyses for the two study groups may be conducted at different times upon relevant study data finalization.

Outlines of analyses for other protocol objectives and outcome measures that are not included in the Primary SAP will be provided in separate SAPs.

1.2 Version History

- The document was initially developed as Version 1.0, based on Protocol Version 1.0, dated October 11, 2019.
- No changes were made after review of Protocol Version 1.0, Letter of Amendment #1, dated January 28, 2020.
- The document was revised after review of Protocol Version 2.0 (dated July 1, 2020) due to the changes in secondary objective: Group A Secondary Objective 7 and Group B Secondary Objective 4. At the time of this review, subset analyses were added as Report Content 11.
- No changes were made based on the review of Protocol Version 2.0, Letter of Amendment #1 (dated February 18, 2022 and released on April 21, 2022). At the time of this review, the document was revised to incorporate ICH E9(R1) recommendations.
    - A new section on estimands (Section 4) was added. Subsequent section numbers were updated. Section 5 heading was renamed to better describe its contents.
    - Items related to analysis sets, outcome measures and handling of missing data were moved to Section 4 and edited for clarification. Additional missing data considerations

were added for sensitivity analyses, given the potential for more missing data than anticipated due to the COVID-19 pandemic.

- A summary about intercurrent events was added in Section 6. Minor edits were made in Section 6 for clarification and readability. Additional details about the statistical analyses with references were added in Sections 4 and 5.

- No changes were made based on the review of Protocol Version 3.0 (dated December 13, 2022).

2 Study Overview

2.1 Study Design

A5379 is a prospective, open-label study to evaluate immunogenicity of the HBV vaccine HEPLISAV-B in two study populations living with HIV: prior HBV vaccine recipients who are deemed non-responders (Group A) and individuals who are naïve to HBV vaccination (Group B). The study is designed separately for the two study populations and will be conducted as separate evaluations for all primary and key secondary analyses. No adjustment of type I error is planned for conducting two population studies under the same protocol mainly for administrative efficiency.

2.1.1 Group A (Non-responders, N=561)

The study is designed as an open-label three-arm study, where participants are randomized in 1:1:1 ratio to the following study arms, stratified by sex at birth (male vs. female) and diabetes diagnosis status (yes vs. no).

Arm 1: Two doses of HEPLISAV-B at weeks 0 and 4
Arm 2: Three doses of HEPLISAV-B at weeks 0, 4, and 24
Arm 3: Three doses of ENGERIX-B at weeks 0, 4, and 24

Randomization will use permuted blocks and balancing by main site.

2.1.2 Group B (Vaccine-Naïve, N=73)

Group B study is designed as a single-arm study.

2.2 Hypotheses

2.2.1 Group A

1. In participants living with HIV, HEPLISAV-B vaccination given as a two-dose series achieves non-inferior seroprotection response (SPR) proportion compared to standard dose ENGERIX-B.
2. In participants living with HIV, HEPLISAV-B vaccination given as a three-dose series achieves superior SPR proportion compared to standard dose ENGERIX-B.
3. HEPLISAV-B vaccination given as a two-dose series or a three-dose series is safe in participants living with HIV.

2.2.2 Group B

1. In participants living with HIV, HEPLISAV-B vaccination given as a three-dose series achieves SPR proportion greater than 55%.
2. HEPLISAV-B vaccination given as a three-dose series is safe in participants living with HIV.

2.3 Study Objectives

This Primary SAP addresses the following primary and secondary objectives in the study protocol. Other study objectives in the protocol will be addressed in subsequent analysis plans.

2.3.1 Primary Objectives

The comparison of SPR between Arms 1 and 3 will be conducted as non-inferiority. Such comparison between Arms 2 and 3 will be conducted as superiority.

Group A

1. To compare the week 12 SPR of a two-dose regimen of HEPLISAV-B (Arm 1) versus the week 28 SPR of a standard three-dose regimen of ENGERIX-B (Arm 3) in hepatitis B virus (HBV) vaccine-experienced participants living with HIV.
2. To compare the week 28 SPR of a three-dose regimen of HEPLISAV-B (Arm 2) versus a standard three-dose regimen of ENGERIX-B (Arm 3) in HBV vaccine-experienced participants living with HIV.
3. To describe adverse events (AEs) reported in each study arm over the duration of the study.

Group B

1. To determine the week 28 SPR of a three-dose regimen of HEPLISAV-B in HBV vaccine-naïve participants living with HIV.
2. To describe AEs reported over the duration of the study.

2.3.2 Secondary Objectives

Group A

1. To compare the week 12 geometric mean titers (GMT) of a two-dose regimen of HEPLISAV-B (Arm 1) versus the week 28 GMT of a standard three-dose regimen of ENGERIX-B (Arm 3) in HBV vaccine-experienced participants living with HIV.
2. To compare the week 28 GMT of a three-dose regimen of HEPLISAV-B (Arm 2) versus a standard three-dose regimen of ENGERIX-B (Arm 3) in HBV vaccine-experienced participants living with HIV.
3. To compare the SPR and GMT 4, 8, 24, and 48 weeks after last vaccination of a two-dose regimen of HEPLISAV-B (Arm 1) versus a standard three-dose regimen of ENGERIX-B (Arm 3) in HBV vaccine-experienced participants living with HIV.

4. To compare the SPR and GMT 8, 24, and 48 weeks after last vaccination of a three-dose regimen of HEPLISAV-B (Arm 2) versus a standard three-dose regimen of ENGERIX-B (Arm 3) in HBV vaccine-experienced participants living with HIV.
5. To compare the SPR and GMT 4, 8, 24 and 48 weeks after last vaccination of a two-dose regimen of HEPLISAV-B (Arm 1) versus a three-dose regimen of HEPLISAV-B (Arm 2) in HBV vaccine-experienced participants living with HIV.
6. To assess SPR and GMT at weeks 4, 8, 12, and 24 between HEPLISAV-B (Arms 1 and 2 combined) and ENGERIX-B (Arm 3) in HBV vaccine-experienced participants living with HIV (Group A).
7. To describe incidence of Grade≥2 AEs within 4 weeks of each injection in each study arm.
8. To assess host characteristics associated with vaccine response.
9. To compare SPR and GMT at week 72 between HEPLISAV-B two-dose (Arm 1) and three-dose arms (Arm 2).

Group B

1. To determine the week 28 GMT of a three-dose regimen of HEPLISAV-B in HBV vaccine-naïve participants living with HIV.
2. To determine the SPR and GMT of a three-dose regimen of HEPLISAV-B at weeks 32, 48, and 72 in HBV vaccine-naïve participants living with HIV.
3. To determine the SPR and GMT of a three-dose regimen of HEPLISAV-B at weeks 4, 8, 12, and 24 in HBV vaccine-naïve participants living with HIV.
4. To describe incidence of Grade ≥2 AEs within 4 weeks of each injection.
5. To assess host characteristics associated with vaccine response.

2.4 Overview of Sample Size Considerations

2.4.1 Group A

A two-sided type I error rate is targeted at the pre-specified overall alpha level of 5% for the two primary analysis comparisons in Group A. To preserve the overall type I error rate in Group A and to allow flexible interim monitoring, a Bonferroni correction is applied, and a two-sided type I error rate of 2.5% each for the non-inferiority comparison between Arm 1 and Arm 3 and for the superiority comparison between Arm 2 and Arm 3 is allocated.

The sample size of N=187 per arm was derived as follows.

1. Non-inferiority comparison between Arms 1 and 3: For the primary objective to show that SPR proportion in Arm 1 is non-inferior to the SPR proportion in Arm 3 within the non-inferiority margin of 10%, we assume that 70% in the control arm (Arm 3) will achieve SPR. We assume the proportion of participants achieving SPR with two doses of HEPLISAV-B (Arm 1) will be higher at 75%. As a non-inferiority design, this comparison is powered to show that the SPR proportion in Arm 1 is not lower than that of Arm 3 (control) by more than the pre-specified non-inferiority margin of 10%. A sample size of 168 each in Arm 1 and Arm 3 achieves 80% power to detect a difference between the two proportions of less than 10%, in a one-sided test with type I error of 1.25% using

normal approximation. Assuming no more than about 10% missing data for SPR, which includes loss to follow-up within each study arm prior to the primary outcome visit, the sample size is increased to 187 per study arm.

2. Superiority comparison between Arms 2 and 3: For the primary objective to compare SPR proportions between Arm 2 and Arm 3 (control), an increase of 15% is assumed in the proportion of participants achieving SPR with three doses of HEPLISAV-B (Arm 2). With the sample size of 147 participants in each study arm, there is 80% power to detect a difference as significant in a two-sided test at a significance level of 2.5% using normal approximation. Formal interim efficacy analyses are planned for the Arm 2 and Arm 3 comparison, should the study enrollment allow such interim analyses to be useful to affect the conduct of the study. Assuming no more than three interim analyses for the study and applying the O'Brien and Fleming approach to preserve the two-sided type I error rate at 2.5%, Arm 2 and Arm 3 sample sizes should be at least 149 per study arm. Assuming no more than about 10% loss in the SPR data within each study arm, the targeted study sample size is 166 each for Arm 2 and Arm 3 to retain 80% power. To maintain 1:1:1 randomization across Arms 1, 2, and 3 throughout enrollment, the sample size in Arm 2 is increased to 187. Therefore, the power for the comparison between Arm 2 and Arm 3 is higher than 80%.

2.4.2 Group B

The study is powered to conclude that the proportion achieving SPR is greater than 55%. Assuming a response proportion of 75%, a sample size of 65 would provide at least 90% power in a two-sided test using normal approximation at a targeted significance level of 5%. Assuming at most 10% missing data, including loss to follow-up prior to the primary outcome visit, the study sample size is increased to 73.

2.5 Overview of Formal Interim Monitoring

The study will be monitored by an independent DAIDS-appointed Data and Safety Monitoring Board (DSMB). The initial interim data review by the DSMB will occur no later than one year after the enrollment of the first participant in the study in either Group A or B.

2.5.1 Group A

Interim monitoring is considered independently for the two primary objectives as follows.

1. Non-inferiority comparison between Arms 1 and 3:
   a. For the primary objective on the comparison between Arm 1 and Arm 3, interim monitoring will not include early formal non-inferiority analyses using the accumulating data on the primary outcome for early study conclusion on non-inferiority. This is because the long-term antibody data in the study provide important supporting information on how the primary results in these study arms should be interpreted for future guidance.
   b. Early stopping due to concerns on poor vaccine responses in Arm 1 beyond the non-inferiority margin of 10% in SPR compared to Arm 3 (control arm) that may be

deemed harmful may occur. For this purpose, the SPR estimates for the primary outcome measure will be provided with a two-sided 99.9% confidence interval around the difference in the proportion estimates (Arm 3 minus Arm 1). As a guideline, a lower bound of the confidence interval above 10% may be considered evidence towards poor response in Arm 1 that suggests potential harm.

2. Superiority comparison between Arms 2 and 3:
   a. Formal efficacy interim analyses are planned for the second primary objective on the comparison between Arm 2 and Arm 3 (control arm), should the study enrollment allow such interim analyses to be useful to affect the conduct of the study. The initial interim efficacy analysis on the primary outcome for this comparison is aimed at when at least 40% of the SPR results at 4 weeks after the vaccination series are available for analysis. The Lan-DeMets spending function for type I error (alpha) with O'Brien-Fleming type boundaries will be employed. With this approach, two-sided type I error rate for efficacy at the 0.025 level will be preserved regardless of the number and timing of the analysis. If the confidence interval at the interim look lies entirely above zero and the interim data review identifies no concerns, early stopping of Arm 2 to conclude Arm 2 superiority may occur.
   b. Early stopping due to concerns about poor vaccine responses in Arm 2 compared to Arm 3 (control arm) may occur. For this purpose, the SPR estimates for the primary outcome measure will be provided with a two-sided 99.9% confidence interval around the difference in the proportion estimates (Arm 3 minus Arm 2), similar to the Arm 3 comparison to Arm 1 discussed above in assessing potential harm. As a guideline, a lower bound of the confidence interval above 10% may be considered as evidence towards poor response in Arm 2 that suggests potential harm.

2.5.2 Group B

An interim efficacy analysis to conclude early that the estimated single-arm SPR proportion at 4 weeks after the vaccination series exceeds the null proportion (55%) will not be conducted. Early stopping due to concerns about poor vaccine responses may occur. If the study enrollment allows interim analysis on the SPR proportion to be useful to affect the conduct of the study, a two-sided 99.9% confidence interval may be provided with the proportion estimate. The interval upper bound below 45% (10% lower than the null proportion) may be used as guidance.

3 Outcome Measures

3.1 Primary Outcome Measures

3.1.1 Group A

1. [For Primary Objectives 1 and 2] SPR defined as HBsAb ≥10 mIU/mL at 8 weeks after the two-dose series (at Week 12) in Arm 1 and at 4 weeks after the three-dose series (at Week 28) in Arms 2 and 3
2. [For Primary Objective 3] Reported AEs from study vaccination initiation to study discontinuation

3.1.2 Group B

1. [For Primary Objective 1] SPR defined as HBsAb ≥10 mIU/mL at 4 weeks after the vaccination series (Week 28)
2. [For Primary Objective 2] Reported AEs from study vaccination initiation to study discontinuation

3.2 Secondary Outcome Measures

3.2.1 Group A

1. HBsAb titer at the following study visits in Arm 1:
    a. Week 4 [Secondary Objective 6]
    b. Week 8 [Secondary Objectives 3, 5, and 6]
    c. Week 12 [Secondary Objectives 1, 3, 5, and 6]
    d. Week 24 [Secondary Objective 6]
    e. Week 28 [Secondary Objectives 3 and 5]
    f. Week 52 [Secondary Objectives 3 and 5]
    g. Week 72 [Secondary Objective 9]
2. SPR defined as HBsAb ≥10 mIU/mL at the following study visits in Arm 1:
    a. Week 4 [Secondary Objective 6]
    b. Week 8 [Secondary Objectives 3, 5, and 6]
    c. Week 12 [Secondary Objectives 3, 5, and 6]
    d. Week 24 [Secondary Objective 6]
    e. Week 28 [Secondary Objectives 3 and 5]
    f. Week 52 [Secondary Objectives 3 and 5]
    g. Week 72 [Secondary Objective 9]
3. HBsAb titer at the following study visits in Arm 2:
    a. Week 4 [Secondary Objective 6]
    b. Week 8 [Secondary Objective 6]
    c. Week 12 [Secondary Objective 6]
    d. Week 24 [Secondary Objective 6]
    e. Week 28 [Secondary Objectives 2 and 5]
    f. Week 32 [Secondary Objectives 4 and 5]
    g. Week 48 [Secondary Objectives 4 and 5]
    h. Week 72 [Secondary Objectives 4, 5, and 9]
4. SPR defined as HBsAb ≥10 mIU/mL at the following study visits in Arm 2:
    a. Week 4 [Secondary Objective 6]
    b. Week 8 [Secondary Objective 6]
    c. Week 12 [Secondary Objective 6]
    d. Week 24 [Secondary Objective 6]
    e. Week 28 [Secondary Objective 5]
    f. Week 32 [Secondary Objectives 4 and 5]
    g. Week 48 [Secondary Objectives 4 and 5]
    h. Week 72 [Secondary Objectives 4, 5, and 9]
5. HBsAb titer at the following study visits in Arm 3:
    a. Week 4 [Secondary Objective 6]
    b. Week 8 [Secondary Objective 6]

c. Week 12 [Secondary Objective 6]
d. Week 24 [Secondary Objective 6]
e. Week 28 [Secondary Objectives 1, 2 and 3]
f. Week 32 [Secondary Objectives 3 and 4]
g. Week 48 [Secondary Objectives 3 and 4]
h. Week 72 [Secondary Objectives 3 and 4]

6. SPR defined as HBsAb ≥10 mIU/mL at the following study visits in Arm 3:
    a. Week 8 [Secondary Objective 6]
    b. Week 12 [Secondary Objective 6]
    c. Week 24 [Secondary Objective 6]
    d. Week 28 [Secondary Objective 3]
    e. Week 32 [Secondary Objectives 3 and 4]
    f. Week 48 [Secondary Objectives 3 and 4]
    g. Week 72 [Secondary Objectives 3 and 4]
7. Grade ≥2 AEs within 4 weeks after each injection [Secondary Objective 7]

3.2.2 Group B

1. HBsAb titer at the following study visits:
    a. Weeks 4, 8, 12, and 24 [Secondary Objective 3]
    b. Week 28 [Secondary Objective 1]
    c. Weeks 32, 48, and 72 [Secondary Objective 2]
2. SPR defined as HBsAb ≥10 mIU/mL at the following study visits:
    a. Weeks 4, 8, 12, and 24 [Secondary Objective 3]
    b. Weeks 32, 48, and 72 [Secondary Objective 2]
3. Grade ≥2 AEs within 4 weeks after each injection [Secondary Objective 4]

4 Estimands and Estimation

* The strategies for handling intercurrent events (e.g. treatment policy strategy, principal stratum strategy, composite variable strategy) are as described in ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials.

4.1 Primary Efficacy Estimands

4.1.1 Primary Objective 1 from Section 2.3.1 for Group A

Estimand Description	Difference in the probabilities of SPR (HBsAb titer ≥10 mIU/mL) between 2-dose regimen of HEPLISAV-B and 3-dose regimen of ENGERIX-B in HBV vaccine-experienced adults living with HIV-1 who failed to achieve a protective level of antibodies against HBsAg.
Treatment	2-dose regimen of HEPLISAV-B vs. 3-dose regimen of ENGERIX-B
Target Population	HBV vaccine-experienced adults living with HIV-1 and on ART who failed to achieve a protective level of antibodies against HBsAg, have suppressed HIV-1 RNA and CD4+ T-cell count ≥100 cells/mm^3, and initiate vaccination series.

Variable	SPR at 12 weeks after the initiation of the HEPLISAV-B vaccine series, or SPR at 28 weeks after the initiation of the ENGERIX- vaccine series.
Handling of Intercurrent Events	1. Incomplete or delayed vaccine series: Participants with incomplete or delayed vaccine series are included. (Treatment Policy Strategy*) 2. Pregnancy: Participants who become pregnant on study have the option of completing the vaccination series and the study. (Principal Stratum Strategy*) 3. Death: Participants who die prior to completion of vaccine series are included. (Treatment Policy Strategy*).
Population-Level Summary	Difference in proportions.

4.1.2 Primary Objective 2 from Section 2.3.1 for Group A

Estimand Description	Difference in the probabilities of SPR (HBsAb titer ≥10 mIU/mL) between 3-dose regimen of HEPLISAV-B and 3-dose regimen of ENGERIX-B in HBV vaccine-experienced adults living with HIV-1 who failed to achieve a protective level of antibodies against HBsAg.
Treatment	3-dose regimen of HEPLISAV-B vs. 3-dose regimen of ENGERIX-B
Target Population	HBV vaccine-experienced adults living with HIV-1 and on ART who failed to achieve a protective level of antibodies against HBsAg, have suppressed HIV-1 RNA and CD4+ T-cell count ≥100 cells/mm3, and initiate vaccination series.
Variable	SPR at 28 weeks after the initiation of the vaccine series.
Handling of Intercurrent Events	1. Incomplete or delayed vaccine series: Participants with incomplete or delayed vaccine series are included. (Treatment Policy Strategy*) 2. Pregnancy: Participants who become pregnant on study have the option of completing the vaccination series and the study. (Principal Stratum Strategy*) 3. Death: Participants who die prior to completion of vaccine series are included. (Treatment Policy Strategy*)
Population-Level Summary	Difference in proportions.

4.1.3 Primary Objective 1 from Section 2.3.1 for Group B

Estimand Description	Probability of SPR (HBsAb titer ≥10 mIU/mL) after HEPLISAV-B vaccination in adults living with HIV-1 without known history of HBV vaccination.
Treatment	3-dose regimen of HEPLISAV-B
Target Population	Adults living with HIV-1 and on ART without known history of HBV vaccination who have suppressed HIV-1 RNA and CD4+ T-cell count ≥100 cells/mm^3, and initiate vaccination series.
Variable	SPR at 28 weeks after the initiation of the vaccine series.

Handling of Intercurrent Events	1. Incomplete or delayed vaccine series: Participants with incomplete or delayed vaccine series are included. (Treatment Policy Strategy*) 2. Pregnancy: Participants who become pregnant on study have the option of completing the vaccination series and the study. (Principal Stratum Strategy*) 3. Death: Participants who die prior to completion of vaccine series are included. (Treatment Policy Strategy*)
Population-Level Summary	Proportion.

4.2 Primary Efficacy Estimation

4.2.1 Analysis Sets for 4.1.1 - 4.1.3

All participants who have met the study eligibility criteria according to the latest protocol and received any study vaccination will be included in each analysis.

4.2.2 Details on Outcome Measures for 4.1.1 – 4.1.3

- SPR at 12 weeks after the study randomization/registration for the 2-dose HEPLISAV-B vaccine series will be determined by antibody result at Week 12 study visit using the visit window specified in the protocol schedule of events. If the completion of vaccine series is delayed up to 4 weeks (as described in Protocol Version 2.0 Section 6.2.3 on Missed Vaccination Visits), then the subsequent antibody result within 8 weeks with an analogous visit window will be used.
- SPR at 28 weeks after the initiation of the 3-dose vaccine series (HEPLISAV-B or ENGERIX-B) will be determined by antibody result at Week 28 study visit using the visit window specified in the protocol schedule of events. If the completion of vaccine series is delayed up to 4 weeks (as described in Protocol Version 2.0 Section 6.2.3 on Missed Vaccination Visits), then the subsequent antibody result within 4 weeks with an analogous visit window will be used.

4.2.3 Handling of Missing Data for 4.1.1 - 4.1.3

Each analysis on SPR will be conducted on participants with available data, under the assumption of missing completely at random (Li, Wang, Liu,Chan, 2011) .

A sensitivity analysis will be conducted with the following imputations.

- Missing SPR will be imputed if both antibody results immediately prior to and after the missed visit are <10 mIU/mL, or if both are ≥10 mIU/mL. This is assuming that there is no change in the response between the visits where data are available.
- If after the above imputation, the total missing SPR results is >10% (above what was accounted for in the study design), then the following additional imputation will be made in the sensitivity analysis:
    - For the recipients assigned to 3-dose vaccine series, the antibody result from the subsequent visit that occurs within 4 weeks of the missed SPR visit will be used to allow the result from Week 32 study visit, accounting for the visit window.

- For the recipients assigned to 2-dose vaccine series, the antibody result from a visit within 4 weeks of the missed SPR visit (8 weeks after the vaccine series) will be used to allow the result from Week 8 study visit (4 weeks after the vaccine series) or from an unscheduled visit that occurs subsequent to the missed visit within 4 weeks. The visit window from the protocol schedule of evaluations will be applied.

The number of imputations in the sensitivity analysis will be summarized by study arm.

4.3 Primary Safety Estimands

4.3.1 Primary Objective 3 from Section 2.3.1 for Group A (Arm 1)

Estimand Description	Probability of adverse events over 72 weeks after the initiation of 2-dose regimen of HEPLISAV-B, in HBV vaccine-experienced adults living with HIV-1 who failed to achieve a protective level of antibodies against HBsAg.
Treatment	2-dose regimen of HEPLISAV-B
Target Population	HBV vaccine-experienced adults living with HIV-1 on ART who failed to achieve a protective level of antibodies against HBsAg, have suppressed HIV-1 RNA and CD4+ T-cell count ≥100 cells/mm^3, and initiate 2-dose regimen of HEPLISAV-B vaccination series.
Variable	Occurrence of adverse event (AE) over 72 weeks after vaccine initiation.
Handling of Intercurrent Events	1. Incomplete or delayed vaccine series: Participants with incomplete or delayed vaccine series are included. (Treatment Policy Strategy*) 2. Pregnancy: Participants who become pregnant on study have the option of completing the vaccination series and the study. (Principal Stratum Strategy*) 3. Death: Death is considered the worst graded event. (Composite Variable Strategy*)
Population-Level Summary	Proportion of participants.

4.3.2 Primary Objective 3 from Section 2.3.1 for Group A (Arm 2):

Description	Probability of adverse events over 72 weeks after the initiation of 3-dose regimen of HEPLISAV-B, in HBV vaccine-experienced adults living with HIV-1 who failed to achieve a protective level of antibodies against HBsAg.
Treatment	3-dose regimen of HEPLISAV-B
Target Population	HBV vaccine-experienced adults living with HIV-1 on ART who failed to achieve a protective level of antibodies against HBsAg, have suppressed HIV-1 RNA and CD4+ T-cell count ≥100 cells/mm^3, and initiate 3-dose regimen of HEPLISAV-B vaccination series.
Variable	Occurrence AE over 72 weeks after vaccine initiation.

Handling of Intercurrent Events	1. Incomplete or delayed vaccine series: Participants with incomplete or delayed vaccine series are included. (Treatment Policy Strategy*) 2. Pregnancy: Participants who become pregnant on study have the option of completing the vaccination series and the study. (Principal Stratum Strategy*) 3. Death: Death is considered the worst graded event. (Composite Variable Strategy*)
Population-Level Summary	Proportion of participants.

4.3.3 Primary Objective 3 from Section 2.3.1 for Group A (Arm 3)

Description	Probability of adverse events over 72 weeks after the initiation of 3-dose regimen of ENGERIX-B, in HBV vaccine-experienced adults living with HIV-1 who failed to achieve a protective level of antibodies against HBsAg.
Treatment	3-dose regimen of ENGERIX-B
Target Population	HBV vaccine-experienced adults living with HIV-1 and on ART who failed to achieve a protective level of antibodies against HBsAg, have suppressed HIV-1 RNA and CD4+ T-cell count ≥100 cells/mm^3, and initiate 3-dose regimen of ENGERIX-B vaccination series.
Variable	Occurrence of AE over 72 weeks after vaccine initiation
Handling of Intercurrent Events	1. Incomplete or delayed vaccine series: Participants with incomplete or delayed vaccine series are included. (Treatment Policy Strategy*) 2. Pregnancy: Participants who become pregnant on study have the option of completing the vaccination series and the study. (Principal Stratum Strategy*) 3. Death: Death is considered the worst graded event. (Composite Variable Strategy*)
Population-Level Summary Statistic	Proportion of participants.

4.3.4 Primary Objective 2 from Section 2.3.1 for Group B

Description	Probability of adverse events over 72 weeks after the initiation of 3-dose regimen of HEPLISAV-B, in adults living with HIV-1 without known history of HBV vaccination.
Treatment	3-dose regimen of HEPLISAV-B
Target Population	Adults living with HIV-1 and ART without known history of HBV vaccination who have suppressed HIV-1 RNA and CD4+ T-cell count ≥100 cells/mm^3, and initiate 3-dose HEPLISAV-B vaccination series.
Outcome Measure	Occurrence of AE over 72 weeks after vaccine initiation.

Handling of Intercurrent Events	1. Incomplete or delayed vaccine series: Participants with incomplete or delayed vaccine series are included. (Treatment Policy Strategy*) 2. Pregnancy: Participants who become pregnant on study have the option of completing the vaccination series and the study. (Principal Stratum Strategy*) 3. Death: Death is considered the worst graded event. (Composite Variable Strategy*)
Population-Level Summary Statistic	Proportion of participants.

4.4 Primary Safety Estimation

4.4.1 Analysis Sets for 4.3.1 - 4.3.4

All participants who have met the study eligibility criteria according to the latest protocol and received any study vaccination will be included in each analysis.

4.4.2 Details on Outcome Measures for 4.3.1 – 4.3.4

All adverse events reported during the study will be included.

4.4.3 Handling of Missing Data for 4.3.1 - 4.3.4

For participants who discontinue study prior to Week 72, assume no additional adverse events occur after loss to follow-up. A sensitivity analysis may be conducted where censoring occurs at the last study visit to estimate proportion using a time-to-event method.

4.5 Key Secondary Estimands

4.5.1 Secondary Objective 1 from Section 2.3.2 for Group A

Description	Difference in the mean antibody titers between 2-dose regimen of HEPLISAV-B and 3-dose regimen of ENGERIX-B in HBV vaccine-experienced adults living with HIV-1 who failed to achieve a protective level of antibodies against HBsAg.
Treatment	2-dose regimen of HEPLISAV-B vs. 3-dose regimen of ENGERIX-B
Target Population	HBV vaccine-experienced adults living with HIV-1 on ART who failed to achieve a protective level of antibodies against HBsAg, have suppressed HIV-1 RNA and CD4+ T-cell count ≥100 cells/mm^3, and initiate vaccination series.
Variable	HBsAb titer at 12 weeks after the initiation of the HEPLISAV-B vaccine series, or HBsAb titer at 28 weeks after the initiation of the ENGERIX-B vaccine series.
Handling of Intercurrent Events	1. Incomplete or delayed vaccine series: Participants with incomplete or delayed vaccine series are included. (Treatment Policy Strategy*) 2. Pregnancy: Participants who become pregnant on study have the option of completing the vaccination series and the study. (Principal Stratum

	Strategy*) 3. Death: Participants who die prior to completion of vaccine series are included. (Treatment Policy Strategy*)
Population-Level Summary	Difference in the geometric mean titer (GMT).

4.5.2 Secondary Objective 2 from Section 2.3.2 for Group A

Description	Difference in the mean antibody titers between 3-dose regimen of HEPLISAV-B and 3-dose regimen of ENGERIX-B in HBV vaccine-experienced adults living with HIV-1 who failed to achieve a protective level of antibodies against HBsAg.
Treatment	3-dose regimen of HEPLISAV-B vs. 3-dose regimen of ENGERIX-B
Target Population	HBV vaccine-experienced adults living with HIV-1 and on ART who failed to achieve a protective level of antibodies against HBsAg, have suppressed HIV-1 RNA and CD4+ T-cell count ≥100 cells/mm^3, and initiate vaccination series.
Variable	HBsAb titer at 28 weeks after the initiation of the vaccine series.
Handling of Intercurrent Events	1. Incomplete or delayed vaccine series: Participants with incomplete or delayed vaccine series are included. (Treatment Policy Strategy*) 2. Pregnancy: Participants who become pregnant on study have the option of completing the vaccination series and the study. (Principal Stratum Strategy*) 3. Death: Participants who die prior to completion of vaccine series are included. (Treatment Policy Strategy*)
Population-Level Summary	Difference in GMT.

4.5.3 Secondary Objective 3 from Section 2.3.2 for Group A on SPR at 48 Weeks After Last Vaccination

Description	Difference in the probabilities of long-term SPR between 2-dose regimen of HEPLISAV-B and 3-dose regimen of ENGERIX-B in HBV vaccine-experienced adults living with HIV-1 who failed to achieve a protective level of antibodies against HBsAg.
Treatment	2-dose regimen of HEPLISAV-B vs. 3-dose regimen of ENGERIX-B
Target Population	HBV vaccine-experienced adults living with HIV-1 and on ART who failed to achieve a protective level of antibodies against HBsAg, have suppressed HIV-1 RNA and CD4+ T-cell count ≥100 cells/mm^3, and initiate vaccination series.
Variable	SPR at 52 weeks after initiation of 2-dose vaccine series and at 72 weeks after initiation of 3-dose vaccine series.

Handling of Intercurrent Events	1. Incomplete or delayed vaccine series Participants with incomplete or delayed vaccine series are included. (Treatment Policy Strategy*) 2. Pregnancy: Participants who become pregnant on study have the option of completing the vaccination series and the study. (Principal Stratum Strategy*) 3. Death: Participants who die prior to completion of vaccine series are included. (Treatment Policy Strategy*)
Population-Level Summary	Difference in proportions.

4.5.4 Secondary Objective 3 from Section 2.3.2 for Group A on GMT at 48 Weeks After Last Vaccination

Description	Difference in the long-term mean titers between 2-dose regimen of HEPLISAV-B and 3-dose regimen of ENGERIX-B in HBV vaccine-experienced adults living with HIV-1 who failed to achieve a protective level of antibodies against HBsAg.
Treatment	2-dose regimen of HEPLISAV-B vs. 3-dose regimen of ENGERIX-B
Target Population	HBV vaccine-experienced adults living with HIV-1 on ART who failed to achieve a protective level of antibodies against HBsAg, have suppressed HIV-1 RNA and CD4+ T-cell count ≥100 cells/mm^3, and initiate vaccination series.
Variable	HBsAb titer at 52 weeks after initiation of 2-dose vaccine series and at 72 weeks after initiation of 3-dose vaccine series.
Handling of Intercurrent Events	1. Incomplete or delayed vaccine series: Participants with incomplete or delayed vaccine series are included. (Treatment Policy Strategy*) 2. Pregnancy: Participants who become pregnant on study have the option of completing the vaccination series and the study. (Principal Stratum Strategy*) 3. Death: Participants who die prior to completion of the vaccine series are included. (Treatment Policy Strategy*)
Population-Level Summary	Difference in GMT.

4.5.5 Secondary Objective 1 from Section 2.3.2 for Group B

Description	Mean titer of HBsAb after HEPLISAV-B vaccination in adults living with HIV-1 without known history of HBV vaccination.
Treatment	3-dose regimen of HEPLISAV-B
Target Population	Adults living with HIV-1 and on ART without known history of HBV vaccination who have suppressed HIV-1 RNA and CD4+ T-cell count ≥100 cells/mm^3, and initiate vaccination series.
Variable	HBsAb titer at 28 weeks after initiation of the vaccine series.

Handling of Intercurrent Events	1. Incomplete or delayed vaccine series: Participants with incomplete or delayed vaccine series are included. (Treatment Policy Strategy*) 2. Pregnancy: Participants who become pregnant on study have the option of completing the vaccination series and the study. (Principal Stratum Strategy*) 3. Death: Participants who die prior to completion of vaccine series are included. (Treatment Policy Strategy*)
Population-Level Summary	GMT

4.6 Key Secondary Estimation

4.6.1 Analysis Sets for 4.5.1 - 4.5.5

All participants who have met the study eligibility criteria according to the latest protocol and received any study vaccination will be included in each analysis.

4.6.2 Details on Outcome Measures for 4.5.1 – 4.5.5

- For HBsAb titer at 12 weeks after the initiation of the 2-dose series and for 28 weeks after the initiation of the 3-dose series (Secondary Estimands in Sections 4.5.1, 4.5.2 and 4.5.5), antibody results corresponding to SPR measurements described in Section 4.2.2 will be used.
- For HBsAb titer at 52 weeks after the initiation of the 2-dose series and 72 weeks after the initiation of the 3-dose series (Secondary Estimands in Sections 4.5.3 and 4.5.4), antibody results at Week 52 study visit and at Week 72 study visit, respectively, will be used.

4.6.3 Handling of Missing Data for 4.5.1 - 4.5.5

Each analysis on antibody titers will be conducted on participants with available data, under the assumption of missing completely at random (Li, Wang, Liu, Chan, 2011).

A sensitivity analysis will be conducted for the missing HBsAb titer data at 12 weeks after the initiation of the 2-dose series and for 28 weeks after the initiation of the 3-dose series (Secondary Estimands in Sections 4.5.1, 4.5.2 and 4.5.5), with imputations analogous to what was described for SPR in Section 4.2.3 in the case that the total missing SPR results is >10%.

A sensitivity analysis will be conducted for the missing HBsAb titer data at 52 weeks after the initiation of the 2-dose series and 72 weeks after the initiation of the 3-dose series (Secondary Estimands in Sections 4.5.3 and 4.5.4), where the missing value will be imputed with the result from the subsequent visit, if there are >10% such imputations.

5 Analysis Considerations

5.1 General Considerations

- All study analyses will be conducted separately for Groups A and B, unless indicated otherwise.
- Considerations for type I error adjustment for conducting interim review(s) of the primary outcome:
  - Group A:
    - For the estimated proportion difference between Arm 1 and Arm 3, if an interim look with a two-sided 99.9% confidence interval occurs to assess potential harm, the type I error (alpha) for the final analysis will not be adjusted. This is because 0.1% alpha spending in the interim look would have a minimal effect on the final confidence interval.
    - For the superiority comparison between Arm 2 and Arm 3, a repeated confidence interval approach using a Lan-DeMets spending function with O'Brien-Fleming type boundaries that accounts for the repeated analyses due to interim efficacy monitoring will be provided.
  - Group B:
    - If an interim look with a 99.9% confidence interval occurs in Group B to assess potential harm, no adjustment will be made to the type I error (alpha) for the final analysis.
- Summaries of continuous variables will include mean with standard deviation, min, Q1, median, Q3, and max.
- For binary and categorical variables, estimated proportions will be provided.
- The data summaries will include the number or participants with data who are included in the analysis.
- Study visits corresponding to the protocol schedule of evaluations for the intended weeks will be used for the analysis, unless stated otherwise.
- In the event of multiple results within a window, the one closest to the targeted scheduled evaluation week will be used.
- Baseline refers to result closest to Week 0 prior to initiation of study vaccination.
- Calculated study visits will be used for laboratory measurements summarized or listed by week.
- No statistical comparisons across groups for baseline characteristics are planned for this randomized clinical trial.
- Any participant-level information will be identified by the masked participant identifier (Public ID).

5.2 Analysis Approaches

5.2.1 Group A Primary:

- For each of the two primary objectives on vaccine response, the primary outcome measure on the SPR will be analyzed as a binary variable.
- A score-based approach similar to the Wilson method for a SPR proportion difference will be used to estimate a stratified confidence interval, known as Newcombe method (Yan

and Su, 2010). Four strata will be defined by sex at birth and screening diabetes status, and the strata will use Mantel-Haenszel weights (Mantel and Haenszel, 1959).

- Non-inferiority comparison between Arms 1 and 3: For the final analysis, a two-sided 97.5% confidence interval will be provided for the estimated proportion difference between Arm 1 and Arm 3 (Arm 3 minus Arm 1). If the resulting confidence interval lies entirely below the non-inferiority margin of 10%, then non-inferiority of Arm 1 compared to Arm 3 (control) will be concluded. Superiority of Arm 1 compared to Arm 3 will be concluded if the confidence interval lies entirely below zero.
- Superiority comparison between Arms 2 and 3: For the final analysis, a two-sided 97.5% stratified confidence interval will be provided for the proportion difference between Arm 2 and Arm 3 (Arm 2 minus Arm 3). A repeated confidence interval approach according to the realized Lan and DeMets implementation of the O'Brien-Fleming sequential stopping boundary that accounts for the repeated analyses due to interim efficacy monitoring will be provided. If the resulting confidence interval lies entirely above zero, then superiority of Arm 2 compared to Arm 3 (control) will be concluded.
- To address the study objectives on safety, the proportion of participants with AEs will be summarized with a two-sided 95% confidence interval in each study arm using the Wilson method, across stratification factors.

5.2.2 Group A Secondary:

- The secondary analyses on SPR will be conducted using a two-sided type I error rate of 2.5% without further correction for multiple analyses. This type I error was chosen to provide confidence intervals of widths comparable to the primary outcome analyses.
- The secondary objectives on the SPR comparisons will be addressed using the following analysis approach. A two-sided 97.5% confidence interval around the difference in proportions will be calculated using the Newcombe method. These will also be stratified confidence intervals, similar to the primary analysis approach.
- For the secondary objectives on the analysis of the antibody titer as a continuous measure, two-sided type I error rate of 5% without correction for multiple analyses will be used. The geometric mean titer will be calculated for each analysis group (study arm or combined study arms, depending on the objective) and compared using a t-test. A two-sided 95% confidence interval around the difference in the geometric means will be calculated assuming t-distribution of $\log_{10}$-transformed antibody titer. The confidence intervals will be provided across stratification factors and within stratum.
- For the secondary objective (e.g. Objective 6) where Arms 1 and 2 are combined to compare to Arm 3 (control), the analysis will occur if the directions in the outcome differences between Arm 1 and Arm 3 and between Arm 2 and Arm 3 are the same. Otherwise, the analysis where Arms 1 and 2 are combined will not be interpretable.
- To address the objective on post-injection AEs, the proportion of participants with events will be summarized with a two-sided 95% confidence interval in each study arm using the Wilson method.
- Logistic regression models will be developed to assess host characteristic factors associated with vaccine response defined by the primary outcome on the SPR. The factors include age, sex, race, diabetes, body mass index (BMI), CD4+ T-cell count, and smoking status at baseline. Each factor will be considered in a separate model that only

controls for the study arm as a covariate, and a p-value <0.20 will determine entry into a full model. Then all-subsets variable selection approach will be used with a p-value cutoff of 0.05 as a criterion to retain in the final model, while keeping the study arm in the model throughout the procedure.

5.2.3 Group B Primary:

- The primary outcome on the SPR at 4 weeks after the vaccination series will be assessed by estimating the proportion of participants who achieve SPR. A two-sided 95% confidence interval around the observed SPR proportion will be provided using the Wilson score method for binomial variables. If the confidence interval lies above 55%, then it will be concluded that the SPR proportion is greater than 55%.
- To address the primary objective on safety, the proportion of participants with AEs will be summarized with a two-sided 95% confidence interval using the Wilson method.

5.2.4 Group B Secondary:

- Each secondary analysis will be conducted using a two-sided type I error rate of 5% without correction for multiple analyses.
- To address the secondary objectives on the SPR at additional study weeks, a two-sided 95% confidence interval around the observed SPR proportion will be provided for each, using the Wilson score method for binomial variables.
- To address the secondary objectives related to antibody titer as a continuous measure, the GMT will be calculated with two-sided 95% confidence intervals, assuming t-distribution of $\log_{10}$-transformed antibody titer.
- To address the study objective on post-injection AEs, the proportion of participants with events will be summarized with a two-sided 95% confidence interval using the Wilson method.
- Logistic regression models will be developed to assess host characteristic factors associated with vaccine response defined by the primary outcome on the SPR. The approach described for Group A (Section 5.2.2 above) will also be used for Group B.

References:

Li X, Wang WW, Liu GF, Chan IS. Handling missing data in vaccine clinical trials for immunogenicity and safety evaluation. J Biopharm Stat 2011;21:294-310.

Yan, X., & Su, X. G. (2010). Stratified Wilson and Newcombe confidence intervals for multiple binomial proportions. Statistics in Biopharmaceutical Research, 2(3), 329-335.

Mantel, N., and Haenszel, W. (1959). “Statistical Aspects of Analysis of Data from Retrospective Studies of Disease.” Journal of the National Cancer Institute 22:719–748.

6 Report Contents

Additional details will be provided in an AIP. In addition to results for primary and secondary outcome measures, baseline characteristics and study status are reported to ClinicalTrials.gov.

1. CONSORT Diagram
2. Study history
    a. A summary of changes to and clarifications of the protocol
    b. A brief summary of the DSMB reviews
3. Study entry
    a. Screening: Number of participants screened for the study
    b. Accrual: Tables of accrual by month and by site
4. Baseline characteristics
    a. Demographics: age, sex, gender, IV drug use, race, ethnicity, country
    b. Weight and BMI
    c. Plasma HIV-1 RNA level, CD4+ and CD8+ T-cell count and percent
    d. ARV regimen
    e. Smoking status
    f. Diabetes status
5. Study status
    a. Listing of premature study discontinuation with reasons. For premature discontinuations, the number of weeks on study will be provided.
6. Study treatment status
    a. Listing of premature discontinuations of vaccination series with reasons. For premature discontinuations, the number of vaccines received will be provided.
    b. Number and times of administered vaccines
7. Adverse events and deaths
    a. Summary of all reportable AEs defined in Section 7.2 of the protocol by MedDRA system organ class (SOC) and preferred term (PT) and by grade.
    b. Summary of the participants who died, including primary cause of death with weeks from study entry.
    c. Listing and narratives of deaths.
8. Pregnancies
    a. Listing and description of all available information related to pregnancy and outcome.
9. HIV-Related Summaries
    a. CD4 cell count and changes from baseline at study visits
    b. HIV-1 RNA at study visits
10. Analysis of Primary Outcome Measures

    Group A Outcomes Described in Section 3.1.1:
    a. Primary Objective 1 described in Section 2.3.1 will be addressed by estimating the difference between Arms 1 and 3 (Arm 3 minus Arm 1) in the proportions of participants who achieve SPR, using the approach described in Section 5.2.1.

b. Primary Objective 2 described in Section 2.3.1 will be addressed by estimating the difference between Arms 2 and 3 (Arm 2 minus Arm 3) in the proportions of participants who achieve SPR, using the approach described in Section 5.2.1.
c. Primary Objective 3 described in in Section 2.3.1 will be addressed by estimating the proportion of participants with reported AEs, using the approach described in Section 5.2.1.

Group B Outcomes Described in Section 3.1.2:

a. Primary Objective 1 described in Section 2.3.1 will be addressed by estimating the SPR proportion, using the approach described in Section 5.2.3.
b. Primary Objective 2 described in Section 2.3.1 will be addressed by estimating the proportion of participants with reported AEs, using the approach described in Section 5.2.1. In addition, descriptive tables summarizing the events and the number of participants experiencing the events will be provided by grade. For the descriptive tables, the worst graded event per participant over time will be used.

11. Analysis of Secondary Outcome Measures

Group A Outcomes Described in Section 3.2.1:

a. Secondary Objectives 1, 2, 3, 4, 5, 6, and 9 from Section 2.3.2 related to GMT will be addressed by estimating the difference in GMT between study arms (or between Arm 3 and the combined Arms 1 and 2 for Secondary Objective 6), using the approach described in Section 5.2.2. In addition, the geometric mean titer will be calculated for each study arm and compared using a t-test, as described in Section 5.2.2.
b. Secondary Objectives 3, 4, 5 and 6 from Section 2.3.2 related to SPR will be addressed by estimating the SPR proportion differences between study arms (or between Arm 3 and the combined Arms 1 and 2 for Secondary Objective 6), using the approach described in Section 5.2.2.
c. Secondary Objective 7 from Section 2.3.2 will be addressed by estimating the proportion of participants with post-injection AEs, using the approach described in Section 5.2.2. In addition, descriptive tables summarizing the events and the number of participants experiencing the events will be provided.
d. Secondary Objective 8 from Section 2.3.2 will be addressed by logistic regression models described in Section 5.2.2.
e. To assess the effect of sex and race on the vaccine response (per NIH guidance on reporting analyses of sex and racial differences in intervention effects for NIH-defined Phase III clinical trials), proportions of subgroups defined by sex and race who achieve the primary outcome will be estimated with confidence intervals, using the approach described in Section 5.2.2. In addition, note that logistic regression models for the primary outcome will include sex and race, and reported as secondary analyses.

Group B Outcomes Described in Section 3.2.2:

a. Secondary Objectives 1, 2 and 3 from Section 2.3.2 related to GMT will be addressed by estimating the GMT, using the approach described in Section 5.2.4.

b. Secondary Objectives 2 and 3 from Section 2.3.2 related to SPR will be addressed by estimating the SPR proportion, using the approach described in Section 5.2.4.
c. Secondary Objective 7 from Section 2.3.2 will be addressed by estimating the proportion of participants with post-injection AEs, using the approach described in Section 5.2.4. In addition, descriptive tables summarizing the events and the number of participants experiencing the events will be provided..
d. Secondary Objective 8 from Section 2.3.2 will be addressed by logistic regression models described in Section 5.2.4. Note that logistic regression models for the primary outcome will include sex and race.

12. Intercurrent Events

Summaries of the number and timing of each intercurrent event in each treatment group will accompany each analysis where intercurrent events are specified in Section 4.

13. Supplementary Analyses of Primary Outcome Measures

The following analyses restricted to participants who complete the vaccine series as prescribed will be conducted.

Group A SPR Outcomes Described in Section 3.1.1:

a. Primary Objective 1 described in Section 2.3.1 will be addressed in the subset by estimating the difference between Arms 1 and 3 (Arm 3 minus Arm 1) in the proportions of participants who achieve SPR, using the approach described in Section 5.2.1.

b. Primary Objective 2 described in Section 2.3.1 will be addressed in the subset by estimating the difference between Arms 2 and 3 (Arm 2 minus Arm 3) in the proportions of participants who achieve SPR, using the approach described in Section 5.2.1.

Group A Outcomes Described in Section 3.2.1:

a. Secondary Objectives 1 and 2 from Section 2.3.2 related to GMT will be addressed in the subset by estimating the difference in GMT between study arms, using the approach described in Section 5.2.2. In addition, the GMT will be calculated for each study arm and compared using a t-test, as described in Section 5.2.2.

Group B SPR Outcomes Described in Section 3.1.2:

a. Primary Objective 1 described in Section 2.3.1 will be addressed in the subset by estimating the SPR proportion, using the approach described in Section 5.2.3.

Group B Outcomes Described in Section 3.2.2:

a. Secondary Objective 1 from Section 2.3.2 related to GMT will be addressed in the subset by estimating the GMT, using the approach described in Section 5.2.4.