STATISTICAL ANALYSIS PLAN

for

Protocol: RV546

Study Title:

Randomized, Double Blind Evaluation of Late Boost Strategies with IHV01 (FLSC in aluminum phosphate) and A244 with or without ALFQ for HIV-uninfected Participants in the HIV Vaccine Trial RV306 / WRAIR 1920

IND #: 27011

Version 3.0

DATE: 21 January 2025

STUDY TITLE

Protocol Number Code:	**RV546**
Development Phase:	Phase I
Products:	IHV01 (FLSC), A244 (with aluminum hydroxide fluid gel adjuvant), ALFQ Adjuvant, and saline placebo
Form/Route:	IM injection
Indication Studied:	Preventative HIV vaccine
Sponsor:	The Surgeon General, Department of the Army
Clinical Trial Initiation Date:	03 February 2022
Clinical Trial Completion Date:	01 July 2024
Date of the Analysis Plan:	21 January 2025
Version Number:	3.0

This study was performed in compliance with Good Clinical Practice.

List of SAP Amendments

Version	Description of Changes	Justification
1.0	N/A (Original Version)	N/A
2.0	Updates to sample size considerations. Minor changes elsewhere for clarification purposes. General formatting updates and spell check.	To match the study redesign in v5.0 of the protocol and clarify language. Corrected spelling of Seroconversion in Table 39.
3.0	Added trial initiation and completion dates in the study information table on page ii.. General page flow to avoid tables breaking across pages where possible.	To add missing information. To improve readability.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Celsius
CI	Confidence Interval
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
ER	Emergency Room
F	Fahrenheit
GGT	Gamma Glutamyl Transferase
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intention to Treat
L	Liter
LLN	Lower Limit of Normal
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mEq	Milliequivalent
mg	Milligram
mITT	Modified Intention to Treat
mL	Milliliter
MAR	Missing at Random

MCAR	Missing Completely at Random
MNAR	Missing Not at Random
N	Number (typically refers to Participants)
NIH	National Institutes of Health
PI	Principal Investigator
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
RCD	Reverse Cumulative Distribution
SAE	Serious Adverse Event
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedures
U	Units
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The statistical analysis plan (SAP) for the Phase I study titled "Randomized, Double Blind Evaluation of Late Boost Strategies with IHV01 (FLSC in aluminum phosphate) and A244 with or without ALFQ for HIV-uninfected Participants in the HIV Vaccine Trial RV306 / WRAIR 1920" expands upon the statistical considerations presented in the protocol. This document includes general statistical principles and planned analyses to address protocol objectives, along with sample tables, listings, and figures.

2. INTRODUCTION

To examine the impact of the interval between priming and boosting in vaccination of healthy volunteers against HIV, the RV306 Phase II clinical trial was conducted in 360 healthy, unvaccinated participants to determine whether similar improvements in quality, magnitude or duration of humoral, cellular and mucosal responses could be afforded by boosting the RV144 regimen at either 12, 15, or 18 months post initial vaccination series, and to determine the optimal boosting interval for further clinical development.The purpose of this study is to define the safety and immunogenicity of IHV01 and A244/Rehydragel with and without ALFQ at a full dose and at a fractional dose in a late boost setting for participants who had previously received a late boost of AIDSVAX®B/E with or without ALVAC in RV306. Safety will be assessed through the frequency and incidence of adverse events and solicited post-vaccination reactions. Blood, lymph nodes, sigmoid tissue, and mucosal specimens/secretions will be collected to assess humoral, cell-mediated, innate, and mucosal immune responses.This analysis plan is based on Version 5.0 of the protocol.

Purpose of the Analyses

These analyses will assess the safety and immunogenicity of IHV01 and A244/AHFG with and without ALFQ at a full dose and at a fractional dose in a late boost setting for participants who had previously received a late boost of AIDSVAX®B/E with or without ALVAC in RV306.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

- To evaluate the safety of 3 novel investigational products in a late vaccine boost setting: the candidate IHV01 and A244/AHFG vaccines and the ALFQ adjuvant

3.1.2. Secondary Objectives

- To evaluate the effect of a full dose of the IHV01 and A244/AHFG vaccines and the ALFQ adjuvant on cellular, humoral, and innate immune responses (peripheral, lymphoid and mucosal).
- To evaluate the effect of fractional dosing of the IHV01 and A244/AHFG vaccines on cellular, humoral, and innate immune responses (peripheral, lymphoid and mucosal).

3.2. Endpoints/Outcome Measures

3.2.1. Safety (Primary) Endpoints

- Solicited local (at the injection site) reactogenicity symptoms, as collected in clinic on Day 1 post-vaccination and from self-reported diary cards on Day 2 through 7: erythema, induration, pain/tenderness, swelling and limitation of leg movement
- Solicited systemic reactogenicity symptoms, as collected in clinic on Day 1 post-vaccination and from self-reported diary cards on Day 2 through 7: fever, tiredness, chills, myalgia, arthralgia, headache, nausea, and rash
- Adverse events (AEs) recorded at all visits, along with timing and possible attribution to Investigational Product
- Serious adverse events (SAEs) recorded at all visits, along with timing and possible attribution to Investigational Product
- Adverse events of special interest (AESIs) recorded at all visits, along with timing and possible attribution to Investigational Product: _____
- Safety laboratory analyses, including: complete blood count, liver function tests, urinalysis, and pregnancy tests for female participants

3.2.2. Immunogenicity Endpoints

3.2.2.1. Primary Immunogenicity Endpoint

The primary immunogenicity endpoint is the magnitude of plasma IgG antibodies as measured by endpoint titer.

3.2.2.2. Secondary Immunogenicity Endpoints

Additional immunogenicity endpoints are as follows:

Humoral Assays	Sample Type	Function Measurement
ADCC, ADCP, and other non-neutralizing antibody functions	Plasma/ Serum	Measures lysis of HIV expressing targets mediated by HIV specific antibodies
HIV-specific binding*	Plasma/ Serum	Binding antibody to vaccine antigens
HIV-specific neutralizing antibodies	Serum	Neutralizing activity against luciferase reporter gene expression
Cellular and Innate Assays	**Sample Type**	**Function Measurement**
Cellular response by cytokines such as IFN-γ and IL2 after stimulation with HIV-specific antigens	PBMC	(1) CD4+ and CD8+ antigen-specific response (2) Cellular functionality (CD4+; CD8+ only if sufficient CD8+ univariate responses) (3) Cellular polyfunctionality (CD4+; CD8+ only if sufficient CD8+ univariate responses)
Lymphocyte proliferation	PBMC, sigmoid biopsies, or lymph node biopsies	Characterize the function of proliferating cells in response to HIV antigens
B-cell ELISPOT	PBMC, sigmoid biopsies, or lymph node biopsies	Measures cytokine secretion from B cells in response to HIV antigens
Flow cytometry for innate immune cell phenotyping and a cytokine array assay	Plasma/ Serum, sigmoid biopsies, or lymph node biopsies	Phenotype NK and other innate cells and characterize the cytokines elicited by the different vaccine regimens
Mucosal Assays	**Mucosal Secretions**	**Function Measurement**
HIV-specific binding antibodies	Semen, rectal secretions, cervico-vaginal secretions	Binding antibody to vaccine antigens
CD4+, CD8+, and other T cell characterization	Cells from lymph nodes biopsy, sigmoid biopsy, and cytobrush	Defines phenotypic characteristics of T cells recognizing the antigen by multicolor flow cytometry

*Plasma IgG antibodies will be considered the primary immunogenicity endpoint

In the context of unknown immune correlates of protection, additional assessments may be performed as new scientific technologies and assessment tools are made available.

3.3. Study Definitions and Derived Variables

The baseline value will be defined as the last value obtained prior to the first vaccination. Individual antibody endpoint titers will be reported with values of C*2k, where k=0, 1, 2, etc. and C may vary depending on the dilutions used for a given assay. Values below each assay's limit of detection will be imputed as one-half the limit of detection. For analysis, the geometric mean of replicates for each sample will be computed and used as the response for all subsequent calculations, where applicable.

Immune response over time (durability) will be assessed by the positive incremental area under the curve (AUC) based on a graph with the analysis value (e.g., log endpoint titer) on the y-axis and visit day on the x-axis.

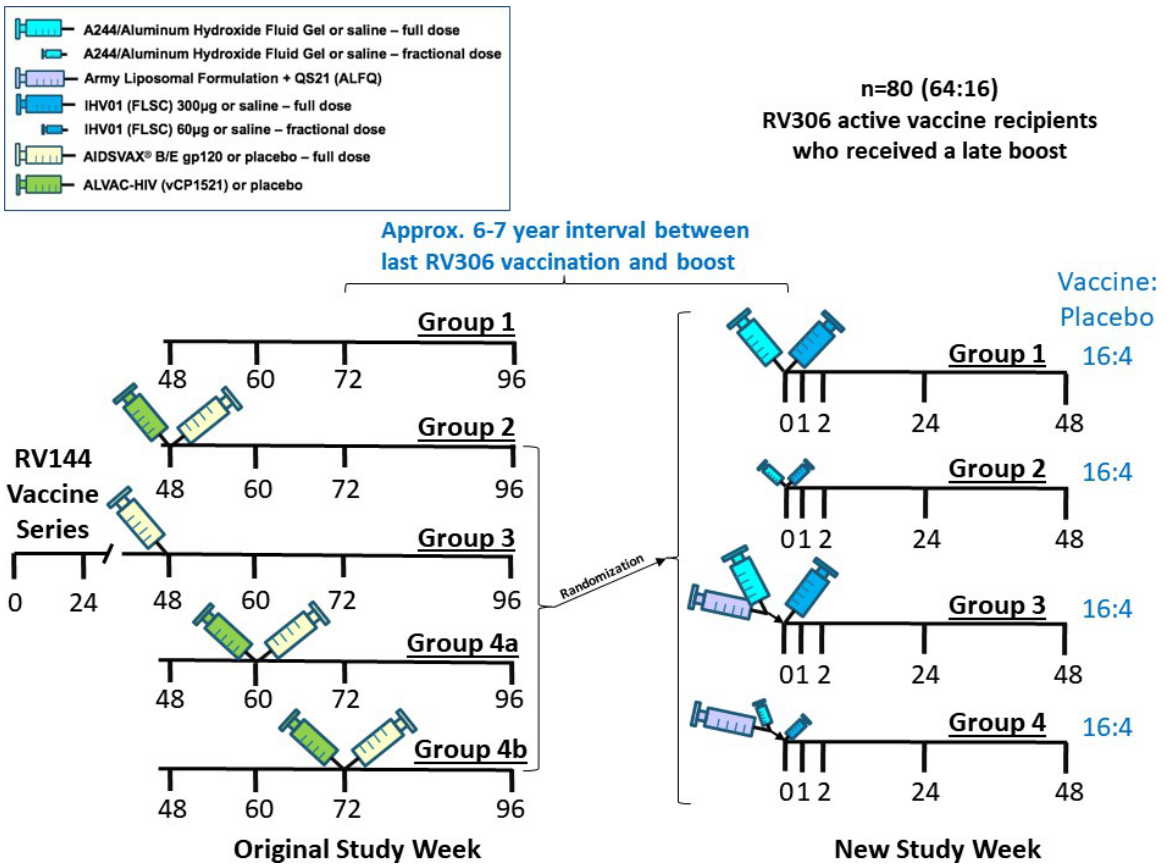
4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase I randomized, double-blind, placebo-controlled clinical trial to define the safety and immunogenicity of IHV01/A244 with and without ALFQ at a full dose and at a fractional dose in a late boost setting for participants who had previously received the AIDSVAX®B/E with or without ALVAC in RV306. Participants will be randomized to receive 2 intramuscular (IM) injections, either IHV01/A244 (target of n=64 total, with n=16 per study arm) or saline placebo (target of n=16 total, with n=4 per study arm), into the same quadriceps muscle at Day 0. Half of the IHV01/A244 recipients will receive the full IHV01 (FLSC) dose (Groups 1 and 3) while the other half (Groups 2 and 4) will receive a fractional dose of each vaccine, which is one fifth of the standard dose. Groups 3 and 4 will also receive ALFQ. Enrollment will be sequential, with Groups 1 and 2 accruing first with a 2:2:1 ratio of full dose to fractional dose to placebo, followed by enrollment into Groups 3 and 4 with the same targeted allocation ratios. After the first 8 participants are enrolled across Groups 1 and 2, the Safety Monitoring Committee (SMC) will review 7 days of safety data from these participants to determine whether enrollment can continue. Enrollment into Groups 1 and 2 will continue unrestricted after any safety concerns raised by the SMC are addressed and the Sponsor gives their approval for the continuation of enrollment. Enrollment into Groups 3 and 4 will commence after enrollment into Groups 1 and 2 has been completed, the SMC has reviewed 7 days of safety data from all Group 1 and Group 2 participants, and the Sponsor gives their approval. Enrollment into Groups 3 and 4 will follow a similar approach with an SMC review of 7 days of safety data from the first 8 participants enrolled across both groups, and Sponsor approval before enrollment can continue unrestricted in Groups 3 and 4.

Participants will receive 2 IM injections, either IHV01/A244 (n=64) or saline placebo (n=16) at Day 0, and return for follow up at 1,7, 14, 168, and 336 days after vaccination (protocol version 5.0, section 7.2). Figure 1 gives a schematic of the study design, with the RV306 groups shown on the left and the RV546 groups on the right.

Figure 1: Study Schematic



Study arms are given below in Table 1. For analysis purposes, participants will be grouped by vaccination regimen received, so placebo participants will be considered the fifth Vaccination Group.

Table 1: Study Arms

Group #	Intervention	Control
Group 1	16 Full IHV01/A244	4 placebo
Group 2	16 Fractional IHV01/A244	4 placebo
Group 3	16 Full IHV01/A244 + ALFQ	4 placebo
Group 4	16 Fractional IHV01/A244 + ALFQ	4 placebo

The schedule of events is given in Table 2 below, for reference.

Table 2: Schedule of Events

Visit	S1	1	2	3	4	5	6 (Exit)	7
Visit Day	**-45 to -16**	**0**	**1**	**7**	**14**	**168**	**336**	**Post Database Lock**
Visit Week		**0**	**1**	**1**	**2**	**24**	**48**	
Visit Month		**0**			**0.5**	**6**	**12**	
Visit Window			**+2d**	**-/+2d**	**-2/+3d**	**-/+7d**	**-/+7d**	
Clinical								
Informed Consent (Main, Storage/Future Use, Genetic, and Optional Procedures)	X							
Test of Understanding	X							
Enrollment and Randomization		X						
Vaccination		X						
Vital Signs[8] and Physical exam[1]	X	X		X	X	X	X	
Medical History & Concomitant Medications	X	X		X	X	X	X	
Adverse Event Documentation (AE, SAE, AESI)		X	X	X	X	X	X	
Diary Card		X	X	X				
HIV Risk Assessment/Risk Counseling	X	X			X	X	X	
Pregnancy Test & Pre/Post Counseling	X	X			X	X	X	
Urinalysis (blood, protein and glucose)	X	X	X	X	X	X	X	
CBC w/ diff & CD4	2	2	2	2	2	2	2	
Creatinine, ALT/AST	3.5			3.5	3.5	3.5	3.5	
Syphilis and Hepatitis B Serology	3.5							
HIV Testing & Pre/Post Counseling	6				6	6	6	
Optional Procedures								
Mucosal Secretions[2,7]; Plasma LH and FSH (cervical secretions only)		X			X	X	X	
STI Testing[7]	X							
Vaginal[2,7] and/or rectal[3,7] and/or penile[7] swab for microbiome and proteome		X			X	X	X	
Endocervical Cytobrush/swab[2,7]		X			X	X	X	
Pap Smear, if none available in last two years[7]	X							

Final Results and Unblinding[5]

Visit	S1	1	2	3	4	5	6 (Exit)	7
Visit Day	**-45 to -16**	**0**	**1**	**7**	**14**	**168**	**336**	**Post Database Lock**
Visit Week		**0**	**1**	**1**	**2**	**24**	**48**	
Visit Month		**0**			**0.5**	**6**	**12**	
Visit Window			**+2d**	**-/+2d**	**-2/+3d**	**-/+7d**	**-/+7d**	
Sigmoid Biopsy[3,7]					X			
Lymph Node Biopsy					X			
Leukapheresis[4]					X (10ml)			
Safety Tests for Biopsy or Leukapheresis (up to max possible volume)[10]					20			
Research								
HIV Binding Antibody		SP			SP	SP	SP	
HIV Neutralizing Antibody Assays		6			6	6	6	
Functional Antibody Assays		SP			SP	SP	SP	
B-Cell Analysis[6]		30		30	30	30	30	
Multiparameter Flow Cytometry		20			20	20	20	
Innate Cell Analysis		20	20	20	20	20	20	
Transcriptomics		20	20	20	20	20	20	
Additional Immunogenicity Testing[6]		30		30	30	30	30	
Daily Volume (mL)	**15**	**128**	**42**	**105.5**	**157.5**	**137.5**	**137.5**	
Daily volume (mL) for participant weighing below 50 kgs	**15**	**93**	**42**	**70.5**	**122.5**	**137.5**	**137.5**	
Cumulative Volume (mL)	**15**	**143**	**185**	**290.5**	**448**	**585.5**	**723**	
Cumulative Volume (mL) for participant weighing below 50 kgs	**15**	**108**	**150**	**220.5**	**343**	**480.5**	**618**	
12-Week Cumulative Volume (mL)[6]					**448**	**137.5**	**137.5**	
12-Week Cumulative Volume (mL) for participant weighing below 50 kgs[6]					**343**	**137.5**	**137.5**	

4.2. Discussion of Study Design, Including the Choice of Control Groups

This study uses a factorial, placebo concurrent control design to assess the safety and immunogenicity of varying doses of the same vaccine with or without the ALFQ adjuvant. This is a Phase I study with a primary objective of characterizing the safety of the study vaccination, so saline placebo was chosen as the control.

4.3. Selection of Study Population

The study population will consist of approximately 80 healthy, HIV-uninfected, adult, RV306 recipients who were randomized to receive active vaccine. All study participants must meet the eligibility criteria enumerated in the protocol (protocol version 5.0, sections 8.4, 8.5).

4.4. Statistical Considerations for the Study Design

4.4.1. Sample Size Considerations

The primary purpose of the study is to evaluate the safety of a single dose of IHV01 and A244/AHFG with or without ALFQ. Table 3 depicts adverse event rates and associated 95% exact Clopper-Pearson confidence intervals in each potential grouping of interest, given 0, 1, 5, 10, or 15 participants with observed events. If zero events were observed within a single active study group (n=16), the upper limit of a 2-sided exact 95% CI would be 20.6% and true event rates above this could be ruled out at the α=0.025 level.

Table 3: Exact 95% Clopper-Pearson CI for the AE Rate in Each Study Group

Group	Sample Size	Number of Participants with an Event(s) Observed				
		0	1	5	10	15
All Active Groups	64	0% (0%, 5.6%)	1.6% (0%, 8.4%)	7.8% (2.6%, 17.3%)	15.6% (7.8%, 26.9%)	23.4% (13.8%, 35.7%)
Fractional Dose (Groups 2+4)	32	0% (0%, 10.9%)	3.1% (0.1%, 16.2%)	15.6% (5.3%, 32.8%)	31.2% (16.1%, 50%)	46.9% (29.1%, 65.3%)
Full Dose (Groups 1+3)						
ALFQ (Groups 3+4)						
No ALFQ (Groups 1+2)						
Any Individual Analysis Group	16	0% (0%, 20.6%)	6.2% (0.2%, 30.2%)	31.2% (11%, 58.7%)	62.5% (35.4%, 84.8%)	93.8% (69.8%, 99.8%)

The assessment of immunogenicity is a secondary objective. Table 4 depicts the minimum detectable differences in standard deviations for a 2-sample t-test of the IgG antibody measures at an alpha of 0.05 for key comparisons of interest. The immunogenicity measures are assumed to be normally distributed after log transformation. For illustration, there would be 80% power to detect a 1.02 standard deviation difference between the mean log IgG titer or mean AUC of individual active groups at the α=0.05 level with a 2-sample t-test. Based on the standard deviations estimated in RV306, the log IgG endpoint titer in Group 1 is likely to have a standard deviation ranging from about 0.5 to 1.0 depending on the time point.

Table 4: Minimal Detectable Differences, in Standard Deviations, for a 2-Sample t-test (2 sided, α=0.05)

Comparison	Sample sizes for comparison groups		Power		
	Group 1	Group 2	80%	85%	90%
All Active vs. Placebo	64	16	0.79	0.85	0.92
Fractional Dose (Groups 2+4) vs. Full Dose (Groups 1+3)	32	32	0.71	0.76	0.82
ALFQ (Groups 3+4) vs. No ALFQ (Groups 1+2)					
Between Individual Analysis Groups	16	16	1.02	1.09	1.18

4.4.2. Allocation of Participants to Study Arms (Randomization)

A randomization schedule will be centrally generated by the protocol statistician. The study will recruit approximately equal numbers of males and females, but formal targets for randomization will not be established. Table 1 shows the planed vaccination group allocation.

Randomization is stratified by clinical site, with a separate list generated for each site. Blocks will be used within each stratum to maintain balance in assignments over time.

Randomized participants who withdraw before receiving study vaccination will be replaced, with the replacement participant receiving the same assignment.

After the protocol amendment to reduce the total sample size, implemented in version 5.0 of the protocol, a new set of assignments was generated for Groups 3 and 4 based on the updated allocation ratios. Randomization into Groups 1 and 2 was stopped prior to the initial target, to approximately maintain these new group sizes.

4.5. Study Products

4.5.1. Study Products Administered

Study products administered include the IHV01 HIV-1 vaccine, the glycoprotein A244, and the ALFQ adjuvant. Saline will be used as placebo for the study.

4.5.2. Identity of Investigational Product(s)

IHV01, an Institute of Human Virology (IHV) product, consists of the FLSC gp120-CD4 chimera subunit HIV-1 vaccine formulated in Aluminum phosphate adjuvant (Alum). The formulation consists of 0.3 mg/mL of FLSC, 2.4 mg/mL of Alum, 5 mM NaOAc, 40 mg/mL mannitol, pH 6.2.

A244, a Duke University product, consists of the gp120 envelope glycoprotein HIV-1 subtype CRF_01AE A244 derived from the CM244 CRF_01AE. The A244 gp120 envelop has an 11-amino N-terminal deletion, similar to the bivalent AIDVAX® B/E protein used in RV144 (Alam, 2013), which has been safely administered to over 9,000 participants. The AHFG adjuvant that is mixed with A244 consists of Rehydragel HPA that has been diluted with sterile water and has an aluminum concentration of 5 ± 1 mg/mL.

ALFQ, a US Army product, is a liposomal adjuvant containing a synthetic monophosphoryl lipid A (3D-PHAD®) with the addition of QS-21.

Saline (sodium chloride for injection USP, 0.9%) will serve as a placebo for the trial.

Refer to Section 7.4 of the protocol for additional information.

4.5.3. Selection of Doses in the Study

Participants will receive a one-time injection of either IHV01 and A244/AHFG (n=64) or saline placebo (n=16) at Day 0. Half of the IHV01 and A244/AHFG recipients will receive the full dose (Groups 1 and 3) of each vaccine while half will receive a fractional dose (Groups 2 and 4) of each vaccine, which is one fifth of the full dose. Groups 3 and 4 will also receive ALFQ.

4.5.4. Selection and Timing of Dose for Each Participant

This is a single-dose study, with participants receiving the assigned study product at Day 0.

4.5.5. Blinding

The PI, study staff, and participants will be blinded as to receipt of active vaccines or placebo but will not be blinded to group allocation as it pertains to the inclusion of ALFQ, due to the planned sequential enrollment. Since the vaccines and placebos are not identical in appearance, to preserve blinding the material inside the syringe will be masked by the pharmacist. In addition, the pharmacy staff preparing the vaccine syringes will not be involved in the clinical assessment of participants and will be instructed not to comment on the appearance of experimental agent to study staff. For all participants, the volume of injection will be consistent.

4.5.6. Prior and Concomitant Therapy

Information pertaining to receipt of non-study vaccines, research agents, immunoglobulin preparations, immunosuppressive medication, antiretroviral drugs, and any blood products will be elicited at study visits and recorded in source documents.

To ensure appropriate medical follow-up for study participants, information regarding concomitant medications used in association with an AE will be collected and recorded in the source documents.

Otherwise, no other concomitant medication information will be collected.

4.5.7. Study Product Compliance

Any randomized participants who withdraw before receiving the study vaccination will be summarized in the participant disposition exhibits and reported in a listing. Those participants will be replaced by others determined to be eligible during screening visits.

4.6. Safety Variables

Safety will be assessed both by direct physical examination and by diary cards (see Appendix O of the protocol), which serve as memory tools for better identification of reactions. During visits on Day 0 (pre- and post-vaccination), Day 1, and Day 7, participants will be assessed for symptoms of local (at the injection site) reactogenicity: erythema, induration, pain/tenderness, swelling and limitation of leg movement, and for symptoms of systemic reactogenicity: fever, tiredness, chills, myalgia, arthralgia, headache, nausea, and rash. After review of the diary card and discussion with the participant, the study staff will document any post-vaccination reaction(s) and all related information (severity, frequency, etc.) concerning such a reaction in the participant's clinic source documents. The frequency and incidence of specific post-vaccination reactions and any reaction will be used for analysis.

AEs and SAEs will be recorded at all visits along with timing and possible attribution to Investigational Product. Because this clinical trial involves an adjuvant, AESIs will also be assessed. As with solicited events, the frequency and incidence of specific post-vaccination reactions and any reaction will be used for analysis.

Safety laboratory analyses of complete blood count, liver function tests, urinalysis, and pregnancy test in females will also be performed according to the SOE. In addition to abnormal findings reported as AEs, changes from baseline will be computed.

Vital signs (body temperature, pulse, respiratory rate, and blood pressure) will be measured both pre- and at about 30 minutes post-vaccination.

4.7. Immunogenicity Variables

Vaccine-induced immune responses will be assessed in study participants as detailed in the SOE.

Humoral responses will be assessed by HIV-specific binding and neutralizing antibody assays at Days 0, 14, 168, and possibly at Day 336. HIV-specific binding antibody responses in the rectal, semen and cervico-vaginal mucosal compartments will be assessed using non-invasive sampling methods (sponge, cup, and masturbation) at Days 0, 14, and 168. Cell-mediated immune responses will be assessed via PBMCs and by utilizing optional invasive sigmoid and lymph node biopsies that will be performed at Day 14, dependent on sample availability. Results of immunology assessments through invasive collection methods in the mucosal compartments are exploratory and will be mostly descriptive as performed in a limited number of participants.

Measurement of CD4+ and CD8+ T-cell effector function will be evaluated through response by cytokines such as IFN-γ and IL2 at Days 0, 14, 168, and possibly at 336. The CD4+ function will also be assessed by the lymphoproliferation responses as measured by the functional CFSE assay at Days 0 and 14. Innate immunity (e.g., NK cells) will be assessed by quantifying ADCC, ADCP and cytokines produced by NK cells at Days 0, 14 and 168, determining innate cells' phenotype and function using various flow cytometric panels at Days 0, 1, 7, and 14, cytokine array assays to characterize the type of cytokines elicited by this vaccine regimen with or without adjuvants, and other related assays. Granulocytes and neutrophils (NET assay) will also be assessed in whole blood at Days 0, 14, and 168.

B-cell responses will be characterized in blood at Days 0, 7, 14, and 168 and in diverse anatomical compartments (provided by sigmoid and lymph nodes biopsies) in a subset of participants, dependent on sample availability.

Leukapheresis will be performed at Day 14 in a subset of willing participants for in-depth investigations of the T-cell responses.

In the context of unknown immune correlates of protection, additional assessments may be performed as new scientific technologies and assessment tools are made available.

4.8. Genomic Variables

Next-generation sequencing methodologies will explore the innate and early adaptive immune responses to vaccination by screening genomic expression profile in PBMCs. Transcriptome data may be generated using RNASeq to investigate gene transcription profile and signature to vaccine antigens in a subset of participants.

Exploratory genomic and transcriptomic analyses will be described in a separate document.

4.9. Other Variables

Age, gender, gender identity, date of birth, level of education, occupation and baseline medical history of participants will be recorded. Participant disposition variables will include the numbers of participants in each group and overall completing visits and study assessments.

Analyses of next-generation sequencing, RNA sequencing, proteome and microbiome analyses will be conducted separately.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. General Principles

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data listings will be sorted by site, vaccination group and participant, and when appropriate by visit number within participant. All summary tables will be structured with a column for each vaccination group in the order presented in the protocol and will be annotated with the total population size relevant to that table/vaccination group, including any missing observations.

5.2. Timing of Analyses

The final study report will be completed when all primary objective data and secondary immunogenicity endpoint data are available. Additional exploratory immunogenicity analyses may be presented in separate reports and/or manuscripts, depending on data availability.

Interim immunogenicity analyses may be performed while the study is ongoing, but the results of any such analyses will not impact the conduct of the trial. Those analyses would follow the principles outlined in this SAP and would align with those conducted as part of the final study report.

5.3. Analysis Populations

A tabular listing of all participants, visits, and observations excluded from the analysis populations will be provided in the final report.

5.3.1. Safety Population

All participants who received the active vaccination or placebo, and for whom any post-dose data is available, will be included in the safety population.

5.3.2. Immunogenicity Population

The immunogenicity population will consist of all eligible participants who received the vaccination or placebo and have at least one measured post dose blood sample collected.

5.4. Covariates and Subgroups

Gender is a key covariate of interest. While the study is not specifically powered to detect gender differences, some safety and immunogenicity analyses will also be described by gender to evaluate potential gender-specific differences.

RV306 vaccination regimen and time from final RV306 study vaccination to RV546 study vaccination will be assessed in exploratory immunogenicity analyses.

5.5. Missing Data

All attempts will be made to collect all data per protocol. No imputation will be performed for missing values. Outliers will not be excluded from the primary analyses but will be discussed in the analysis report. The number of non-missing values in each group will be described for all analyses.

5.6. Interim Analyses and Data Monitoring

While no formal analyses are planned, interim immunogenicity analyses may be performed while the study is ongoing, but the results of any such analyses will not impact the conduct of the trial. These analyses would follow the principles outlined in this SAP and would align with those conducted as part of the final study report. The interim data would be assigned a blinded unique identifier separate from participant ID to ensure maintenance of blinding.

Any analyses conducted prior to the end of the scheduled follow-up visits will not compromise the integrity of the trial in terms of participant retention or safety or immunogenicity endpoint assessments.

5.7. Multicenter Studies

Data will be pooled across both clinical sites. Center effects are not anticipated because the sites are using standardized procedures for vaccination and assessment of solicited and unsolicited adverse events, and the study relies on central laboratories for the assessments of clinical laboratory endpoints and individual immunogenicity endpoints. Baseline characteristics will be presented by site, to assess the balance of any possible confounders between sites.

5.8. Multiple Comparisons/Multiplicity

For comparisons of safety outcomes, 5%-level two-sided tests will be made. Some of these may be implicit comparisons based on the overlap of group-level confidence intervals (i.e. non-overlapping 95% CIs mean rejecting the null hypothesis of no difference between groups at the 0.05-level).

To compare primary immunogenicity outcomes (antigen-specific plasma IgG binding responses, as measured by log AUC over time) across all groups, 5%-level two-sided tests will be used. When differences are found, pairwise comparisons between vaccination groups will be made using the Bonferroni-Holm step-down procedure [1] and a 5% significance threshold for the adjusted p-values; if no difference is found across all groups, no pairwise comparisons will be made. Collapsed comparisons will be considered separately and will be made with 2.5%-level two-sided tests, even when no pairwise differences are observed.

Further exploratory comparisons for immunogenicity endpoints across all groups will be adjusted for multiplicity by a Bonferroni adjustment: multiplying p-values by the number of assays in the same set (e.g. across antigens for a given antibody test; see Section 3.2.2 for sets of assays). Then a similar process as above will be followed, with pairwise comparisons following a significant overall test and Bonferroni-Holm step-down procedure (with a 5% significance level) to account for the multiple pairwise tests.

These adjustments are intended to improve control of the type-I error across comparisons for the same outcome measure and time point (e.g. Geometric Mean Titers (GMTs) for gp120A244 plasma IgG binding at Day 14) rather than across outcome measures and/or time. This level of type-I error control will still allow for exploratory findings that would be assessed further in future studies.

6. STUDY PARTICIPANTS

6.1. Demographic and Other Baseline Characteristics

Participant demographics and baseline characteristics, listed in Section 4.9, will be summarized by vaccination group, using the statistics described in Section 5.1. Additionally, these will be summarized by clinical site.

6.2. Disposition of Participants

The number of participants who enroll in the trial, and the number and percentage of participants who complete each assessment, will be presented by vaccination group (with pooled placebo recipients). The percentage of participants who withdraw from the trial or discontinue the study drug, and reasons for withdrawal or discontinuation, will be summarized by group and given in a listing. Missed visits and withdrawals due to COVID-19 will be listed, and they will be summarized by group if there are sufficiently many of these. The impact of missing data due to COVID-19 will be discussed in the CSR.

6.3. Prior and Concurrent Medical Conditions

Prior and concurrent medical conditions, collected as part of medical history assessments, will be summarized by vaccination group. Any medical conditions reported subsequent to enrollment that meets study exclusion criteria will be presented in a listing.

6.4. Prior and Concomitant Medications

Any concomitant medications reported subsequent to enrollment that meet study exclusion criteria (see criterion #5) will be presented in a listing.

6.5. Measurements of Study Product Compliance

This is a single-dose study, so dosing non-compliance is not expected to be frequent, but any participants receiving the wrong study vaccination and those that are randomized but not vaccinated will be presented in a listing.

6.6. Protocol Deviations

All major protocol deviations will be summarized by vaccination group and presented in a listing.

7. SAFETY EVALUATION

All summaries and analysis of safety data will be presented for the Safety Population. Safety summaries will be presented by vaccination group. The denominator for the percentages may be based on the number of non-missing observations for an assessment or based on the number of participants in a population. This will be described for each exhibit.

7.1. Primary Safety Analysis

7.1.1. Unsolicited Adverse Events

Unsolicited AEs will be listed and summarized by MedDRA system order class (SOC) and preferred term (PT) for each vaccination group. These will be described overall and within 28 days post-vaccination. A participant will be counted only once per PT per reporting period. SAEs, unexpected AEs, and AESIs will be summarized and listed. The number and percentage of participants reporting each PT, along with the associated 95% exact Clopper-Pearson CI for the underlying probability of the event, will be presented.

The likelihood of reporting AEs, SAEs, and AESIs will be compared between collapsed groups (Groups 1+2 vs. Groups 3+4 to assess ALFQ safety, Groups 1+3 vs. Groups 2+4 to assess vaccine dose) via exact binomial tests. If computational challenges arise, Chi-squared tests may be used instead. Calculated confidence intervals will be used to compare pairs of individual vaccination groups, instead of formal hypothesis testing; when CIs for the same event in two groups do not overlap, this corresponds to a p-value of less than 0.05 for the analogous exact binomial test.

Unsolicited AEs will also be tabulated by investigator-determined relationship to investigational product and severity for each vaccination group.

Incident HIV infections, as diagnosed by the algorithm in Section 11.1.4.4 of the protocol, will be presented in a listing.

7.1.2. Solicited Reactogenicity Events

The occurrence of local and systemic reactogenicity symptoms will be assessed similarly to unsolicited AEs, with the number and proportion of participants experiencing each safety event at any point during the reactogenicity period (first 7 days after vaccination), along with the associated exact 95% CI. Collapsed comparisons will be made as in Section 7.1.1 as well.

7.1.3. Clinical Laboratory Data

Clinical laboratory values, including change from baseline, will be summarized by vaccination group. The values will be graded according to the toxicity scale (see Protocol Appendix B) and, if clinically significant, reported as AEs.

Clinical labs will be presented by visit, grade, and vaccination group. Additionally, descriptive summary statistics (mean, SD, median, minimum, maximum) will be presented for each clinical lab, along with change from baseline summaries. If multiple baseline values are obtained, only the most recent value will be analyzed. For change-from-screening summaries, participants with an undefined change from screening, due to missing data, will be excluded.

Clinical laboratory values will be presented in listings as well.

8. IMMUNOGENICITY EVALUATION

8.1. Primary Immunogenicity Analysis

The primary immunogenicity endpoint is the magnitude of plasma IgG (antigen-specific) responses as measured by the endpoint titer, the same variable assessed in RV306. GMTs will be calculated for each group at each visit and the per-participant peak across all visits, along with 95% CIs (exponentiating the CI limits for the log GMT based on the normal distribution). Hypothesis testing is planned for targeted time points; this will be performed in order to aid in interpretation by helping to determine immune responses for potential further examination in future studies. First, group GMTs will be compared across all vaccination groups via ANOVA (null hypothesis that all groups share the same GMT) at the 5%-level, and if that is found to be significant, pairwise comparisons via 2-sided t-tests and the Bonferroni-Holm step-down procedure will be made and a 1% significance threshold will be applied. The two collapsed comparisons will be via 2-sided t-tests of log-GMTs at the α=0.025-level. If the data appear especially non-normal, nonparametric testing will be considered instead.

The reverse cumulative distribution (RCD) of titers (with endpoint titer on the x-axis and the proportion of participants with at least that titer on the y-axis) at each visit will be shown by vaccination group, separately for each antigen.

Seroconversion or seropositivity post-vaccination will be defined based on criteria given by the performing lab, and the number and percent of participants in each group achieving seroconversion/seropositivity at each visit will be presented along with the associated exact 95% Clopper-Pearson CI. The same group comparisons will be performed, via exact binomial tests and the same handling of significance and multiplicity.

Immune response over time (durability) will be assessed by the positive incremental area under the curve (AUC) based on a graph with log endpoint titer on the y-axis and visit day on the x-axis. For comparability between participants with different numbers of samples (visits) available, these values will be scaled by the week of the last available sample. If no sample is available for visits other than the first and last, no explicit imputation will be done, and the AUC will be calculated based on available samples. Log AUC will be analyzed similarly to the visit-by-visit titers.

The week of peak response will also be described by vaccination group, with no hypothesis testing planned. If, by chance, there are equivalent peak responses at two visits, the first will be considered the peak.

8.2. Additional Immunogenicity Analyses

Further immunogenicity analyses (see Section 3.2.2 for planned sets of assays) will be considered exploratory for testing purposes (see Section 5.8 for how significance and multiplicity will be handled), but they will otherwise follow a similar process as the primary immunogenicity analysis. For assays that are not conducted via titer experiments, the analysis values will be handled as log GMTs are, after appropriate transformation of the data to be

approximately normal when necessary; instead of RCD curves, boxplots will show the assay values for each group, by visit.

The kinetics of log IgG titers over time will be assessed via generalized estimating equations (GEE) models, with the immune response appropriately-transformed to assume normally-distributed error terms and RV546 vaccine dosage, adjuvant, study day, and all 2- and 3-way interactions included as covariates. These covariates will be assessed for significance at the 1%-level, and any findings will be considered hypothesis-generating. An unstructured working covariance matrix will be preferred, but other choices may be necessary due to computational challenges or poor model fit. These details will be described in the final report. Similar models may be fit for other assays, and these would also be considered exploratory.

To assess the relationship between possible confounders and the appropriately-transformed titers at the primary endpoint time point, a linear regression model will be fit as well, adjusting for vaccination group, age, sex, RV306 vaccination group, and time between final RV306 vaccination and RV546 vaccination. Covariates will be assessed for significance at the 1%-level, and again findings will be considered hypothesis-generating. Similar models may be fit for other assays also.

9. REPORTING CONVENTIONS

P-values ≥ 0.001 and ≤ 0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and other statistics will be reported to one decimal place beyond the analysis data. The minimum and maximum will use the same number of decimal places as the analysis data. Proportions will be presented as two decimal places; values greater than zero but less than 0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but less than 1% will be presented as "<1"; values greater than 99% but less than 100% will be reported as ">99%". Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

10. TECHNICAL DETAILS

SAS version 9.4 or above and R version 3.6 or above will be used to generate all tables, figures, and listings. Other software may be used for processing of assays, and further details will be presented in the final report if they are available.

11. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

12. REFERENCES

1. Pitisuttithum, P., Nitayaphan, S., Chariyalertsak, S., Kaewkungwal, J., Dawson, P., Dhitavat, J., ... & Polonis, V. (2020). Late boosting of the RV144 regimen with AIDSVAX B/E and ALVAC-HIV in HIV-uninfected Thai volunteers: a double-blind, randomised controlled trial. The Lancet HIV.
2. Holm, S. (1979). A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*, **6**, 65–70. http://www.jstor.org/stable/4615733

13. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

APPENDICES

APPENDIX 1. TABLE SHELLS

LIST OF TABLES

Table 5: Participant Disposition by Vaccination Group

Participant Disposition	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		Full IHV01/A244 + ALFQ (N=X)		Fractional IHV01/A244 + ALFQ (N=X)		Placebo (N=X)		All Participants (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%
Screened	--	--	--	--	--	--	--	--	--	--	x	--
Enrolled/Randomized	x	100	x	100	x	100	x	100	x	100	x	100
Received Study Vaccination (Visit 1, Day 0)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Visit 2 (Day 1)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Visit 3 (Day 7)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Visit 4 (Day 14)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Visit 5 (Day 168)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed Follow-up (Visit 6, Day 336)	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Completed All Scheduled Blood Draws	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

Note: N = Number of randomized participants

Table 6: Summary of Categorical Demographic and Baseline Characteristics by Site

Variable	Characteristic	[Site 1] (N=X)		[Site 2] (N=X)		All Participants (N=X)		p-value
		n	%	n	%	n	%	
Age	20-29	x	xx	x	xx	x	xx	0.xx
	30-39							-
	40-49							-
	50+							-
Sex	Male							0.xx
	Female							-
Level of Education	Primary school							0.xx
	Secondary school							-
	Vocational							-
	Bachelor degree							-
	Higher than bachelor degree							-
Occupation	No occupation							0.xx
	Student							-
	Government employee							-
	Private sector employee							-
	Merchant/Self-employed							-
	Agriculturist/Farmer							-
	Other							-
Note: N = Number of randomized participants. Exact binomial test used to compare variables between sites.								

Table 7: Summary of Continuous Demographic and Baseline Characteristics by Site

Variable	Statistic	[Site 1] (N=X)	[Site 2] (N=X)	All Participants (N=X)	p-value
Age	Mean	xx	xx	xx	0.xx
	Standard Deviation	xx	xx	xx	-
	Median	xx	xx	xx	-
	Minimum	x	x	x	-
	Maximum	x	x	x	-
BMI	Mean	xx	xx	xx	0.xx
	Standard Deviation	xx	xx	xx	-
	Median	xx	xx	xx	-
	Minimum	x	x	x	-
	Maximum	x	x	x	-
Note: N = Number of randomized participants. t-test used to compare variables between sites.					

Table 8: Summary of Categorical Demographic and Baseline Characteristics by Vaccination Group

Variable	Statistic	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		Full IHV01/A244 + ALFQ (N=X)		Fractional IHV01/A244 + ALFQ (N=X)		Placebo (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Age	20-29	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	30-39												
	40-49												
	50+												
Sex	Male												
	Female												
Level of Education	Primary school												
	Secondary school												
	Vocational												
	Bachelor degree												
	Higher than bachelor degree												
Occupation	No occupation												
	Student												
	Government employee												
	Private sector employee												
	Merchant/Self-employed												
	Agriculturist/Farmer												
	Other												

Note: N = Number of randomized participants

Table 9: Summary of Continuous Demographic and Baseline Characteristics by Vaccination Group

Variable	Characteristic	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		Full IHV01/A244 + ALFQ (N=X)		Fractional IHV01/A244 + ALFQ (N=X)		Placebo (N=X)		All Participants (N=X)	
		n	%	n	%	n	%	n	%	n	%	n	%
Age	Mean	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Standard Deviation												
	Median												
	Minimum												
	Maximum												
BMI	Mean												
	Standard Deviation												
	Median												
	Minimum												
	Maximum												

Note: N = Number of randomized participants

Table 10: Summary of Participants with Pre-Existing Medical Conditions by MedDRA System Organ Class and Vaccination Group

MedDRA System Organ Class	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		Full IHV01/A244 + ALFQ (N=X)		Fractional IHV01/A244 + ALFQ (N=X)		Placebo (N=X)		All Participants (N=X)	
	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 1]	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[SOC 2]												

Note: N = Number of randomized participants; n = Number of participants reporting medical history within the specified SOC. A participant is only counted once per SOC.

Table 11: Distribution of Protocol Deviations by Category, Type, and Vaccination Group

Category	Deviation Type	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		Full IHV01/A244 + ALFQ (N=X)		Fractional IHV01/A244 + ALFQ (N=X)		Placebo (N=X)		All Participants (N=X)	
		No. of Part.	No. of Dev.	No. of Part.	No. of Dev.	No. of Part.	No. of Dev.	No. of Part.	No. of Dev.	No. of Part.	No. of Dev.	No. of Part.	No. of Dev.
Eligibility/enrollment	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Did not meet inclusion criterion	x	x	x	x	x	x	x	x	x	x	x	x
	Met exclusion criterion	x	x	x	x	x	x	x	x	x	x	x	x
	ICF not signed prior to study procedures	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up visit schedule	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Out of window visit	x	x	x	x	x	x	x	x	x	x	x	x
	Missed visit/visit not conducted	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Protocol procedure/assessment	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Incorrect version of ICF signed	x	x	x	x	x	x	x	x	x	x	x	x
	Blood not collected	x	x	x	x	x	x	x	x	x	x	x	x
	Urine not collected	x	x	x	x	x	x	x	x	x	x	x	x
	[Insert other deviation types observed]	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Vaccine administration	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Required procedure done incorrectly	x	x	x	x	x	x	x	x	x	x	x	x
	Study product temperature excursion	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Blinding policy/procedure	Any type	x	x	x	x	x	x	x	x	x	x	x	x
	Study assignment unblinded	x	x	x	x	x	x	x	x	x	x	x	x
	Other	x	x	x	x	x	x	x	x	x	x	x	x
Note: N = Number of participants enrolled													

Note: Example categories and deviation types given

Table 12: DAIDS Table for Grading the Severity of Adverse Events

See: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

SAFETY SUMMARY

Table 13: Overall Summary of Adverse Events

	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		Full IHV01/A244 + ALFQ (N=X)		Fractional IHV01/A244 + ALFQ (N=X)		Placebo (N=X)		All Participants (N=X)	
Participants[a] with	n	%	n	%	n	%	n	%	n	%	n	%
At least one local solicited adverse event	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
Mild (Grade 1)												
Moderate (Grade 2)												
Severe (Grade 3)												
At least one systemic solicited adverse event	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
Mild (Grade 1)												
Moderate (Grade 2)												
Severe (Grade 3)												
At least one unsolicited adverse event	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
At least one related unsolicited adverse event	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
Mild (Grade 1)	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
Moderate (Grade 2)	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
Severe (Grade 3)	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
At least one severe (Grade 3) unsolicited adverse event	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
Related	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
Unrelated	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
At least one adverse event of special interest	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
At least one serious adverse event[b]	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
At least one related, serious adverse event	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
At least one adverse event leading to early termination	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x

N = Number of participants in the Safety Population

[a] Participants are counted once for each category regardless of the number of events.

[b] See listing of Serious Adverse Events

Table 14: Adverse Events Occurring in 5% of Participants in Any Vaccination Group by MedDRA System Organ Class and Preferred Term, and Vaccination Group

MedDRA System Organ Class	MedDRA Preferred Term	Full IHV01/A244 (N=X)			Fractional IHV01/A244 (N=X)			Full IHV01/A244 + ALFQ (N=X)			Fractional IHV01/A244 + ALFQ (N=X)			Placebo (N=X)			All Participants (N=X)		
		n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events																			
All	All	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x
SOC1	PT1	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x
Etc.	Etc.																		
Other (Non-Serious) Adverse Events																			
All	All	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x
SOC1	PT1	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x
Etc	Etc																		
Solicited Adverse Events																			
All	All	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x
SOC1	PT1	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x
Etc	Etc																		
Clinical Laboratory Adverse Events																			
All	All	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x
SOC1	PT1	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x	x	x.x	x
Etc	Etc																		

Note: N = Number of participants in the Safety Population; n = Number of participants reporting event; Events = Total frequency of events reported.

Table 15: Collapsed Comparisons of the Proportion of Participants Experiencing Adverse Events by Event Type

Event Type	Full IHV01/A244 (N=X) n (%)	Fractional IHV01/A244 (N=X) n (%)	p-value[a]	Any ALFQ (N=X) n (%)	No ALFQ (N=X) n (%)	p-value[a] 0.xx
Solicited Adverse Events						
Any Solicited Symptom	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx
Moderate (Grade 2)[b]	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx
Severe (Grade 3)[b]	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx
Any Systemic Symptom	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx
Moderate (Grade 2)[b]	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx
Severe (Grade 3)[b]	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx
Any Local Symptom	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx
Moderate (Grade 2)[b]	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx
Severe (Grade 3)[b]	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx
Unsolicited Adverse Events						
Any Serious Adverse Event	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx
Any Adverse Event of Special Interest	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx
Any Related, Unexpected Adverse Event	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx
Any Unexpected Adverse Event Within 28 Days of Study Vaccination	x (x.x)	x (x.x)	0.xx	x (x.x)	x (x.x)	0.xx

Note: N = Number of participants in the Safety Population; n = Number of participants reporting each symptom

[a]Exact binomial tests used

[b]Maximum severity reported

SOLICITED ADVERSE EVENTS

Table 16: Number and Percentage of Participants Experiencing Solicited Reactogenicity Events with 95% Confidence Intervals, by Event and Vaccination Group

	Full IHV01/A244 (N=X)			Fractional IHV01/A244 (N=X)			Full IHV01/A244 + ALFQ (N=X)			Fractional IHV01/A244 + ALFQ (N=X)			Placebo (N=X)			All Participants (N = X)		
Event	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Reactogenicity	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Any Systemic Reactogenicity	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
[Systemic Event 1]	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
[Systemic Event 2]	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Any Local Reactogenicity	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
[Local Event 1]	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
[Local Event 2]	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Note: N = Number of participants in the Safety Population																		

Tables with similar format:

Table 17: Number and Percentage of Male Participants Experiencing Solicited Reactogenicity Events with 95% Confidence Intervals, by Event and Vaccination Group

Table 18: Number and Percentage of Female Participants Experiencing Solicited Reactogenicity Events with 95% Confidence Intervals, by Event and Vaccination Group

Table 19: Number and Percentage of Participants Experiencing Solicited Reactogenicity Events by Event, Maximum Severity, and Vaccination Group

Event	Severity	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		Full IHV01/A244 + ALFQ (N=X)		Fractional IHV01/A244 + ALFQ (N=X)		Placebo (N=X)	
		n	%	n	%	n	%	n	%	n	%
Any Reactogenicity	None	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Mild	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Moderate	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Severe	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
Systemic Reactogenicity											
Any Systemic Reactogenicity	None	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Mild	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Moderate	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Severe	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[Systemic Event 1]	None	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Mild	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Moderate	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Severe	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[Systemic Event 2]	None	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Mild	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Moderate	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Severe	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
Local Reactogenicity											
Any Local Reactogenicity	None	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Mild	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Moderate	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Severe	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[Local Event 1]	None	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Mild	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Moderate	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Severe	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[Local Event 2]	None	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Mild	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Moderate	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Severe	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x

Note: N = Number of participants in the Safety Population who received the specified dose; n = Number of participants reporting each event; severity is the maximum severity reported post dosing for each participant for each day.

Tables with similar format to Table 19:

Table 20: Number and Percentage of Male Participants Experiencing Solicited Reactogenicity Events by Event, Maximum Severity, and Vaccination Group

Table 21: Number and Percentage of Female Participants Experiencing Solicited Reactogenicity Events by Event, Maximum Severity, and Vaccination Group

UNSOLICITED ADVERSE EVENTS

Table 22: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, and Vaccination Group

MedDRA® System Organ Class	MedDRA® Preferred Term	Full IHV01/A244 (N=X)				Fractional IHV01/A244 (N=X)				Full IHV01/A244 + ALFQ (N=X)				Fractional IHV01/A244 + ALFQ (N=X)				Placebo (N=X)			
		n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events
Serious Adverse Events																					
Any SOC	Any PT	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
[SOC 1]	Any PT	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
	[PT 1]	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
	[PT 2]	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
[SOC 2]	Any PT	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
	[PT 1]	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
	[PT 2]	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
Adverse Events of Special Interest																					
Any SOC	Any PT	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
[SOC 1]	Any PT	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
	[PT 1]	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
	[PT 2]	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
[SOC 2]	Any PT	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
	[PT 1]	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
	[PT 2]	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
Other Non-Serious Unsolicited Adverse Events																					
Any SOC	Any PT	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
[SOC 1]	Any PT	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
	[PT 1]	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
	[PT 2]	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
[SOC 2]	Any PT	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
	[PT 1]	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x
	[PT 2]	x	x.x	x.x, x.x	x	x	x.x	x.x, x.x	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x	x	x.x	xx, xx	x

Note: N = Number of participants in the Safety Population; n = Number of participants reporting each SOC/PT.
A participant is only counted once per PT.

Tables with similar format:

Table 23: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, and Vaccination Group, Male Participants

Table 24: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, and Vaccination Group, Female Participants

Table 25: Number and Percentage of Participants Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Maximum Severity, Relationship, and Vaccination Group

MedDRA® System Organ Class	MedDRA® Preferred Term	Any Incidence		Severity[1]						Relationship to Treatment[2]			
				Mild		Moderate		Severe		Not Related		Related	
		n	%	n	%	n	%	n	%	n	%	n	%
Full IHV01/A244 (N=X)													
Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												
Fractional IHV01/A244 (N=X)													
[repeat for all groups]													

Note: N = Number of participants in the Safety Population.

[1] For severity, a participant is counted once per preferred term and is summarized according to the highest reported severity.

[2] For relationship, a participant is only counted once per preferred term and is summarized according to the closest reported relationship.

Table 26: Number and Percentage of Participants Experiencing Unsolicited Adverse Events Within 28 Days of Study Vaccination, by MedDRA® System Organ Class and Preferred Term, Maximum Severity, Relationship, and Vaccination Group

MedDRA® System Organ Class	MedDRA® Preferred Term	Any Incidence		Severity[1]						Relationship to Treatment[2]			
				Mild		Moderate		Severe		Not Related		Related	
		n	%	n	%	n	%	n	%	n	%	n	%
Full IHV01/A244 (N=X)													
Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												
Fractional IHV01/A244 (N=X)													
[repeat for all groups]													

Note: N = Number of participants in the Safety Population.

[1] For severity, a participant is counted once per preferred term and is summarized according to the highest reported severity.

[2] For relationship, a participant is only counted once per preferred term and is summarized according to the closest reported relationship.

Table 27: Summary of Laboratory Results by Parameter, Maximum Severity, Visit, and Vaccination Group – [Parameter]

Visit	Vaccination Group	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline (Day 0)	Full IHV01/A244	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Fractional IHV01/A244	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Full IHV01/A244 + ALFQ	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Fractional IHV01/A244 + ALFQ	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
[Additional visits]	Full IHV01/A244	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Fractional IHV01/A244	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Full IHV01/A244 + ALFQ	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Fractional IHV01/A244 + ALFQ	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
Max Severity Post Baseline	Full IHV01/A244	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Fractional IHV01/A244	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Full IHV01/A244 + ALFQ	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Fractional IHV01/A244 + ALFQ	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x
	Placebo	x	x	x.x	x	x.x	x	x.x	x	x.x	x	x.x

Note: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments. N = Number of participants in the Safety Population with available samples; n = Number of participants reporting each severity

Table 28: Laboratory Summary Statistics by Visit and Vaccination Group – [Parameter]

Time Point	Vaccination Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline (Day 0)	Full IHV01/A244	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Fractional IHV01/A244	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Full IHV01/A244 + ALFQ	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Fractional IHV01/A244 + ALFQ	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x
[Additional visits]	Full IHV01/A244	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Fractional IHV01/A244	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Full IHV01/A244 + ALFQ	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Fractional IHV01/A244 + ALFQ	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x
[Additional visits, Fold Change from Baseline]	Full IHV01/A244	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Fractional IHV01/A244	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Full IHV01/A244 + ALFQ	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Fractional IHV01/A244 + ALFQ	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x
Note: N = Number of participants in the Safety Population with results available						

IMMUNOGENICITY

Table 29: Durability of Response as Measured by Area Under the Response Curve, by Antigen and Vaccination Group – [Assay name]

Antigen	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		Full IHV01/A244 + ALFQ (N=X)		Fractional IHV01/A244 + ALFQ (N=X)		Placebo (N=X)		p-value[a]
	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)	
gp120 A244gD-D11	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
gp120 MNgD- D11	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
gp70V1V2 92TH023	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
gp70V1V2 Case A2	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
[Additional antigens]											

Note: N = Number of participants in the Immunogenicity Population; n = Number of participants with available analysis values

[a]ANOVA used to compare mean log AUC across all vaccination groups

Table 30: Pairwise Comparisons of Log AUC Between Vaccination Groups by Antigen – [Assay name]

Antigen	Comparison	p-value[a]	Adjusted p-value[b]
gp120A244gD-D11	Full IHV01/A244 vs. Placebo	0.xx	0.xx
	Fractional IHV01/A244 vs. Placebo	0.xx	0.xx
	Full IHV01/A244 + ALFQ vs. Placebo	0.xx	0.xx
	Fractional IHV01/A244 + ALFQ vs. Placebo	0.xx	0.xx
	Full IHV01/A244 vs. Fractional IHV01/A244	0.xx	0.xx
	Full IHV01/A244 vs. Full IHV01/A244 + ALFQ	0.xx	0.xx
	Full IHV01/A244 vs. Fractional IHV01/A244 + ALFQ	0.xx	0.xx
	[Additional pairwise comparisons]	0.xx	0.xx
[Additional antigens]			

[a]Two-sided t-test used to compare log AUC group means

[b]Step-down Bonferroni-Holm procedure used

Table 31: Collapsed Comparisons of Log AUC by Antigen – [Assay name]

Antigen	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		p-value[a]	ALFQ (N=X)		No ALFQ (N=X)		p-value[a]
	n	Mean (95% CI)	n	Mean (95% CI)		n	Mean (95% CI)	n	Mean (95% CI)	
gp120A244gD-D11	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
[Additional antigens]										

Note: N = Number of participants in the Immunogenicity Population; n = Number of participants with available analysis values

[a]Two-sided t-tests used

Table 32: Geometric Mean Titers and Associated 95% CIs by Visit, Antigen, and Vaccination Group – [assay name]

Visit	Antigen	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		Full IHV01/A244 + ALFQ (N=X)		Fractional IHV01/A244 + ALFQ (N=X)		Placebo (N=X)		p-value[a]
		n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)	
Baseline (Day 0)	gp120A244gD-D11	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
	[Additional antigens]	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
		xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
[Additional visits or Peak]		xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx

Note: N = Number of participants in the Immunogenicity Population; n = Number of participants with available samples

[a]ANOVA used to compare log titer group means across all vaccination groups

Note: This will be adapted for assays with continuous analysis values, as appropriate

Table 33: Pairwise Comparisons of Geometric Mean Titers Between Vaccination Groups, by Visit and Antigen – [Assay name]

Visit	Antigen	Comparison	p-value[a]	Adjusted p-value[b]
Visit 2 (Day 1)	gp120A244gD-D11	Full IHV01/A244 vs. Placebo	0.xx	0.xx
		Fractional IHV01/A244 vs. Placebo	0.xx	0.xx
		Full IHV01/A244 + ALFQ vs. Placebo	0.xx	0.xx
		Fractional IHV01/A244 + ALFQ vs. Placebo	0.xx	0.xx
		Full IHV01/A244 vs. Fractional IHV01/A244	0.xx	0.xx
		Full IHV01/A244 vs. Full IHV01/A244 + ALFQ	0.xx	0.xx
		Full IHV01/A244 vs. Fractional IHV01/A244 + ALFQ	0.xx	0.xx
		[Additional pairwise comparisons]	0.xx	0.xx
	[Additional antigens]			
[Additional visits or Peak]				

[a]Two-sided t-test used to compare log titer group means

[b]Step-down Bonferroni-Holm procedure used

Table 34: Collapsed Comparisons of Geometric Mean Titers, by Visit and Antigen – [Assay name]

Visit	Antigen	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		p-value[a]	ALFQ (N=X)		No ALFQ (N=X)		p-value[a]
		n	GMT (95% CI)	n	GMT (95% CI)		n	GMT (95% CI)	n	GMT (95% CI)	
Visit 2 (Day 1)	gp120A244gD-D11	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
	[Additional antigens]										
[Additional visits or Peak]											

Note: N = Number of participants in the Immunogenicity Population; n = Number of participants with available samples

[a]Two-sided t-tests used

Table 35: GEE Model to Evaluate the Longitudinal Immune Response and Relationship with Vaccine Dosage and Adjuvant – [Assay name]

Model Parameter	Value	Parameter Estimate	SE	p-value
Intercept	Intercept	xxx.x	xxx.x	x.xxx
Vaccine Dosage	Fractional Dose (reference)			
	Full Dose	xxx.x	xxx.x	x.xxx
Adjuvant	None (Reference)			
	ALFQ	xxx.x	xxx.x	x.xxx
Study Day	Day 0 (Reference)			
	Day 14	xxx.x	xxx.x	x.xxx
	Day 168	xxx.x	xxx.x	x.xxx
	Day 336	xxx.x	xxx.x	x.xxx
Dosage*Adjuvant Interaction	[All interaction levels]	xxx.x	xxx.x	x.xxx
		xxx.x	xxx.x	x.xxx
Dosage*Study Day Interaction	[All interaction levels]	xxx.x	xxx.x	x.xxx
Adjuvant*Study Day Interaction	[All interaction levels]	xxx.x	xxx.x	x.xxx
Dosage*Adjuvant*Study Day Interaction	[All interaction levels]	xxx.x	xxx.x	x.xxx

Note: N=[XXX] participants in the Immunogenicity Population with results available for at least one post vaccination visit included in the GEE model.

Table 36: Linear Regression Model to Evaluate the Relationship Between the Immune Response and Potential Confounders– [Assay name]

Model Parameter	Value	Parameter Estimate	SE	p-value
Intercept	Intercept	xxx.x	xxx.x	x.xxx
Biological Sex	Male (Reference)			
	Female	xxx.x	xxx.x	x.xxx
Time from Final RV306 Dose to RV546 Dose	Years (Continuous)	xxx.x	xxx.x	x.xxx
RV306 Vaccination Group	Group 2 (Reference)			
	Group 3	xxx.x	xxx.x	x.xxx
	Group 4A	xxx.x	xxx.x	x.xxx
	Group 4B	xxx.x	xxx.x	x.xxx
Vaccination Group	Placebo (Reference)			
	Fractional IHV01/A244	xxx.x	xxx.x	x.xxx
	Full IHV01/A244	xxx.x	xxx.x	x.xxx
	Fractional IHV01/A244 + ALFQ	xxx.x	xxx.x	x.xxx
	Full IHV01/A244 + ALFQ	xxx.x	xxx.x	x.xxx
Note: N=[XXX] participants in the Immunogenicity Population with results available included in the model.				

Table 37: Seroconversion Percentages by Visit, Antigen, and Vaccination Group – [Assay name]

Visit	Antigen	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		Full IHV01/A244 + ALFQ (N=X)		Fractional IHV01/A244 + ALFQ (N=X)		Placebo (N=X)		p-value[a]
		n	Estimate (95% CI)	n	Estimate (95% CI)	n	Estimate (95% CI)	n	Estimate (95% CI)	n	Estimate (95% CI)	
Visit 2 (Day 1)	gp120A244gD-D11	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
	[Additional antigens]	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
[Additional visits]		xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
		xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx

Note: N = Number of participants in the Immunogenicity Population; n = Number of participants with available samples

[a]Exact binomial tests used to compare proportions across all vaccination groups

Table 38: Pairwise Comparisons of Seroconversion Percentages Between Vaccination Groups, by Visit and Antigen – [Assay name]

Visit	Antigen	Comparison	p-value[a]	Adjusted p-value[b]
Baseline (Day 1)	gp120A244gD-D11	Full IHV01/A244 vs. Placebo	0.xx	0.xx
		Fractional IHV01/A244 vs. Placebo	0.xx	0.xx
		Full IHV01/A244 + ALFQ vs. Placebo	0.xx	0.xx
		Fractional IHV01/A244 + ALFQ vs. Placebo	0.xx	0.xx
		Full IHV01/A244 vs. Fractional IHV01/A244	0.xx	0.xx
		Full IHV01/A244 vs. Full IHV01/A244 + ALFQ	0.xx	0.xx
		Full IHV01/A244 vs. Fractional IHV01/A244 + ALFQ	0.xx	0.xx
		[Additional pairwise comparisons]	0.xx	0.xx
	[Additional antigens]			
[Additional visits]				

[a]Exact binomial test used to compare seroconversion

[b]Step-down Bonferroni-Holm procedure used

Table 39: Collapsed Comparisons of Seroconversion Percentages, by Visit and Antigen – [Assay name]

Visit	Antigen	Full IHV01/A244 (N=X)		Fractional IHV01/A244 (N=X)		p-value[a]	ALFQ (N=X)		No ALFQ (N=X)		p-value[a]
		n	Seroconversion % (95% CI)	n	Seroconversion % (95% CI)		n	Seroconversion % (95% CI)	n	Seroconversion % (95% CI)	
Visit 2 (Day 1)	gp120A244gD-D11	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx	xx	xx.x (xx.x, xx.x)	xx	xx.x (xx.x, xx.x)	0.xx
	[Additional antigens]										
[Additional visits]											

Note: N = Number of participants in the Immunogenicity Population; n = Number of participants with available samples

[a] Exact binomial tests used

Table 40: Summary of Peak Week of Response, by Antigen and Vaccination Group – [Assay name]

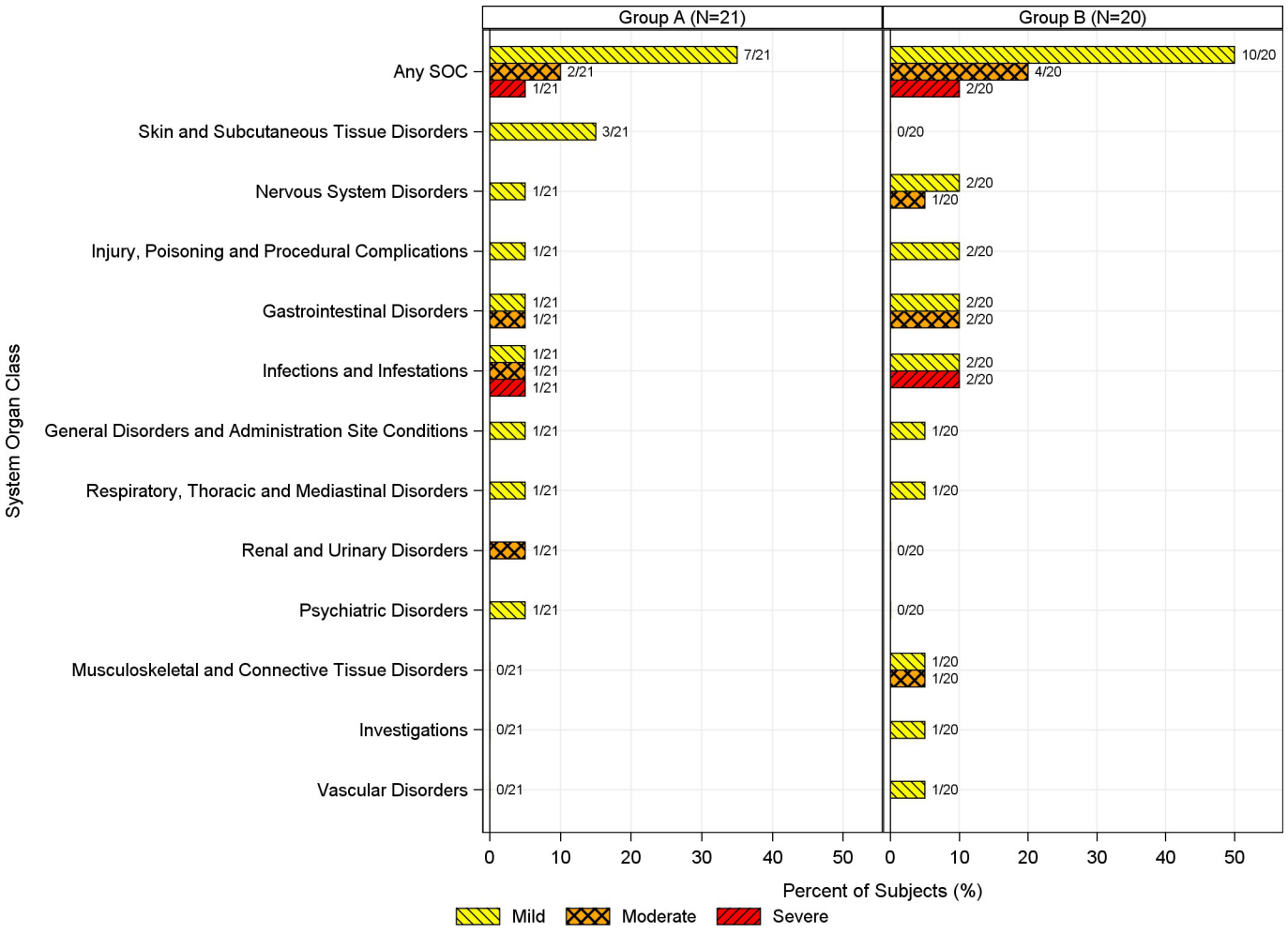
Vaccination Group	N	Mean	Standard Deviation	Median	Min, Max
Full IHV01/A244	x	xx.x	xx.x	xx.x	xx.x, xx.x
Fractional IHV01/A244	x	xx.x	xx.x	xx.x	xx.x, xx.x
Full IHV01/A244 + ALFQ	x	xx.x	xx.x	xx.x	xx.x, xx.x
Fractional IHV01/A244 + ALFQ	x	xx.x	xx.x	xx.x	xx.x, xx.x
Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x
Note: N = Number of participants in the Immunogenicity Population					

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

Figure 2: CONSORT Flow Diagram

Figure 3: Maximum Severity of Solicited Systemic Reactogenicity Events per Participant Over the Reactogenicity Period, by Vaccination Group



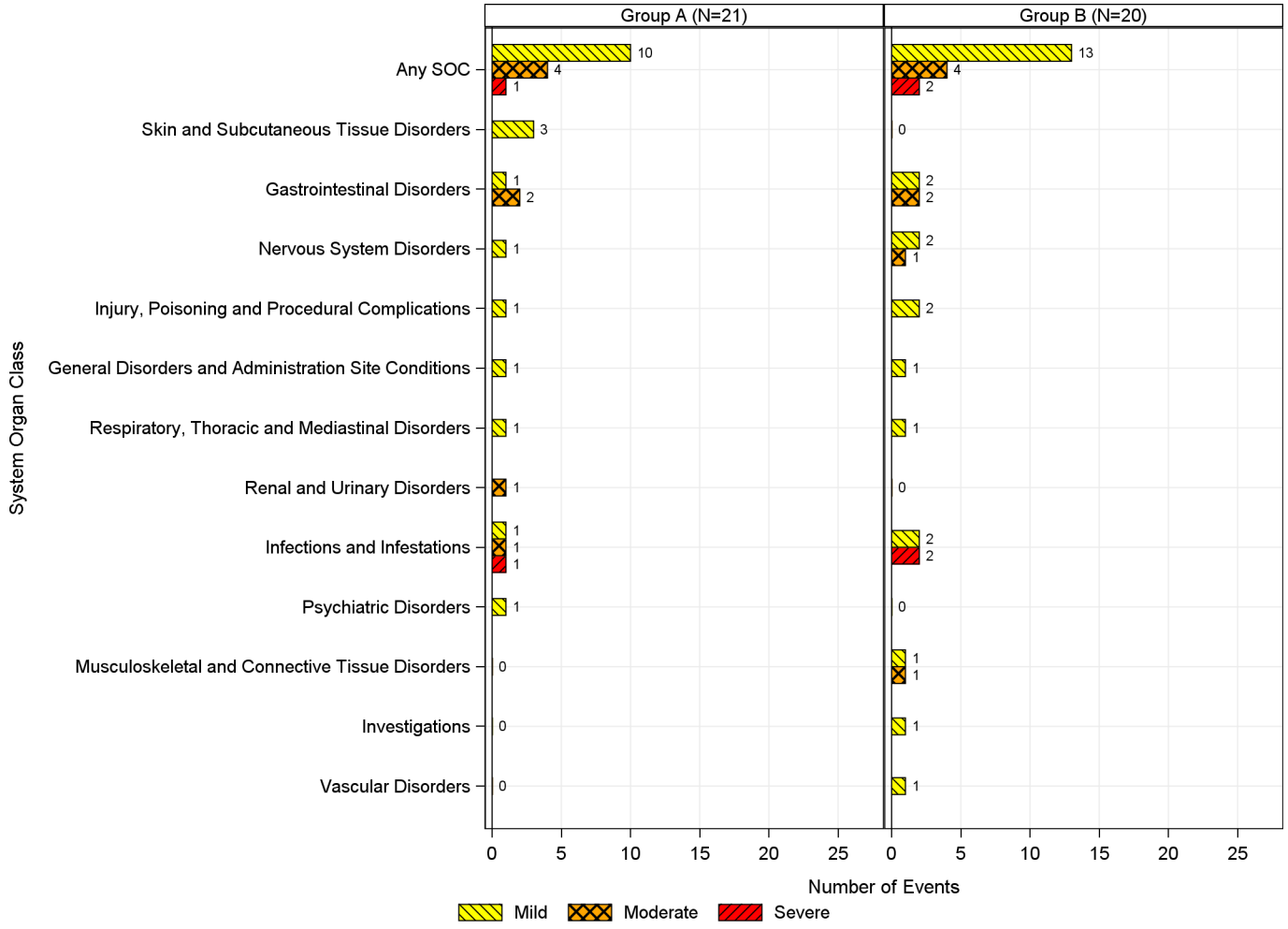
Note: This is an example figure. Vaccination groups will be in separate panels, each systemic event and Any Systemic Reactogenicity will be on the y-axis, and the percent of participants reporting each maximum severity over the entire reactogenicity period will be on the x-axis.

Figures with similar format:

Figure 4: Maximum Severity of Solicited Local Symptoms per Participant Over the Reactogenicity Period by Vaccination Group

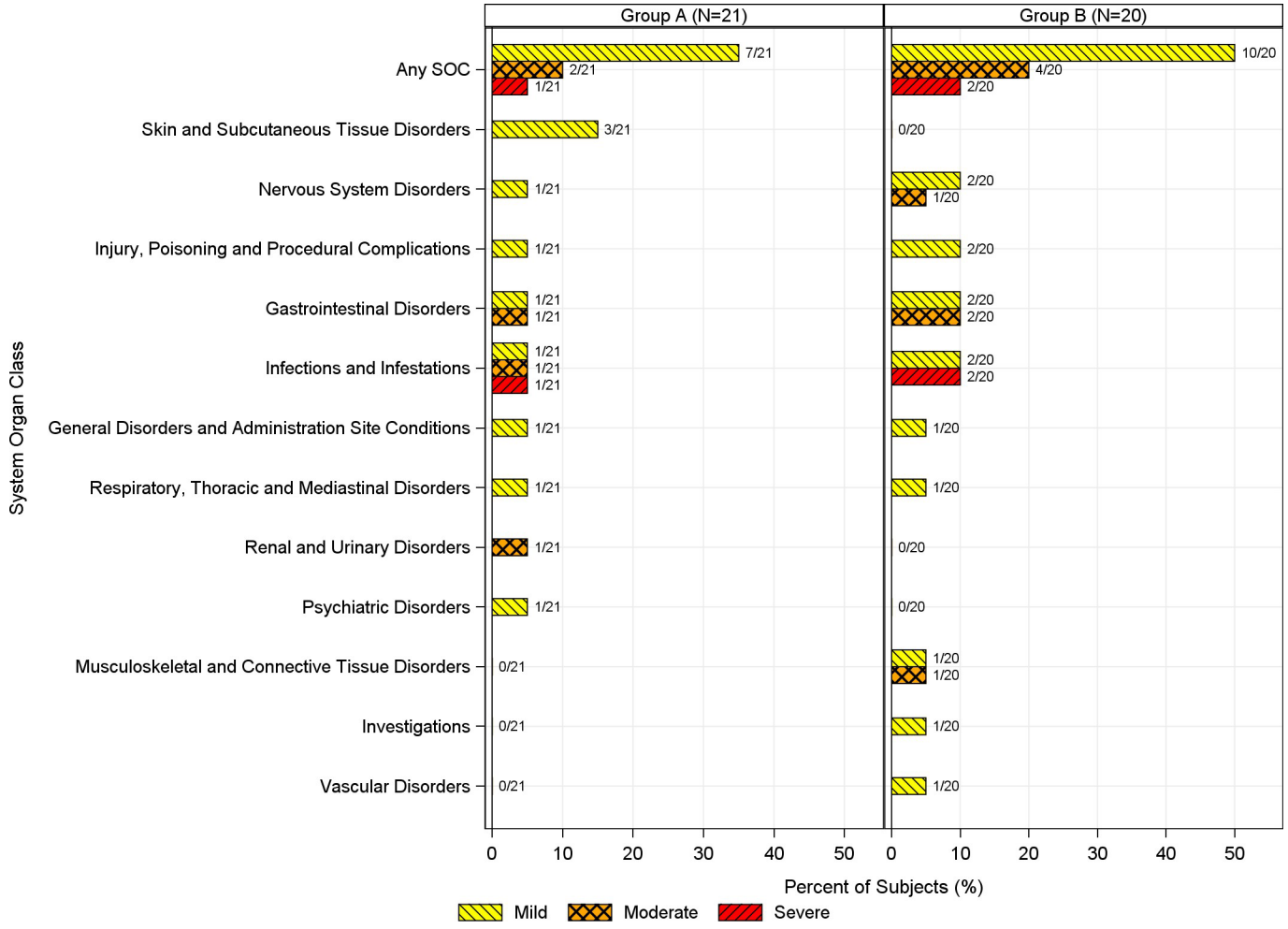
Note: Vaccination groups will be in separate panels, each local symptom and Any Local Symptom will be on the y-axis, and the percent of participants reporting each maximum severity over the entire reactogenicity period will be on the x-axis.

Figure 5: Frequency of Related Unsolicited Adverse Events by MedDRA® System Organ Class and Vaccination Group



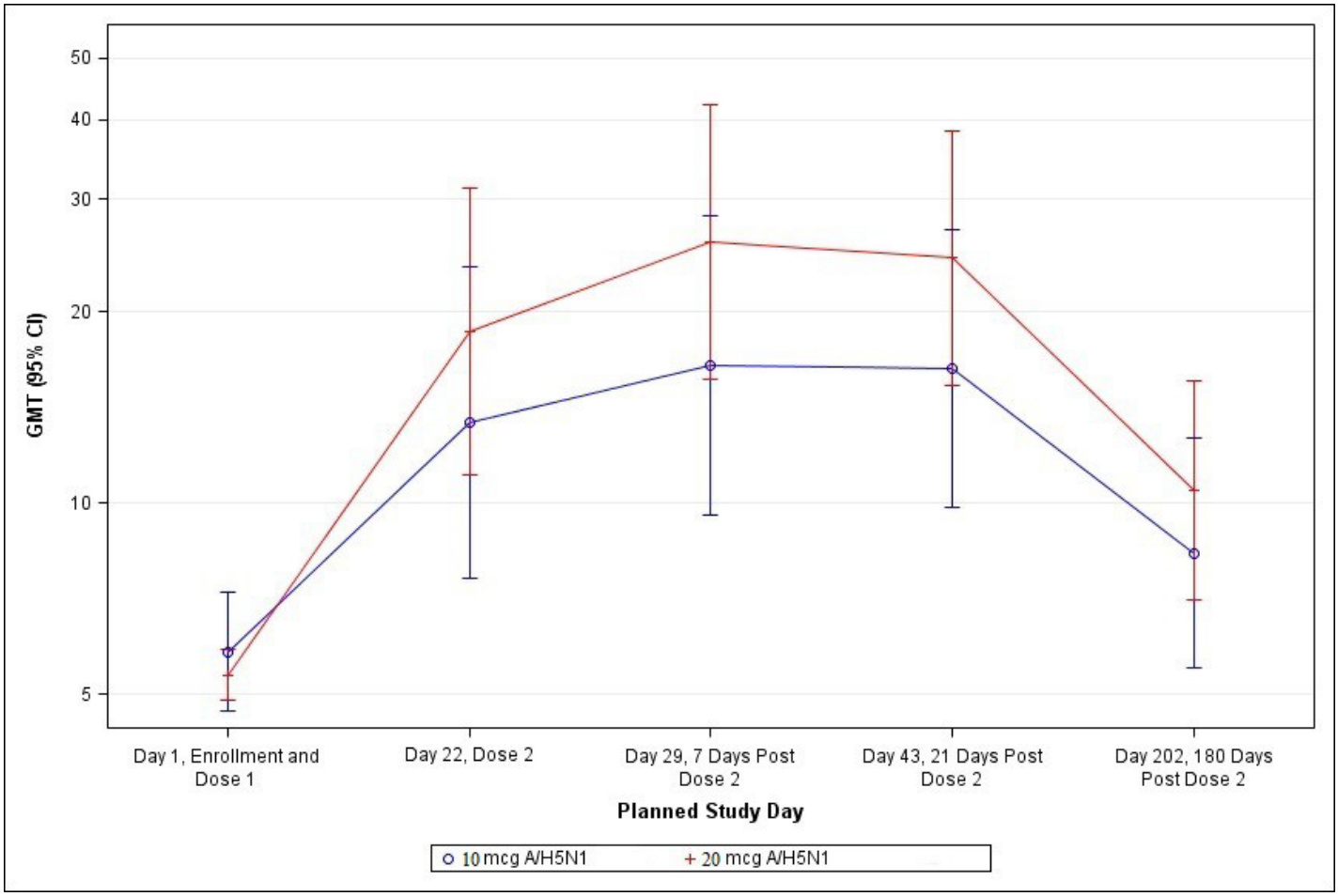
Note: Vaccination groups will be in separate panels, each SOC and Any SOC will be on the y-axis, and the total number of events of each severity will be on the x-axis.

Figure 6: Incidence of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity



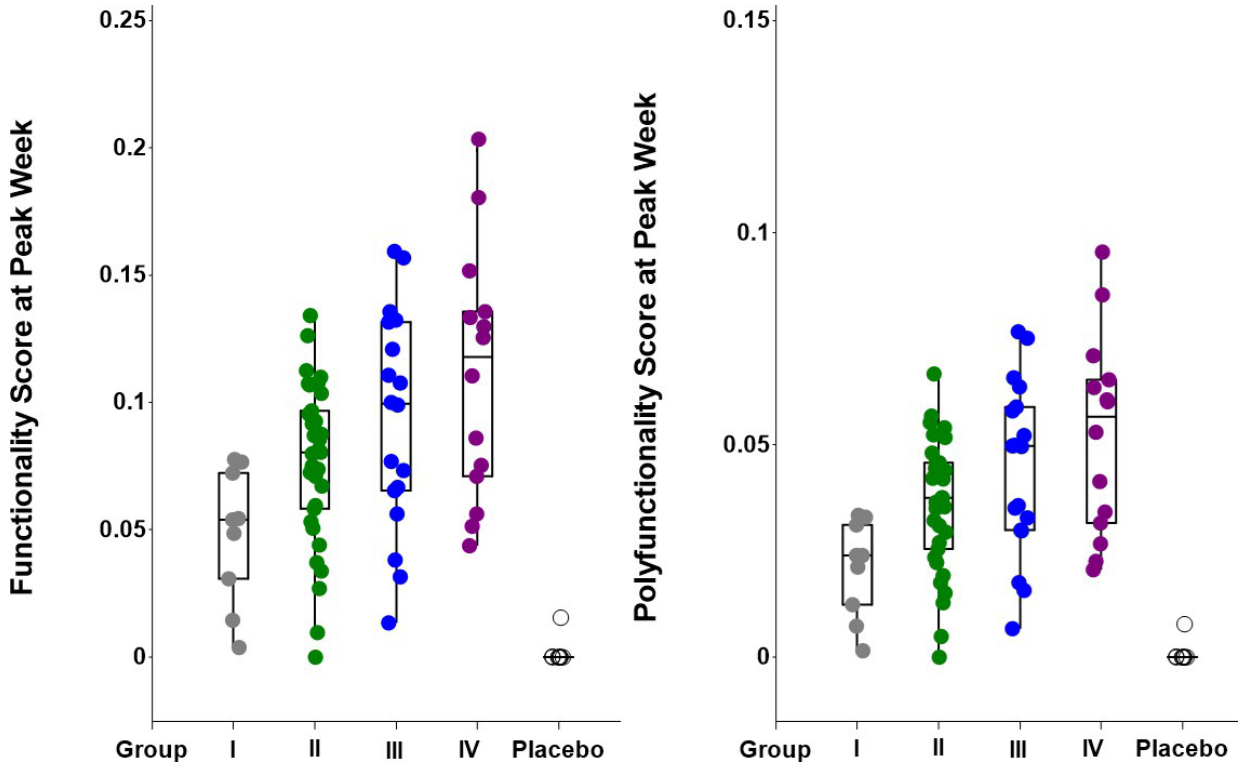
Note: Vaccination groups will be in separate panels, each SOC and Any SOC will be on the y-axis, and the percent of participants reporting each maximum severity will be on the x-axis.

Figure 7: Geometric Mean Titer and 95% CI for [specify assay] by Study Day and Vaccination Group



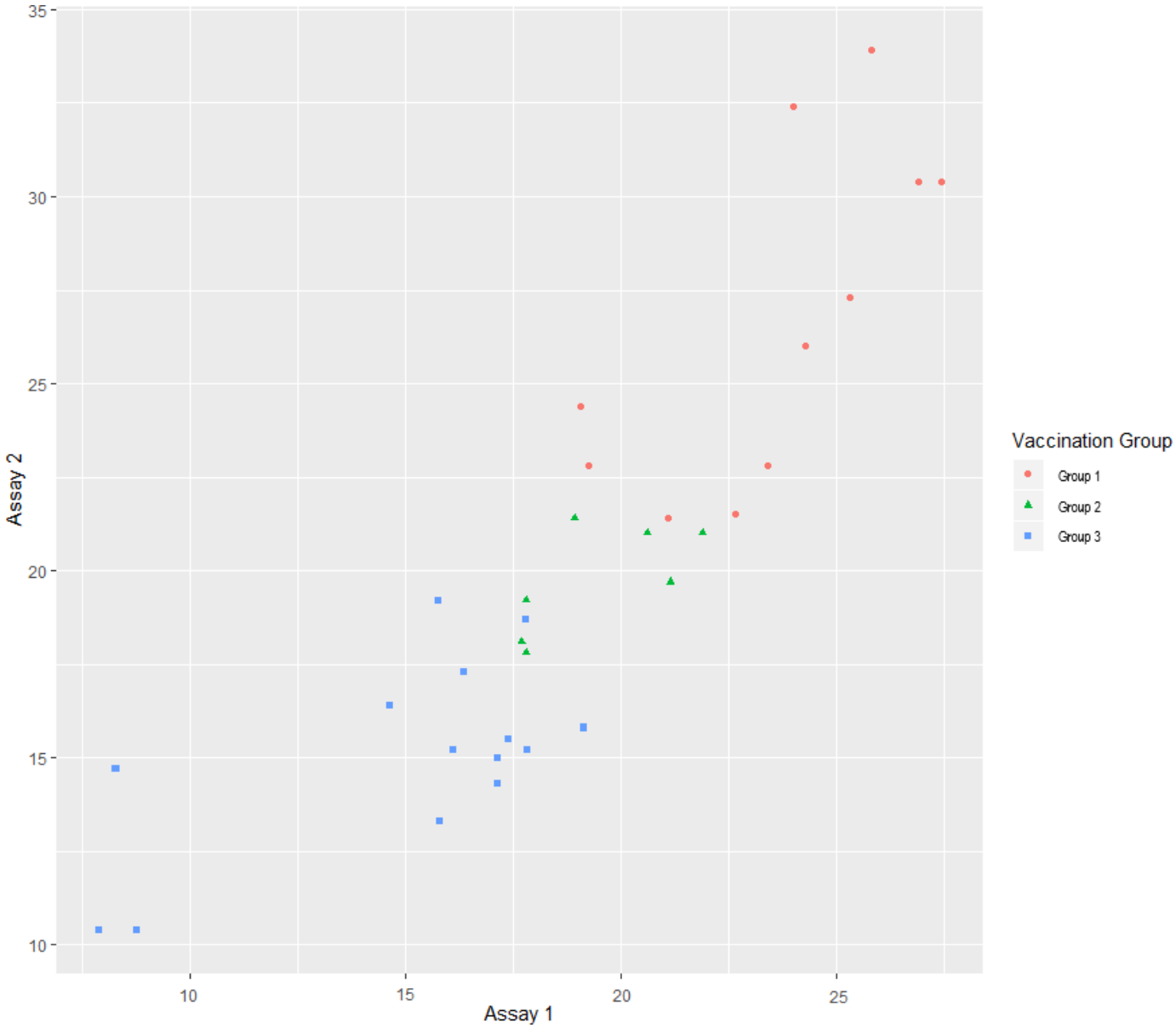
Note: This is an example figure. GMTs and associated 95% CIs are shown on the y-axis and Study Day is shown on the x-axis, with colors and line shapes denoting vaccination group. Similar figures may be generated for collapsed comparisons of ALFQ vs. non-ALFQ groups and fractional vs. full dosing groups. Figures of this type will be presented for titer values. For assays with continuous analysis values, analogous figures will show mean values and associated CIs on the y-axis instead.

Figure 8: Boxplots of [Assay Name] by Vaccination Group



Note: This is an example figure. Visits will be shown in separate panels, where applicable, with separate panels for each visit. Analysis values on the y-axis and vaccination groups along the x-axis. Similar figures may be generated for collapsed comparisons of ALFQ vs. non-ALFQ groups and fractional vs. full dosing groups.

Figure 9: Correlation of Peak [Assay Name] Response with Peak [Assay Name] Response by Vaccination Group



Note: This is an example figure. Groups will be in different shapes and colors, and the Spearman rank-order correlation estimates will be presented for each group in the legend.

APPENDIX 3. LISTINGS

LIST OF LISTINGS

Listing 1: Participants Receiving Study Vaccination

Subject Number	Date of Study Vaccine Administration	Study Group	Injection Site (Left Arm/Right Arm)

Listing 2: Discontinuations and Early Terminations

Subject Number	Study Day of Discontinuation	Reason for Discontinuation	If Due to AE, AE Number	Terminated from Study?

Listing 3: Participants Not Receiving Assigned Study Vaccination

Subject Number	Date of Enrollment	Assigned Study Group	Reason for Termination

Listing 4: Protocol Deviations

Subject Number	Study Group	Deviation Number	Deviation	Study Day
[N/A if screening failure]				

Listing 5: Prior and/or Concurrent Medical Conditions Meeting Exclusion Criteria

Subject Number	Study Group	Exclusion Criterion	Study Day Criterion Met	MedDRA System Organ Class	MedDRA Preferred Term
	[N/A if screening failure]		[N/A if screening failure]		

Listing 6: Prior and Concomitant Medications Meeting Exclusion Criteria

Subject Number	Study Group	Exclusion Criteria	Study Day Criterion(a) Met	Medication Name
	[N/A if screening failure]		[N/A if screening failure]	

Listing 7: Analysis Populations

Subject Number	Study Group	Analysis Population Inclusions	Analysis Population Exclusions (Study Day)

Listing 8: Incident HIV Infections

Subject Number	Study Group	Study Day of Reported HIV Infection	Comments

Listing 9: Serious Adverse Events

Subject Number	Study Group	Adverse Event Number	Adverse Event	Study Day Reported	Duration	Number of Days Post-Vaccination the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Vaccination	If Not Related, Alternate Etiology	Study Vaccine Change	Resolution	Comments

Listing 10: Non-Serious, Related Unsolicited Adverse Events

Subject Number	Study Group	Adverse Event Number	Adverse Event	Study Day Reported	Duration	Severity	Relationship to Study Vaccine	Study Vaccine Change	Resolution	Comments

Listing 11: Clinical Laboratory Values

Subject Number	Study Group	Visit	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High
						[Units may be +/- or N/A for some lab tests]			

Listing 12: Pregnancies

Subject Number	Study Group	Pregnancy Outcome	Date of Delivery	Date of Termination	If Terminated, Due to a Verified Congenital Anomaly?	Infant Sex	Infant Weight at Birth (g)	Estimated Gestational Age of Infant at Birth (weeks)	Was the Infant Born with Congenital Anomalies?
				[N/A for deliveries]					

Listing 13: Missed Visits, Discontinuations, and Withdrawals Due to COVID-19

Subject Number	Clinical Site	Missed Visits	Reason(s) for Missed Visit (Visit Number)	Participant Discontinued? (Date of Discontinuation)	Reason(s) for Discontinuation	Participant Terminated from Study? (Date of Termination)	Reason(s) for Termination
			e.g. Withdrawn due to positive SARS-CoV-2 test (Visits X, Y)				