Janssen Vaccines & Prevention B.V.*

Clinical Protocol

A Multi-center, Randomized, Double-blind, Placebo-controlled Phase 3 Efficacy Study of a Heterologous Vaccine Regimen of Ad26.Mos4.HIV and Adjuvanted Clade C gp140 and Mosaic gp140 to Prevent HIV-1 Infection Among Cis-gender Men and Transgender Individuals who Have Sex with Cis-gender Men and/or Transgender Individuals

MOSAICO

Protocol VAC89220HPX3002; Phase 3
AMENDMENT 7

JNJ-55471494, JNJ-55471520, JNJ-55471468, JNJ-64219324, JNJ-65184340

* Janssen Vaccines & Prevention B.V. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor of the study. The sponsor is identified on the Contact Information page that accompanies the protocol.

US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).
IND: 016263

EudraCT NUMBER: 2018-003666-13

Additional study numbers: HVTN 706

Status: Approved
Date: 28 February 2023
EDMS number: EDMS-ERI-164221409, 17.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 7	**28 February 2023**
Amendment 6	27 October 2021
Amendment 5	19 May 2021
Amendment 4	10 March 2021
Amendment 3	02 July 2020
Amendment 2	20 June 2019
Amendment 1	09 May 2019
Original Protocol	14 January 2019

Amendment 7 (28 February 2023)

Overall Rationale for the Amendment: Decision has been made to terminate the Mosaico study (VAC89220HPX3002/HVTN 706) prematurely by meeting the stopping rules for non-efficacy. Based on the non-efficacy results of the Mosaico study as well as the outcome of immune correlates analysis in the Imbokodo study (VAC89220HPX2008/HVTN 705), the immunogenicity analyses as specified in the secondary endpoint of the Mosaico study are no longer relevant. The sponsor will continue to evaluate immunogenicity as described under the exploratory endpoints. Additional changes are listed below.

The changes made to the clinical protocol VAC89220HPX3002/HVTN 706 Amendment 7 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS 2.1 Objectives and Endpoints 9.3 Immunogenicity Evaluations	Secondary objective & endpoint related to immunogenicity has been moved to exploratory objectives and endpoints. In addition, the description of the endpoint is more generalized.	Knowledge of previously specified secondary immune outcomes of the vaccine is not critical for understanding the study outcomes.
SYNOPSIS TIME AND EVENTS SCHEDULE 9.1.7 Visits for Participants who Become HIV-1 Infected During the Study 9.3 Immunogenicity Evaluations 11.8 Immunogenicity Analysis	It has been clarified that assays for humoral and cellular responses are no longer required, but that they may be performed, if appropriate. In addition, the option to use alternative assays is included.	Knowledge of the immunogenicity of the vaccine in participants who become HIV-1 infected is not critical for understanding the study outcomes.
SYNOPSIS 11.2 Analysis Populations 11.5.1 Vaccine Efficacy Analysis	Addition of the Modified Intent-to-Treat-3 (mITT-3) population for efficacy analysis, and potentially for immune correlates. The mITT population was specifically removed for the analysis of vaccine immunogenicity and immune correlates.	During the COVID-19 pandemic, many participants received their vaccination out-of-window. The mITT-3 population includes participants in the FAS population who had a negative HIV test 4 weeks post 3rd vaccination visit (ie, at the Month 7 Visit), who received all planned vaccinations at the first three vaccination visits, even if these visits were out-of-window. This population will be an additional population for

Section number and Name	Description of Change	Brief Rationale
		efficacy analysis, and potentially for immune correlates. The mITT population includes participants in the FAS population (having received at least one vaccination) who are HIV-1 negative on the date of first vaccination. Since immune responses are known to increase substantially after multiple vaccinations, it has no added value to use this population for the analysis of immunogenicity and immune correlates.
TIME AND EVENTS SCHEDULE	Clarified that the request for redraw is considered as the initial positive HIV test result.	Changes were made to provide confirmation that for the purposes of the protocol, the request for redraw is considered as the initial positive HIV test. Due to the HIV testing algorithm steps, a scheduled or exposure sample that leads to a request for redraw is very likely to be HIV positive. The request for redraw is what triggers the #.X visit of the time and events schedule for participants who become HIV-1 infected.
9.4 Safety Evaluations	Clarified that sexually transmitted infection (STIs) detected from study samples are considered medically attended adverse events (MAAEs).	The protocol could be interpreted that an STI diagnosed from a study collected sample will not meet criteria for a MAAE. However, even if the STI is diagnosed from a study sample, as soon as any follow-up (discussion or treatment) is performed, the event meets MAAE criteria.

Amendment 6 (27 October 2021)

Overall Rationale for the Amendment: Upon request of CBER, it is specified that a serum sampling for a PF4 antibody ELISA test should be performed in case of a potential AESI of TTS, if possible, and that a test for anti-PF4 will also be performed on a stored pre-vaccination sample, if possible. Additional changes are listed below.

The changes made to the clinical protocol VAC89220HPX3002/HVTN 706 Amendment 6 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
TIME AND EVENTS SCHEDULE 9.4 Safety Evaluations 12.3.4.1 Thrombosis with Thrombocytopenia Syndrome	Specified that a serum sampling for a PF4 antibody ELISA test should be performed in case of a potential AESI of TTS, if possible, and that a	Upon request of CBER

	test for anti-PF4 will also be performed on a stored pre-vaccination sample, if possible.	
ABBREVIATIONS 1.1.2 Background on the Study Vaccines 12.3.4.1 Thrombosis with Thrombocytopenia Syndrome REFERENCES	The qualitative statement of 'very rare' incidences of TTS was replaced by reporting ratios. It was added that cases of venous thrombosis have also occurred at more common sites, eg, lower extremities. Onset of symptoms was changed from 1 to 2 weeks to 1 to 4 weeks, and sometimes even later after vaccination (up to 42 days as per the American Society of Hematology). Added that these events have also occurred in men and in individuals older than 60 years. Changed statement that TTS 'can be fatal' to 'has been fatal in some cases'. Added that participants should also be instructed to report any leg pain, changes in mental status or the occurrence of seizures.	Align wording on TTS with changes in TTS wording in the Ad26.Mos(4).HIV Investigator's Brochure Edition 8 Addendum 1, dated 19 Oct 2021, that were made on request of CBER.
Synopsis 3.1 Overview of Study Design 9.4 Safety Evaluations 12.3.1 All Adverse Events 12.3.4.1 Thrombosis with Thrombocytopenia Syndrome	In the definition of TTS, 'symptomatic thrombocytopenia' was replaced by 'thrombocytopenia'.	For consistency with the definitions of thrombocytopenia of the CDC, Brighton Collaboration and Medicines and Healthcare products Regulatory Agency, which do not include symptomatology, the adjective "symptomatic" is removed.
REFERENCES	The reference to the Brighton Collaboration case definition of thrombotic events and thrombocytopenia was updated.	Update
12.3.4 Adverse Events of Special Interest	Clarified that no specific AESI form is present in the eCRF, but rather is a checkbox to indicate if an AE is a potential AESI.	Clarification
12.3.4.1 Thrombosis with Thrombocytopenia Syndrome	Clarified that TTS is reported using the SAE form and not a separate or different AESI specific form.	Clarification
6 DOSAGE AND ADMINISTRATION 9.1.2 Visit Windows	Clarified that cases of out of window study vaccination due to adhering to the required timeframe between a per protocol allowed COVID-19 vaccination and the study vaccination do not require	Clarification and recommendation

	safety review team approval of whether the participant can still be vaccinated, although cases should still be notified to the sponsor. Added that in case of out of window study vaccinations there should be an interval of at least 28 days between subsequent study vaccinations.	
12.3.3 Pregnancy	Clarified that any postnatal sequelae in an infant will be collected if possible.	Clarification upon ethics committee request.
1.1.2 Background on the Study Vaccines REFERENCES	The background section of the protocol has been updated with a summary of the HPX2008/HVTN 705 results.	Update
TIME AND EVENTS SCHEDULE 9.1.5 Post-vaccination Follow-up Phase 10.2 Discontinuation of Study Vaccination/Withdrawal from the Study	Specified that participants who received the first 3 vaccinations but discontinue study vaccination before receiving the 4th vaccination, should continue with safety, immunogenicity and HIV diagnosis assessments as planned. All other participants who discontinue study vaccination, should continue with safety and HIV diagnosis assessments as planned.	To minimize blood draws and testing for participants not contributing to the per-protocol population to be used for the primary efficacy analysis.
4.3 Prohibitions and Restrictions	Clarified that for surgeries mentioned in exclusion criterion 3, it will be per investigator's judgement whether the surgery would interfere with protocol assessments during the study. The safety review team will be available for consultation, where appropriate.	Clarification

Amendment 5 (19 May 2021)

Overall Rationale for the Amendment: This amendment has been created to provide information and guidance for investigators on signs and symptoms and on medical management should very rare events of thrombosis with thrombocytopenia syndrome (TTS) occur, as observed in another Ad26-based vaccine program (Ad26.COV2.S, COVID-19 vaccine). The Ad26.Mos4.HIV vaccine uses the same Ad26 vector as Ad26.COV2.S, but has different transgene inserts. To date, no cases of TTS have been reported in Janssen's Ad26.Mos4.HIV clinical studies nor in any other Ad26-based non-COVID-19 vaccine programs from Janssen. Nonetheless, TTS will be followed in this protocol as adverse event of special interest (AESI) that needs to be reported to the sponsor within 24 hours of awareness. Additional changes are listed below.

The changes made to the clinical protocol VAC89220HPX3002/HVTN 706 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
Synopsis TIME AND EVENTS SCHEDULE ABBREVIATIONS 1.1.2 Background on the Study Vaccines 1.2.5 Overall Benefit/Risk Assessment 2.1 Objectives and Endpoints 3.1 Overview of Study Design 4.2 Exclusion Criteria 9.1.4 Vaccination 9.1.5 Post-vaccination Follow-up Phase 9.1.7 Visits for Participants who Become HIV-1 Infected During the Study 9.1.8 Early Withdrawal/Exit Visit 9.4 Safety Evaluations 10.2 Discontinuation of Study Vaccination/Withdrawal from the Study 11.6 Safety Analysis 11.6.2 Unsolicited Adverse Events, AESIs, MAAEs and Serious Adverse Events 12 ADVERSE EVENT REPORTING 12.2 Special Reporting Situations 12.3.1 All Adverse Events 12.3.4 Adverse Events of Special Interest REFERENCES Attachment 4: Thrombotic Events to be Reported as Potential AESIs	TTS is to be reported as an AESI, within 24 hours of awareness. A potential TTS/AESI is defined as thrombotic events or symptomatic thrombocytopenia.	Following observation of very rare events of TTS after vaccination with Janssen's Ad26-based COVID-19 vaccine, TTS will be followed as an AESI in this study.
4.2 Exclusion Criteria	Clarification added that exclusion criterion 3 pertains to surgery that is already planned before enrollment	Clarification
17.1 Protocol Clarification Communications	Process for protocol clarification communications added	Alignment with Janssen internal Standard Operation Procedures.
Title page	IND number added	Clarification

Amendment 4 (10 March 2021)

Overall Rationale for the Amendment: This amendment is written to specify that it is allowed for study participants to receive a COVID-19 vaccine that has been either licensed or authorized for emergency use (eg, through Emergency Use Authorization [EUA], Emergency Use Listing [EUL] procedure or similar program) and to still enroll or continue in the current study. The time intervals that should be respected between COVID-19 vaccination and study vaccination are specified. Additional changes are listed below.

The changes made to the clinical protocol VAC89220HPX3002/HVTN 706 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
ABBREVIATIONS 4.2 Exclusion Criteria 8 PRESTUDY AND CONCOMITANT THERAPY	Exclusion criteria 5 and 8 have been modified to make clear that authorized COVID-19 vaccinations are allowed in the study. The time interval that should be respected between study vaccination and COVID-19 vaccination is specified.	To allow participants to receive a COVID-19 vaccine that has been either licensed or authorized for emergency use (eg, EUA, EUL or similar program)
TIME AND EVENTS SCHEDULE 8 PRESTUDY AND CONCOMITANT THERAPY 9.1.5 Post-vaccination Follow-up Phase 9.1.6 Post-M30 Follow-up Phase 9.1.7 Visits for Participants who Become HIV-1 Infected During the Study 9.1.8 Early Withdrawal/Exit Visit	Added that COVID-19 vaccination is to be recorded as of any time before screening until the end of the study for a participant.	To record COVID-19 vaccination in study participants
9.1.3 Screening Phase (Day -45 to Month 0)	Added that for participants who are rescreened, the STI testing (syphilis, chlamydia and gonorrhea) does not have to be repeated, unless the test was performed more than 3 months prior to the planned first vaccination or unless clinically indicated.	To reduce burden for participants and facilitate entry in this study.
4.1 Inclusion Criteria	Clarified that being negative for HIV infection means having a negative test result for HIV infection.	Based on feedback from investigators, clarification was added that a negative HIV test needs to be available within 28 days before vaccination
TIME AND EVENTS SCHEDULE 9.1.2 Visit Windows	Clarified that the contact between investigator and participant after the last day of the reactogenicity period, can also be done sooner, if indicated. The lower allowed window (- 7 days) is specified.	Text added to Section 9.1.2 for consistency with Time and Events Schedule footnote v. The lower allowed window is specified in both places.
9.4 Safety Evaluations SYNOPSIS 12.3.1 All Adverse Events	The sections describing the collection and recording of AEs has been amended to be aligned with Section 9.1.3.	Changes were originally made in protocol Amendment 3/Italy-specific 1 (on request of AIFA) and now also included in the global protocol amendment.
1.2.4 Potential Risks REFERENCES	Text regarding the hypothesis on the mechanism for possible increase of HIV-1 acquisition risk with an Ad5-vectored vaccine has been updated to include conclusions from article of Curlin et al, 2020, which refute the original hypothesis on activation of vector-specific CD4+ t cells at mucosal surfaces after Ad5 vaccination.	Text updated based on availability of new data.
TIME AND EVENTS SCHEDULE 9.2 Efficacy Evaluations	Added that a local HIV PCR test is allowed in case of recent HIV exposure.	Addition/correction, alignment with SSP.

Amendment 3 (2 July 2020)

Overall Rationale for the Amendment: The amendment is written to address comments from Health Authorities, to allow for clarifications to be added, and for minor inconsistencies and errors to be corrected. An appendix has been included to outline temporary measures while access to the sites is restricted during public health crises such as e.g., COVID-19 outbreak and to provide investigators with flexibility to conduct study assessments while ensuring the safety and well-being of participants and site staff during the pandemic. These measures will not be described in the body of the protocol but rather outlined in Appendix 18.

The changes made to the clinical protocol VAC89220HPX3002/HVTN 706 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
4.1 Inclusion Criteria Attachment 1: Definition of Individual of Childbearing Potential and List of Acceptable Highly Effective Contraceptive Methods	Inclusion criterion 7, specifying contraceptive measures to be taken during the study, has been adjusted. In inclusion criterion 7, it is now indicated that the acceptable effective contraceptive methods are based on the Clinical Trial Facilitation Group guidance and the full list of acceptable contraceptive measures is provided in Attachment.	Changes were made upon request of Health Authorities.
1.2.4 Potential Risks	It has been clarified that for Ad26.Mos.HIV, Ad26.Mos4.HIV, Clade C gp140 and Mosaic gp140, no preclinical developmental or reprotoxicity studies have yet been performed. Also, no clinical studies in pregnant women have been conducted to date. It has been added that the sponsor is planning to conduct a nonclinical reprotoxicity study in parallel with the HPX3002 study.	
SYNOPSIS ABBREVIATIONS 3.2 Study Design Rationale 11.3 Sample Size Determination ~~11.9 Analysis Timepoints~~	The option for a potential interim analysis has been deleted from the protocol. One primary analysis (no interim analysis) with timing dependent on Target Number of Infections (TNI) will be performed as the single pre-specified approach independent from presumptive evidence external to the study.	Changes were made upon request of EMA. EMA did not support the timing of the statistical analysis to be driven by evidence external to the study and recommended to simplify the statistical testing strategy to a case-driven vaccine efficacy trial design.

Section number and Name	Description of Change	Brief Rationale
11.9 Independent Data and Safety Monitoring Board	It has been clarified that the unblinded, closed DSMB report including evaluations of HIV infections will be shared with FDA Center for Biologics Evaluation and Research (CBER)/Office of Vaccines Research and Review (OVRR). To ensure the blinding of the study team, an independent regulatory expert will act as an intermediary between the DSMB and CBER/OVR.	Changes were made upon request of FDA.
TIME AND EVENTS SCHEDULE 9.2 Efficacy Evaluations	To avoid delays in initiation of combined antiretroviral treatment, local HIV PCR testing is allowed only in case of suspected acute HIV infection and when a request for redraw is received from the central laboratory for confirmation of an HIV positive test.	Changes were made to avoid delays in initiation of combined antiretroviral treatment as recommended by universal HIV treatment guidelines
TIME AND EVENTS SCHEDULE 9.1.3 Screening Phase (Day -45 to Month 0)	The term oral swab has been replaced with oropharyngeal swab and it has been clarified that (1) urine sample, (2) rectal swab and (3) oropharyngeal swab are all required. If required by standard local procedure, the collection of a urethral swab will be considered equivalent to a urine sample.	Clarifications with regard to the required tests have been added.
SYNOPSIS TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design 9.1.3 Screening Phase (Day -45 to Month 0) 9.4 Safety Evaluations 12.3.1 All Adverse Events REFERENCES	Clarifications have been added to the sections describing the collection and recording of AEs and medically significant events and the language related to AE collection has been aligned with updated templates and guidance.	Changes were made to align with updated internal templates and guidance documents. In addition, language has been aligned across sections.

Section number and Name	Description of Change	Brief Rationale
4.1 Inclusion Criteria	It has been clarified in inclusion criterion 3 that gender non-conforming individuals could have either receptive or insertive anal and/or vaginal condomless intercourse. In addition, it is added that the potential participants could in the last 6 months, apart from any stimulant, also have used any other drug and/or substance which in the local context may be associated with increased HIV transmission in order to be eligible for the study	Addition of "insertive" anal intercourse allows for inclusion of gender non-conforming individuals with male genitalia. Previously, these individuals could enter the study but only if they consider themselves transgender individuals whereas the very definition of 'gender non-conforming individual' should allow for their entry also per the criterion 3. In addition to stimulants, several other drugs and/or substances could lead to behavior associated with increased risk of HIV. Therefore, the inclusion criterion has been extended to include participants at increased risk of HIV infection due to the use of drugs, other than stimulants and/or substances associated with increased HIV transmission.
1.1.1 Background on the Disease and Treatment	The background section of the protocol has been updated with the recent information on the stop of study HVTN702 due to lack of efficacy of the investigational HIV vaccine.	Recently, study HVTN 702 or Uhambo, a Phase 2b/3 conducted in South Africa was stopped as the vaccine regimen did not demonstrate efficacy. The study evaluated an investigational prime-boost vaccine regimen (ie, ALVAC-HIV [vCP2438] + Bivalent Subtype C gp120/MF59) which is a regimen adapted from the one that was used and demonstrated modest efficacy in an earlier study conducted in Thailand (study RV144). The vaccine regimen was adapted to the HIV subtype Clade C most common in southern Africa.

Section number and Name	Description of Change	Brief Rationale
4.2 Exclusion Criteria	Exclusion criterion 3 has been amended to clarify that the criterion concerns surgery requiring hospitalization and to adjust the time window during which surgery requiring hospitalization (defined as inpatient stay for longer than 24 hours or overnight stay) will lead to exclusion of the potential participant from the study. Potential participants who had surgery requiring hospitalization within 4 weeks before screening, or will not have fully recovered from surgery requiring hospitalization or has surgery requiring hospitalization planned 28 days before or after planned administration of the first or subsequent study vaccination(s) that would interfere with protocol assessments (as per the investigator's judgement and after HPX3002/HVTN 706 safety review team consultation) will be excluded from the study.	Clarifications have been made and the time window during which surgery requiring hospitalization is disallowed has been aligned with internal templates and guidance documents.
16.1 Study-Specific Design Considerations	It is clarified that potential participants, when they complete the test of understanding (TOU), will receive further information and counseling after each missed question, from their first attempt onwards, rather than after each failed attempt.	To increase the likelihood of potential participants passing the TOU, the study-personnel should provide information and counseling after each missed question and not wait until the participant did not achieve the passing score.
TIME AND EVENTS SCHEDULE 9.1.3 Screening Phase (Day -45 to Month 0) 9.1.4 Vaccination 9.1.5 Post-vaccination Follow-up Phase 9.1.6 Post-M30 Follow-up Phase	Collection of gender identity on an annual basis during the conduct of the study has been added to the protocol	Non-collection of gender identity on a regular basis throughout the study could lead to an underestimation of transgender and gender non-conforming participants in the analyses because transition during the study will be missed.
TIME AND EVENTS SCHEDULE 9.1.7 Visits for Participants who Become HIV-1 Infected During the Study	The completion of the social impact questionnaire has been removed from the visit #.X. In addition, for HIV infected participants, if, in the opinion of the investigator/site staff, the completion of the social impact questionnaire during Visit Inf1, Inf2 or the early withdrawal visit can cause undue burden to the participant, it can be omitted.	To decrease the burden on the HIV infected participant, the social impact questionnaire does not need to be completed during the visit #.X and may be omitted during the other visits in case the investigator/site staff is of the opinion that it can cause undue burden to the participant.

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design 18 COVID-19 Appendix: Guidance on Study Conduct During the COVID-19 Pandemic	A COVID-19 Appendix has been added to provide guidance to investigators for managing study-related procedures during the COVID-19 pandemic.	For safety reasons and restrictions applied during the COVID-19 pandemic, participants may not be able to come to the study site for scheduled procedures.
Title page	The Confidentiality Statement was revised and the statement 'CONFIDENTIAL – FOIA Exemptions Apply in U.S. was added to the running footer	Changes were made to comply with an update from Janssen's Legal department.
TIME AND EVENTS SCHEDULE 4.1 Inclusion Criteria 9.1.2 Visit Windows 9.1.3 Screening Phase (Day -45 to Month 0)	Language with regard to the screening HIV test has been aligned across the HPX3002 protocol: the test should be performed within 28 days, ie, negative test ≤28 days, prior to first vaccination.	Inconsistencies and minor errors have been corrected. Minor clarifications have been added.
1.2.4 Potential Risks	It has been clarified that in case any significant new risks are identified, the investigators (and not only the principal investigator as per the HPX3002 protocol amendment 2) and participants will be informed.	
4.1 Inclusion Criteria	Participants of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening. The inclusion criterion 8 has been corrected to reflect this. This correction is in line with the information on pregnancy tests at screening in other sections of the HPX3002 protocol.	
12.1.3 Severity Criteria	The definition of grade 3 (severe) fever has been corrected, ie, ≥39.3 to <40.0°C OR ≥102.7°F to <104.0°F. The '<' was missing in HPX3002 protocol amendment 2.	
SYNOPSIS 3.1 Overview of Study Design 4.2 Exclusion Criteria	The language related to the use of PrEP has been adjusted to more accurately reflect that, once the participant is enrolled in the study and received the first vaccination, the use of PrEP will not lead to exclusion from the study.	
TIME AND EVENTS SCHEDULE 9.1.2 Visit Windows 9.1.6 Post-M30 Follow-up Phase	It has been clarified that the post Month 30 visits, scheduled every 3 months, will be scheduled relative to the Month 30 visit.	

Section number and Name	Description of Change	Brief Rationale
11.3 Sample Size Determination	It is clarified that only if the primary H0 is rejected, VE(7-30 months) will be tested as secondary hypothesis, using a fixed sequence testing strategy, without adjustment for the Type-I error, and using all available durability data between Month 24 and Month 30.	
11.4 Study Monitoring	The abbreviation 'VE' stands for 'vaccine efficacy' but was wrongly defined as 'viral efficacy' in Table 4. This has been corrected.	
6 DOSAGE AND ADMINISTRATION	The text has been reworded to clarify that vaccine administration occurs by IM injection, preferably into the deltoid muscle.	
Attachment 2: Test of Understanding	Questions 6 and 8 in the TOU have been reworded to improve clarity	
ABBREVIATIONS	The abbreviations for the Center for Biologics Evaluation and Research (CBER) and the Office of Vaccines Research and Review (OVRR) have been added.	

Amendment 2 (20 June 2019)

Overall Rationale for the Amendment: The amendment is written to remove questionnaires from the protocol, to allow for clarifications to be added, and for minor inconsistencies and errors to be corrected. The changes made to the clinical protocol VAC89220HPX3002/HVTN 706 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
9.1.4 Vaccination 9.1.5 Post-vaccination Follow-up Phase 9.5 Participant Reported Outcomes 9.5.1 Social Impact Measured Using Questionnaire 9.5.2 Sexual Activity Questionnaire 9.5.4 Other Participant Reported Outcomes ~~Attachment 2: Sexual Activity Questionnaire~~ ~~Attachment 3: Questionnaire on the Use of PrEP~~ ~~Attachment 5: Social Impact Questionnaire~~	Questionnaires unrelated to the in/exclusion criteria, including questions with regard to absenteeism and vaccine acceptance, have been removed from the protocol and will be added to the Study Specific Procedures Binder.	To allow for (local) adaptations to the questionnaires, the sexual activity questionnaire, questionnaire on the use of PrEP and the social impact questionnaire and questions with regard to absenteeism and vaccine acceptance were moved from the protocol to the Study Specific Procedures Binder. The test of understanding is retained in the protocol since it is linked to the inclusion criteria to the study.
TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design 9.1.4 Vaccination	The questionnaire on the use of and adherence (if applicable) to PrEP will be completed at the Day 1 visit.	To allow for accurate collection of information on the participants' prior use of PrEP, it is clarified that each participant will be asked to complete the questionnaire on the use of PrEP on Day 1. The questionnaire has been updated accordingly.

Section number and Name	Description of Change	Brief Rationale
6 DOSAGE AND ADMINISTRATION	The instructions on the drug administration has been clarified to indicate that the deltoid muscle is the preferred administration site and reference to the Study Specific Procedures Binder has been added for instructions in case an alternative site would be needed.	Alternative injection sites may be needed to allow for eg, participants with heavy tattoos to be included in the study.
SYNOPSIS TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design 10 PARTICIPANT COMPLETION/DISCONTINUATION OF STUDY VACCINATION/ WITHDRAWAL FROM THE STUDY	It is clarified that after the end of the study, participants may be offered the possibility to enter a long-term follow-up phase or program.	In order to allow collection of additional durability data, study participants may be offered the possibility to enter a long-term follow-up phase or program.
4.2 Exclusion Criteria	The missing time window during which pregnancy and breast-feeding is not allowed has been added, ie, while enrolled in the study or within **90** days after the last dose of study vaccination	Inconsistencies and minor errors have been corrected. Minor clarifications have been added.
TIME AND EVENTS SCHEDULE	Inconsistencies between the Time and Events Schedule and the body of the protocol with regard to the completion of the questionnaire on the use of and adherence (if applicable) to PrEP at the exit/withdrawal visit has been corrected.	
TIME AND EVENTS SCHEDULE 9.1.5 Post-vaccination Follow-up Phase	Reference to footnote ‘cc’ to the Visit 2a, 3a, 4a and 7a was corrected to footnote ‘v’ which indicates that these are not site visits but contacts between site staff and participants to discuss presence of any signs and symptoms of reactogenicity.	
TIME AND EVENTS SCHEDULE	Inconsistencies in the use of ‘early withdrawal/exit’ versus ‘exit’ visit was corrected.	
TIME AND EVENTS SCHEDULE 9.1.5 Post-vaccination Follow-up Phase	Inconsistencies between the Time and Events Schedule and the body of the protocol with regard to the collection of unsolicited AEs has been corrected.	
SYNOPSIS 3.1 Overview of Study Design	It is clarified that once participants received the first vaccination, in the event they change their minds, they will be allowed to start PrEP according to the site PrEP plan.	

Amendment 1 (09 May 2019)

Overall Rationale for the Amendment: The amendment is written in response to the feedback received from Health Authorities, partners and the community. The changes made to the clinical protocol VAC89220HPX3002/HVTN 706 are listed below, including the rationale of each change and a list of all applicable sections.

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS TIME AND EVENTS SCHEDULE 1.2.5 Overall Benefit/Risk Assessment 2.1 Objectives and Endpoints 3.1 Overview of Study Design 9.1.1 Overview 9.1.4 Vaccination 9.4 Safety Evaluations 11.3 Sample Size Determination 11.6.2 Unsolicited Adverse Events, MAAEs and Serious Adverse Events 12 ADVERSE EVENT REPORTING 12.3.1 All Adverse Events	Solicited signs and symptoms will be entered in a diary for 7 days after each vaccination by all participants instead of a subset of participants at selected sites. Solicited adverse events will be recorded for all participants.	The recording of solicited adverse events in all participants was requested by Health Authorities.
ABBREVIATIONS 9.4 Safety Evaluations 12.1.3 Severity Criteria	Tables including severity grading scales for the solicited adverse events have been added to the protocol. In addition, it is clarified that for solicited administration site adverse events an adjusted version of the DAIDS grading table will be used while for solicited systemic adverse events the unmodified DAIDS grading table will be used. Also, for the grading of adverse events not identified in the table the general DAIDS grading will be used. Finally, it is clarified that the DAIDS addenda grading tables for microbicides studies will be used for the grading of genito-urinary disorders, sexually transmitted infections (STIs), uterine bleeding and pregnancy complications although this is not a microbicide study.	The severity grading scales have been added upon request from the Health Authorities.

Section number and Name	Description of Change	Brief Rationale
TIME AND EVENTS SCHEDULE 9.1.1 Overview 9.1.2 Visit Windows 9.1.4 Vaccination 9.1.5 Post-vaccination Follow-up Phase 9.4 Safety Evaluations	The post-reactogenicity contact between the site staff and participants has been added as separate visits in the Time and Events Schedule and additional detail was added. The site staff and the participant will make multiple efforts in good faith to be in contact after the last day of the reactogenicity period, or sooner if indicated, to review reactogenicity data. Participants who self-report any postvaccination reaction greater than mild is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has resolved completely. Participants should bring their diary to the site at the next visit to complete review of the diary and document solicited adverse events into the clinic note and subsequently into the eCRF.	Given the diary will be used as a source document for the recording of solicited AEs, it is of the utmost importance that the information included is as accurate and detailed as possible. Therefore, the contact with the site following the reactogenicity period has been more clearly defined in the protocol. Follow-up of diary entries close to the diary completion date, will allow for accurate corrections of and additions to the diary. In addition, during these contacts the participant may receive further instructions/education on how to complete the diary. The contact will also allow for close follow-up of safety and scheduling of additional safety follow-up visits, as needed.
SYNOPSIS TIME AND EVENTS SCHEDULE ABBREVIATIONS 2.1 Objectives and Endpoints 3.1 Overview of Study Design 9.1.4 Vaccination 9.1.5 Post-vaccination Follow-up Phase 9.1.6 Post-M30 Follow-up Phase 9.1.7 Visits for Participants who Become HIV-1 Infected During the Study 9.1.8 Early Withdrawal/Exit Visit 9.4 Safety Evaluations 11.6.2 Unsolicited Adverse Events, MAAEs and Serious Adverse Events 12 ADVERSE EVENT REPORTING 12.3.1 All Adverse Events	Medically-attended adverse events (MAAEs) will be recorded from signing of the ICF onwards until the end of the study.	In line with the Guidance for Industry – Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review[a] and upon request of the Health Authorities, the recording of MAAEs is added to the protocol. Recording of MAAEs will allow collection of potential immune-mediated medical conditions (PIMMCs) and new onset of chronic diseases and will allow for a better characterization of the safety profile of VAC89220 overall.

[a] US Food & Drug Administration. Guidance for Industry - Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review – Technical Specifications Document. Available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM605147.pdf. Accessed: 17 April 2019.

Section number and Name	Description of Change	Brief Rationale
ABBREVIATIONS 9.1.3 Screening Phase (Day -45 to Month 0) 9.4 Safety Evaluations 11.1 Participant Information 11.6.2 Unsolicited Adverse Events, MAAEs and Serious Adverse Events	Potentially immune-mediated medical conditions (PIMMCs) reported as MAAEs will be considered events of interest. A list of PIMMCs defined for this study is presented in Attachment 6 of the protocol. In addition, history and family history of immune disorders will be recorded in the eCRF.	Upon request of the Health Authorities, adverse events of special interest for this study are identified in the protocol. No adverse events of special interest were identified based on the nonclinical and clinical data from the vaccine components to date. However, based on regulatory feedback, special attention will be put on PIMMCs that are reported as MAAEs. These events will be collected and analyzed.
12.1.2 Attribution Definitions	The definitions for 'related' and 'unrelated' adverse events have been updated.	To allow for pooling of safety data from the proof-of-concept study HPX2008/HVTN 705 and the current study VAC89220HPX3002/HVTN 706, the definitions of 'related' and 'unrelated' adverse events have been aligned.
SYNOPSIS TIME AND EVENTS SCHEDULE 2.1 Objectives and Endpoints 3.1 Overview of Study Design 9.1.4 Vaccination 9.1.5 Post-vaccination Follow-up Phase 9.1.6 Post-M30 Follow-up Phase 9.1.7 Visits for Participants who Become HIV-1 Infected During the Study 9.1.8 Early Withdrawal/Exit Visit 9.5 Participant Reported Outcomes 9.5.4 Other Participant Reported Outcomes 11.6.4 Other Parameters	In addition to the participant reported outcomes (PRO) questionnaires included in the initial protocol, other PROs, including the level of absenteeism, defined as health-related productivity loss due to sick-leave, and the level of vaccine regimen acceptance have been added to the protocol.	Apart from collecting data on the social impact of the vaccine study, it was considered important to collect additional information on the possible effect of the vaccinations and of HIV-1 infection in terms of work loss and work productivity. In addition, in order to get a better understanding of the acceptance of the 4-vaccination course as a HIV prevention tool, the participants will be asked to rate their experience with the vaccination regimen.
SYNOPSIS TIME AND EVENTS SCHEDULE 2.1 Objectives and Endpoints 3.1 Overview of Study Design 9.1.4 Vaccination 9.1.5 Post-vaccination Follow-up Phase 9.1.6 Post-M30 Follow-up Phase 9.1.7 Visits for Participants who Become HIV-1 Infected During the Study 9.1.8 Early Withdrawal/Exit Visit ~~9.6 Health Care Resource Utilization~~ 11.6.4 Other Parameters 15 STUDY-SPECIFIC MATERIALS	The collection of medical and non-medical resource utilization/Health Care Research Utilization (HCRU) data, as such, was removed from the protocol.	The collection of MAAEs, absenteeism and follow-up information on HIV infected participants throughout the study will provide sufficient information on HCRU without the need for additional questionnaires.

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design 9.1.4 Vaccination 9.1.5 Post-vaccination Follow-up Phase 9.1.8 Early Withdrawal/Exit Visit 9.5 Participant Reported Outcomes 9.5.3 Questionnaire on the Use of PrEP Attachment 3: Questionnaire on the Use of PrEP	The questionnaire on the use of pre-exposure prophylaxis (PrEP) will be completed by all participants instead of the participants who self-report they use PrEP only. The questionnaire has been modified accordingly.	To avoid bias, protocol assessments were aligned for all participants as much as possible.
Attachment 2: Sexual Activity Questionnaire Attachment 3: Questionnaire on the Use of PrEP	The sexual activity questionnaire and the questionnaire on the use of PrEP have been updated.	Questionnaires were updated taking the feedback from partners and the community into consideration.
Attachment 2: Sexual Activity Questionnaire Attachment 3: Questionnaire on the Use of PrEP	It has been added to the protocol that adaptations to the sexual activity questionnaire and the questionnaire on the use of PrEP are allowed for local purposes, after IRB and protocol team (cross-functional) approval.	Given the wide geographical coverage of the study, it may be needed to make minor adaptations to the questionnaires to account for cultural and regulatory differences.
Title Page SYNOPSIS 2.1 Objectives and Endpoints 3.1 Overview of Study Design 4.1 Inclusion Criteria	Inclusion criterion 3 has been modified to include more detail on the target study population. Other sections in the protocol have been adapted accordingly.	In order to better characterize the target study population: - more detail has been added in the inclusion criteria with regard to the population as such, ie, cis-gender men and transgender individuals having sex with cis-gender men and/or transgender individuals and gender non-conforming individuals having receptive anal and/or vaginal condomless intercourse, AND - major criteria to determine if a potential participant is at increased risk for HIV-1 infection has been added to the inclusion criteria.

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design 4.2 Exclusion Criteria 8 PRESTUDY AND CONCOMITANT THERAPY	The exclusion criteria have been modified to exclude potential participants who have used long acting PrEP within 24 months prior to Day 1. In addition, reference to 'oral PrEP' has been replaced by 'PrEP'	Given the availability of long acting PrEP (eg, cabotegravir) which is administered as an intramuscular injection and has a long pharmacokinetic tail, the use of long acting PrEP will be disallowed from 24 months prior to Day 1. As the use of PrEP is allowed once participants received the first vaccination, including injectable long-acting PrEP, if available, reference to 'oral PrEP' has been replaced by 'PrEP'.
4.2 Exclusion Criteria	The exclusion criteria have been modified to exclude potential participants who share needles during injection of drugs and other substances instead of potential participants with active or recent use of any illicit IV drug.	Drug substance use is linked to risky sexual behaviors. Given the target population of men who have sex with men (MSM) and transgender individuals considered at increased risk for HIV-1 infection and the fact that drug use can add to sexual risk behavior, potential participants who use injection drugs will be allowed in the study. Due to the different way of transmission, individuals sharing needles will be excluded from the study.
4.2 Exclusion Criteria	The window during which the use of HIV-related mAb, whether licensed or investigational, is disallowed has been adjusted from within 24 months prior to Day 1 to within 12 months prior to Day 1.	The time window from 24 months to 12 months prior to Day 1 for the use of HIV-related mAb was adjusted based on more accurate estimates of mAb washout times including Fc-modified versions currently in development. The original estimate was too conservative and could exclude participants who have no biologically meaningful level of antibody left.
SYNOPSIS TIME AND EVENTS SCHEDULE 9.1.6 Post-M30 Follow-up Phase 10.1 Completion	The definition of study completion has been updated.	To allow for timely completion of the study, the study will be considered completed once the last participant has completed the Month 30 visit or has discontinued earlier. HIV infected participants still in the study at that time will be

Section number and Name	Description of Change	Brief Rationale
		informed that they should return to the site for the Visit #.X, if not completed yet, but no further site visits will be required.
3.2 Study Design Rationale	The regimen selection rationale has been updated to reflect the most recently available data.	Phase 1/2a data that recently became available strengthen the vaccine regimen selected for the Phase 3 HPX3002 study. The protocol language has been updated accordingly.
TIME AND EVENTS SCHEDULE 9.3 Immunogenicity Evaluations	It is clarified in the protocol that venous blood samples for determination of immune responses from participants who become HIV infected will, depending on the vaccine efficacy outcome, be used for the evaluation of immune markers that have a sieving effect on any breakthrough infections and for the evaluation of any immune markers that are associated with post-infection control of HIV in participants if differences between active and placebo recipients are observed, potentially including immune responses to all vaccine antigens.	In the initial protocol it was indicated that samples for the determination of the immune responses from participants who become HIV infected would be analyzed upon discretion of the study responsible immunologist. The Health Authorities requested clarification on the criteria which will determine the selection of samples for analysis and analyses performed.
SYNOPSIS TIME AND EVENTS SCHEDULE 2.1 Objectives and Endpoints 9.1.1 Overview 9.1.4 Vaccination 9.1.5 Post-vaccination Follow-up Phase 9.1.7 Visits for Participants who Become HIV-1 Infected During the Study 9.3 Immunogenicity Evaluations	It is clarified that venous blood samples for cellular immune response will be collected in participants at sites with access to sponsor approved PBMC processing facilities and will be analyzed in a subset.	To gather as much data as possible, blood samples for cellular immune response will be taken in participants at sites with access to sponsor approved processing facilities and not a subset of participants at all sites or all participants at randomly selected sites.
SYNOPSIS TIME AND EVENTS SCHEDULE 1.2.4 Potential Risks 9.1.4 Vaccination 9.1.7 Visits for Participants who Become HIV-1 Infected During the Study 9.3 Immunogenicity Evaluations	The possibility to perform limited genetic testing has been added to the protocol. For these analyses, leftover blood from samples for determination of cellular response will be used. In addition, a blood sample will be collected from participants who become HIV infected at the Visit #.X.	To allow for the exploration of potential effect of host genetic factors in the immune response to the vaccine regimen and/or vaccine efficacy, the possibility for limited genetic testing has been added to the study protocol.
SYNOPSIS 2.1 Objectives and Endpoints	The analysis of frequency and magnitude of cellular and humoral immune responses in participants that become HIV-1 infected will not be limited to Env-specific responses.	Health Authorities requested to include the possibility of the assessing immune responses to Gag and Pol and not to limit the assessment to Env-specific responses.

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS 9.3 Immunogenicity Evaluations	Ad26 seropositivity and titer will be assessed at Baseline AND post-vaccination.	Upon request from the Health Authorities, assessment of post-vaccination Ad26 seropositivity and titer was added to the protocol.
SYNOPSIS TIME AND EVENTS SCHEDULE 2.1 Objectives and Endpoints 9.1.5 Post-vaccination Follow-up Phase 9.1.8 Early Withdrawal/Exit Visit	Venous blood samples for cellular immune response assays will be collected on Day 1 and Month 7. Blood samples from other time points will only be used to determine humoral immune responses.	To decrease the burden on participants, the time points for venous blood collection to assess cellular immune responses have been limited to Day 1 and Month 7.
SYNOPSIS 2.1 Objectives and Endpoints	The evaluation of vaccine efficacy (VE) by and adjusting for potential (baseline) confounders has been moved from the exploratory objectives to the secondary objectives.	Given the importance of the analysis of the VE by and adjusting for potential confounding factors, it was felt more appropriate to have this as a secondary objective.
TIME AND EVENTS SCHEDULE 8 PRESTUDY AND CONCOMITANT THERAPY 9.1.5 Post-vaccination Follow-up Phase 9.1.6 Post-M30 Follow-up Phase	In addition to the use of PrEP, hormonal therapy and hormone-based contraception, the use of post-exposure prophylaxis (PEP) will also be recorded at Visit 9 to Visit 13 and during the post-M30 follow-up phase.	As the use of PEP could be a potential confounder for VE, it is considered important to record the use of PEP not only during the vaccination period but also during the post-vaccination and post-M30 follow-up phases.

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS 3.1 Overview of Study Design 11.1 Participant Information	Reference to male circumcision as a prevention tool for HIV infection has been deleted from the protocol. Male circumcision will be recorded as part of the demographic data.	There is no unanimous position on the protective effect of male circumcision against HIV infection in the MSM and transgender population[a] and the World Health Organization guidelines[b] do not recommend adult male circumcision as a prevention tool for HIV infection in this population. Therefore, male circumcision will not be recommended to participants as an HIV-1 prevention tool. Data on male circumcision will be collected as part of the demographic data.
TIME AND EVENTS SCHEDULE 9.1.6 Post-M30 Follow-up Phase	During the post-M30 follow-up phase, a test for syphilis and for chlamydia and gonorrhea should be performed approximately every 6 months.	The testing for sexual transmitted infections, including syphilis, chlamydia and gonorrhea, is considered an essential part of the prevention measures.
TIME AND EVENTS SCHEDULE 9.1.2 Visit Windows 9.1.7 Visits for Participants who Become HIV-1 Infected During the Study 9.1.2 Visit Windows	The target visit day and visit window for Visit #.X has been deleted and it is clarified that this visit should be scheduled as soon as possible after the initial positive HIV-1 test and could be a scheduled or unscheduled visit.	To allow for a confirmatory HIV test to be performed as close as possible to the initial test, the target visit day and allowed visit window for the confirmatory visit (Visit #.X) has been deleted.
TIME AND EVENTS SCHEDULE 9.1.2 Visit Windows	The visit window for Visit 7 (vaccination 4) has been adjusted to -14/+28 days to -14/+42 days. The visit window for Visit Inf1 and Visit Inf2 (previously Visit 1' and Visit 2') has been adjusted from +/- 14 days to +/- 28 days	To avoid participants missing the last vaccination and/or post-HIV-1 infection follow-up visits, the visit windows of these visits have been extended.
1.1.2 Background on the Study Vaccines	For the list of excipients of Ad26.Mos4.HIV, Clade C gp140 and	Investigator Brochures were updated in March and

[a] Goodreau SM, Carnegie NB, Vittinghoff E, et al. Can male circumcision have an impact on the HIV epidemic in men who have sex with men?. PLoS ONE. 2014;9(7):e102960.

Pintye J, Baeten JM. Benefits of male circumcision for MSM: evidence for action. Lancet Glob Health. 2019;7(4):e388-e389.

Yuan T, Fitzpatrick T, Ko NY, et al. Circumcision to prevent HIV and other sexually transmitted infections in men who have sex with men: a systematic review and meta-analysis of global data. Lancet Glob Health. 2019;7(4):e436-e447.

[b] World Health Organization. Guidelines: Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people: recommendations for a public health approach. 2011. Available at: https://apps.who.int/iris/bitstream/handle/10665/44619/9789241501750_eng.pdf;jsessionid=3F17E7A555BA3024CEAE319D5FA3A6BF?sequence=1. Accessed: 2 April 2019.

Section number and Name	Description of Change	Brief Rationale
14.1 Physical Description of Study product(s) REFERENCES	Mosaic gp140 and details on data from studies HPX2003 and HPX2004, reference to the appropriate Investigator's Brochure (IB) has been added.	February, respectively. Excipients for the Clade C and Mosaic gp140 HIV Bivalent Vaccine, Recombinant are described in this most recent version only.
1.2.4 Potential Risks REFERENCES	The section describing the risks related to aluminum has been aligned with updated template language.	Changes were made to align with updated internal templates and guidance documents.
SYNOPSIS 9.4 Safety Evaluations 12.3.1 All Adverse Events	Wording with regard to the reporting of unsolicited adverse events and special reporting situations that are not related to study-related procedures or non-investigational sponsor-products has been aligned with updated internal template language.	
Throughout the protocol	The term 'prime/boost' regimen has been replaced by 'heterologous' regimen throughout the protocol in line with updated internal guidance.	
Throughout the protocol	To align with CDISC terminology 'solicited local adverse events' was replaced with 'solicited administration site adverse events' throughout the protocol.	
Title Page	The study name MOSAICO was added to the Cover page.	Administrative change
17.11 Use of Information and Publication	The time for the sponsor and partners to review manuscripts and presentations including information from the study before submission is adjusted from at least 60 days to at least 21 days. However, at the request of the sponsor and/or the partners, such submission may be delayed up to 60 days.	Upon request of the partners,
4.2 Exclusion Criteria	More information has been added on how it is assessed if a potential participant has a known allergy or history of anaphylaxis or other serious adverse reactions to vaccines.	Upon request of the Health Authorities, partners and the community, clarifications were made, and specifications added throughout the protocol.
4.2 Exclusion Criteria	It is clarified that potential participants who received any HIV-vaccine candidate, irrespective if it is prophylactic or therapeutic vaccine, are excluded from the study. In addition, it is clarified that potential participants who have proof they received only placebo vaccine can be included in the study.	
4.2 Exclusion Criteria	It is specified that isolated seizure with clear etiology or febrile seizures during childhood are not exclusionary.	

Section number and Name	Description of Change	Brief Rationale
4.1 Inclusion Criteria	It is clarified that contraceptive requirements specified in the inclusion criteria only apply to participants assigned female at births and who did not have sexual reassignment surgery.	
4.1 Inclusion Criteria	It is specified that testosterone is not considered an acceptable contraceptive method.	
SYNOPSIS 3.1 Overview of Study Design 4.2 Exclusion Criteria	It is clarified that only potential participants who choose to use PrEP, are excluded from the study. Due to the high effectiveness of PrEP, these potential participants are not considered to be at increased risk for HIV-1 infection. In addition, it is specified that PrEP use during the study should be according to the site PrEP plan.	
9.3 Immunogenicity Evaluations	It is clarified that the planned venous blood collected per the Time and Events schedule will be sufficient to allow for exploratory immune analyses in addition to the prespecified ones.	
TIME AND EVENTS SCHEDULE 9.2 Efficacy Evaluations	It is clarified that blood samples for viral sequencing may be analyzed to study the presence of transmitted drug resistance, to assess whether VE differs by genotypic characteristics of HIV and whether there is evidence of vaccine-induced immune pressure on the viral genotype, depending on the vaccine efficacy outcome.	
16.2.3 Informed Consent	It is clarified that the informed consent form needs to be in a language that the potential participant can read and/or understand as potential participants who are unable to read are allowed in the study.	
SYNOPSIS 3.1 Overview of Study Design 9.1.7 Visits for Participants who Become HIV-1 Infected During the Study	It is clarified that participants who become HIV-1 infected during the study will be referred to a local clinic for medical treatment and follow-up on their HIV-1 infection as soon as possible after the diagnosis of the infection.	
SYNOPSIS 3.1 Overview of Study Design	It is added to the protocol that all efforts will be made to ensure that the study population includes good representation from the population at the highest risk of HIV infection in terms of race, ethnicity, gender identity and age.	

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS TIME AND EVENTS SCHEDULE 3.1 Overview of Study Design	It is clarified that blood will be collected for antiretroviral (ARV) detection in dried blood. In addition, it has been added that additional ARV detection can be done on stored blood samples, if required, as described in the Study Specific Procedures Binder.	
SYNOPSIS ABBREVIATIONS 1 INTRODUCTION	The term 'sponsor' (eg, sponsor and partners, HPX3002/HVTN 706 safety review team etc) is been specified throughout the protocol. In addition, additional partners have been specified.	
Throughout the protocol	To term 'study intervention' is specified (eg, study product, study vaccine etc) throughout the protocol to avoid confusion as it may be misinterpreted as the study product plus study procedures.	
SYNOPSIS 3.1 Overview of Study Design	'Lubricants' is added as standard of prevention that may be provided by the sponsor and its partners.	
SYNOPSIS ABBREVIATIONS 1.2.5 Overall Benefit/Risk Assessment 3.1 Overview of Study Design	It is clarified that the NIAID HIV vaccine Data and Safety Monitoring Board (DSMB; in the initial HPX3002 protocol referred to as an independent Data Monitoring Committee [DMC]) will serve as an independent DSMB for this study to monitor data on an ongoing basis.	
TIME AND EVENTS SCHEDULE 9.1.3 Screening Phase (Day -45 to Month 0)	It is clarified that for the assessment of chlamydia/gonorrhea a rectal and oral swab, and urine sample is needed	
TIME AND EVENTS SCHEDULE 9.1.7 Visits for Participants who Become HIV-1 Infected During the Study 9.4 Safety Evaluations	It is clarified that CD4+ cell counts will be assessed through a locally performed test.	
10.1 Completion	It is clarified that at the end of the study participants may be offered the possibility to enter a follow-up study or program, but not necessarily all participants will be offered this possibility.	
14.3 Preparation, Handling, and Storage	It is specified that study vaccine must be stored upright in a secured location at controlled temperature.	
SYNOPSIS	In alignment with the body of the protocol, it is added to the synopsis that exploratory immunogenicity assessments, currently not specified in the protocol, may be performed.	Inconsistencies and minor errors have been corrected.

Section number and Name	Description of Change	Brief Rationale
SYNOPSIS	For clarity, the timing of the primary analysis is added to the hypothesis in the synopsis.	
SYNOPSIS 9.4 Safety Evaluations 12.1.3 Severity Criteria 15 STUDY-SPECIFIC MATERIALS	Swelling and induration are terms that are used interchangeable. Within the protocol these terms were simplified to swelling	
4.1 Inclusion Criteria 10.2 Discontinuation of Study Vaccination/Withdrawal from the Study	Participants should be HIV-1 AND HIV-2 negative <28 days prior to first vaccination to be eligible for the study. Vaccination will be discontinued in participants who become HIV-1 or HIV-2 infected.	
9.1.3 Screening Phase (Day -45 to Month 0) 9.1.4 Vaccination	The allowed screening period has been corrected and aligned to 45 days with HIV test to be performed within 28 days.	
4.1 Inclusion Criteria 4.3 Prohibitions and Restrictions	Per the prohibitions and restrictions section participants will not be able to donate eggs (ova, oocytes). The inclusion criterion requiring participants to agree not to donate eggs is, therefore, redundant.	
6 DOSAGE AND ADMINISTRATION 9.1.2 Visit Windows	Information on the action to be taken in case a participant is not vaccinated within the allowed time window, ie, to be discussed and decided with the HPX3002/HVTN 706 safety review team on a case-by-case basis, was made consistent across the protocol. In addition, it has been reiterated that all efforts should be made to follow the vaccination schedule per the protocol and that vaccinations should generally not be administered outside of the prespecified window.	
9.4 Safety Evaluations	Not all laboratory tests will be analyzed by a central laboratory. The type of laboratory (central or local) that will perform the different tests has been specified for all tests.	
16.1 Study-Specific Design Considerations	Total blood volumes taken during the study have been corrected, also taking into consideration changes in blood draws for immunogenicity assays (see above).	

Section number and Name	Description of Change	Brief Rationale
TIME AND EVENTS SCHEDULE 8 PRESTUDY AND CONCOMITANT THERAPY 9.1.3 Screening Phase (Day -45 to Month 0) 9.1.4 Vaccination 9.1.5 Post-vaccination Follow-up Phase 9.1.6 Post-M30 Follow-up Phase 9.1.8 Early Withdrawal/Exit Visit	The protocol has been aligned with regard to the collection of concomitant medication. Concomitant therapies such as analgesics/antipyretic medications and non-steroidal anti-inflammatory drugs, hormonal therapy, hormone-based contraception, systemic corticosteroids, antihistaminics, mAbs, or vaccinations must be recorded from the first study vaccination to 1 month after the last study vaccination (not needed at Month 30 and early exit visit). The use of PrEP, PEP, hormonal therapy and hormone-based contraception should be recorded at additional time points as specified in the Time and Events Schedule. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening adverse events reported per protocol requirements. For participants who become HIV infected, all ARVs and all concomitant therapies administered in conjunction with new or worsening adverse events reported per protocol requirements should be reported.	
TIME AND EVENTS SCHEDULE	The Time and Events Schedule has been corrected to reflect that no blood will be collected for dried blood spot at screening.	
Throughout the protocol	The terms Visit 1', Visit 2' and Early Exit' have been replaced with Visit Infected 1 (Inf1), Visit Inf2, and Early Exit Inf, respectively.	To avoid confusion with Visit 1, Visit 2 and Exit visit of the main Time and Events Schedule, the Visit 1' and Visit 2' of the Time and Events schedule for participants who become HIV infected have been replaced with Visit Inf1, Visit Inf2, and Early Exit Inf, respectively.
Throughout the protocol	HVTN study identifiers, HVTN 117, HVTN 118, HVTN 705 and HVTN 706 were added to the Janssen study names VAC89220HPX2004, HPX2003, HPX2008 and HPX3002, respectively	For clarity and completeness HVTN study identifiers were added.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted, and minor textual changes were made following the request of partners and community.

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SYNOPSIS

A Multi-center, Randomized, Double-blind, Placebo-controlled Phase 3 Efficacy Study of a Heterologous Vaccine Regimen of Ad26.Mos4.HIV and Adjuvanted Clade C gp140 and Mosaic gp140 to Prevent HIV-1 Infection Among Cis-gender Men and Transgender Individuals who Have Sex with Cis-gender Men and/or Transgender Individuals

The aim of this study is to demonstrate the efficacy of a heterologous human immunodeficiency virus type 1 (HIV-1) vaccine regimen consisting of Ad26.Mos4.HIV and a combination of aluminum phosphate-adjuvanted Clade C glycoprotein (gp) 140 and Mosaic gp140 (Mos gp140).

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives		Endpoints	
Primary			
1	To evaluate the vaccine efficacy (VE) of a heterologous vaccine regimen utilizing Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140 for the prevention of HIV-1 infection in HIV-1 seronegative cis-gender men and transgender individuals having sex with cis-gender men and/or transgender individuals.	1	Confirmed HIV-1 infections diagnosed between Month 7 and Month x (with 24≤x≤30) visits in the per-protocol (PP) population.
Secondary			
1	To evaluate the safety and reactogenicity of a heterologous vaccine regimen utilizing Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140 for the prevention of HIV-1 infection in HIV-1 seronegative cis-gender men and transgender individuals having sex with cis-gender men and/or transgender individuals.	1	• Reactogenicity: Solicited administration site and systemic adverse events for 7 days after each vaccination • Unsolicited adverse events for 28 days after each vaccination • Adverse events of special interest (AESIs) for 6 months after the last vaccination • Medically-attended adverse events (MAAEs) for the entire duration of the study • Serious adverse events for the entire duration of the study • Discontinuations from the study or vaccination due to adverse events
2	To evaluate VE at other timepoints and in other analysis populations.	2	Confirmed HIV-1 infections over different time intervals (eg, VE[0-x months], VE[13-x months]) and in different populations (eg, modified intent-to-treat [mITT], mITT-2, mITT-3, full immunization set [FIS])
3	To evaluate VE by and adjusting for potential (baseline) confounders.	3	Potential confounders include but are not limited to: demographic characteristics, baseline Ad26 seropositivity status and titer, sexual risk behavior, and pre-exposure prophylaxis (PrEP) use.

Objectives		Endpoints	
Exploratory			
1	To evaluate whether VE differs by phenotypic characteristics of HIV, such as neutralization sensitivity, and whether there is evidence of vaccine-induced immune pressure on the viral phenotype.	1	Confirmed HIV-1 infection diagnosed after Day 1 through Month 30 and inferred transmitted viral isolate(s) phenotype(s) from HIV-1–infected mITT participants at the earliest available post-infection timepoint, and possible subsequent visits.
2	To evaluate whether VE differs by genotypic characteristics of HIV, such as signature site mutations, and whether there is evidence of vaccine-induced immune pressure on the viral sequences.	2	Confirmed HIV-1 infection diagnosed after Day 1 through Month 30 and inferred transmitted viral sequence(s) genotype(s) from HIV-1–infected mITT participants at the earliest available post-infection timepoint, and possible subsequent visits, using sieve analysis methods.
3	To evaluate vaccine effects on virologic and immunologic outcomes among participants that become HIV-1–infected during the study, accounting for antiretroviral (ARV) use.	3	HIV-1 viral load and $CD4^+$ count over a 6-month period after diagnosis. The frequency and magnitude of HIV-1 cellular (participants at sites with access to sponsor approved PBMC processing facilities) and humoral immune responses in participants that become HIV-1–infected during the study.
4	To evaluate immune correlate(s) of risk of HIV-1 infection and/or correlates of VE.	4	Magnitude and/or frequency of immune responses to vaccination in HIV-1 infected vaccine recipients (cases) relative to a subset of HIV-1 uninfected vaccine recipients (controls) and placebo cases and controls, as relevant. The association of immune response(s) that are identified as-being associated with VE in Study VAC89220HPX2008 /HVTN 705 (further referred to as HPX2008/HVTN 705[a], in HIV-1 infected vaccine recipients (cases) relative to a subset of HIV-1 uninfected vaccine recipients (controls) and placebo cases and controls, as relevant.
5	To evaluate the occurrence of vaccine-induced seropositivity/seroreactivity (VISP/R, further referred to as VISP) following vaccination with heterologous vaccine regimen utilizing Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140.	5	The frequency of confirmed VISP, determined utilizing a pre-specified diagnostic algorithm to distinguish HIV- 1 infection from VISP (refer to the Study-Specific Procedures Binder for more information) at different time points following vaccination.

[a] VAC89220HPX2008/HVTN 705 proof-of-efficacy study: A multicenter, randomized, double-blind, placebo-controlled phase 2b efficacy study of a heterologous prime/boost vaccine regimen of Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 in preventing HIV-1 infection in women in sub-Saharan Africa.

Objectives		Endpoints	
6	To describe PROs.	6	Social impact and vaccine regimen acceptance, sexual activity, absenteeism and PrEP use collected through questionnaires completed by study participants.
7	To describe HCRU over the study period.	7	Collection of MAAEs, level of absenteeism and follow-up of HIV infections throughout the study.
8	To evaluate the immune responses elicited by the vaccine regimen.	8	The frequency and magnitude of HIV-1-specific cellular and humoral immune responses.

Hypothesis

This study is designed to test the primary hypothesis of VE in the PP population:

Null hypothesis (H0): VE(7-x months) ≤20% versus the alternative hypothesis (H1): VE(7-x months) >20%, with 24≤x≤30.

The timing of the primary analysis will be determined by when the Target Number of Infections (TNI) is reached within a given follow-up period x (24≤x≤30).

If the lower bound of the 95% confidence interval (CI) for VE(7-x months) is >20% at the primary analysis, the corresponding H0 will be rejected.

OVERVIEW OF STUDY DESIGN

This is a multi-center, randomized, parallel-group, placebo-controlled, double-blind, Phase 3 study to demonstrate efficacy of a heterologous prophylactic HIV-1 vaccine regimen consisting of Ad26.Mos4.HIV and a combination of aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140. Safety, reactogenicity and immunogenicity will also be evaluated. The study population will include healthy adults considered to be at increased risk of acquiring HIV-1 infection. A target of 3,800 participants, consisting of HIV-1-uninfected cis-gender men and transgender individuals having sex with cis-gender men and/or transgender individuals, aged ≥18 to ≤60 years, will be randomized in a 1:1 ratio to the study vaccine or placebo. Randomization will be stratified by site. Sample size re-assessment may be performed based on blinded study data or external study data (eg, Phase 2b Study HPX2008/HVTN 705). The target number of HIV-1 infections may be re-assessed based on external study data (eg, Phase 2b Study HPX2008/HVTN 705) only.

Participants will receive intramuscular (IM) doses of study vaccine or placebo at four time points as indicated in the table below.

Table: Vaccination Schedule

Group	N	Month 0	Month 3	Month 6	Month 12
1	1,900	Ad26.Mos4.HIV	Ad26.Mos4.HIV	Ad26.Mos4.HIV + Clade C gp140, Mosaic gp140, adjuvanted	Ad26.Mos4.HIV + Clade C gp140, Mosaic gp140, adjuvanted
2	1,900	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo

Total dose of Ad26.Mos4.HIV is $5x10^{10}$ viral particles (vp)/0.5 mL injection.
Clade C gp140, Mosaic gp140, adjuvanted: adjuvanted protein formulation with a dosage strength of 80 mcg Clade C protein, 75 mcg Mosaic protein and 425 mcg aluminum (as aluminum phosphate adjuvant). Note: previously the dose of Clade C gp140 and/or Mosaic gp140 was reported as mcg of glycoprotein: 125 mcg Clade C gp140 and 125 mcg Mosaic gp140 glycoprotein correspond with 80 mcg and 75 mcg of protein, respectively.

The study comprises of a screening period of 45 days, a 12-month vaccination period and a follow-up period of at least 18 months after the fourth vaccination (until Month 30) in participants who remain HIV-1 negative or up to 6 months after diagnosis of HIV-1 infection in participants who become HIV-1 infected. Participants who completed their Month 30 visit will be followed for HIV infection, MAAEs and serious adverse events until the end of the study (ie, when the last participant completed the Month 30 visit or discontinued earlier). At the end of the study, participants may be offered the possibility to enter a long-term follow-up phase or program (to collect, amongst others, additional durability data).

After vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions. In addition, participants will record solicited signs and symptoms in a diary for 7 days post-vaccination. Unsolicited adverse events will be recorded for all participants until 28 days after each preceding vaccination. AESIs will be collected until 6 months after the last vaccination. Serious adverse events, MAAEs, and adverse events leading to discontinuation will be collected for all participants until the end of the study.

An HIV test will be performed approximately every 3 months. Upon discretion of the investigator, additional HIV tests may be performed during unscheduled visits; participants should refrain from performing any HIV testing outside of the study protocol. Blood samples will be collected at specific visits for determination of humoral immune responses (all participants) and for determination of cellular immune responses (participants at sites with access to sponsor approved PBMC processing facilities). At specific clinic visits, participants will complete Participant Reported Outcomes (PRO) questionnaires, including a social impact questionnaire, a sexual activity questionnaire, a questionnaire on the use of PrEP and questions with regard to the level of absenteeism and the vaccine regimen acceptance.

If a participant becomes HIV-1 infected during the study (confirmed HIV test), the participant will remain in the study but no further scheduled vaccinations will be administered. The participant will be followed-up until approximately 6 months after the diagnosis (see the Time and Events Schedule for Participants Who Become HIV-1 Infected) and will be referred to a local clinic for medical treatment and follow-up on their HIV-1 infection as soon as possible after the diagnosis of the infection.

The sponsor and its partners are committed to ensuring that all study participants receive access to the highest standard of prevention, which may include, but is not limited to, HIV testing, risk reduction counseling, provision of male condoms and lubricants, access to management of sexually transmitted infections (STIs), and appropriate referrals for PrEP and post-exposure prophylaxis (PEP) according to national and/or local guidelines. Note: potential participants choosing to use PrEP will not be eligible for

participation in the study as, due to the high effectiveness of PrEP, these individuals are not considered to be at increased risk of HIV acquisition. However, once enrolled in the study and having received their first vaccination, a participant who changes his/her mind regarding PrEP use is permitted to take PrEP according to the site PrEP plan and will continue to receive further vaccinations. In case of PrEP use during the study, safety monitoring for PrEP will be the responsibility of the prescribing physician. HIV testing should be performed within the study to avoid unblinding due to VISP elicited by the vaccine. Participants should refrain from HIV testing outside of the study protocol. As part of the study protocol, blood samples will be collected for ARV detection in dried blood spot and stored at pre-specified sample collection days for assessment of quantitative concentrations of tenofovir diphosphate. Additional ARV detection can be done on stored blood samples if required as per the Study Specific Procedures Binder. The use of PrEP and adherence to PrEP (if applicable) will be monitored by means of a questionnaire which will be completed by all participants approximately every 3 months.

The NIAID HIV vaccine Data and Safety Monitoring Board (further referred to as DSMB) will serve as an independent DSMB for this study and will monitor data on an ongoing basis to ensure the continuing safety of the participants and will formally monitor the efficacy endpoint.

A COVID-19 Appendix provides guidance to investigators for managing study-related procedures during the COVID-19 pandemic.

PARTICIPANT POPULATION

Screening for eligible participants will be performed within 45 days before the first administration of study vaccine or placebo at Day 1.

Study participants must be healthy (on the basis of medical history, physical examination [including vital sign measurement]), HIV-uninfected adult cis-gender men and transgender individuals having sex with cis-gender men and/or transgender individuals, aged ≥18 to ≤60 years, who are considered to be at increased risk for HIV infection. All efforts will be made to ensure that the study population includes good representation from the population at highest risk of HIV infection in terms of race, ethnicity, gender and age.

DOSAGE AND ADMINISTRATION

Each participant will receive doses of study vaccine or placebo at 4 time points according to randomization, on Month 0 (Day 1), 3, 6, and 12, administered by IM injection into the deltoid. For visits with only one injection (ie, at Month 0 [Day 1] and 3), preferably the deltoid of the non-dominant upper arm is used. When 2 injections are to be given at one visit (ie, at Month 6 and 12), it is required to use a different deltoid for each injection. Two injections in the same deltoid are allowed only if medically indicated.

Table: Description of Study Products

Test articles	Ad26.Mos4.HIV	Clade C gp140, Mosaic gp140, aluminum phosphate	Placebo
Description	See Section Vaccine Information.		
Dose/delivery (0.5 mL injection)	$5x10^{10}$ vp	80 mcg Clade C protein*, 75 mcg Mosaic protein*, adjuvanted with aluminum phosphate (425 mcg aluminum)	0.9% saline
Frequency	Month 0 (Day 1), 3, 6, and 12	Month 6 and 12	Month 0 (Day 1) and 3 (1 injection), Month 6 and 12 (2 injections)
Route of administration	IM in deltoid	IM in deltoid	IM in deltoid
Delivery method	Refer to the Study-Specific Procedures Binder for details.		

* 80 mcg Clade C gp140 and 75 mcg Mosaic gp140 of protein correspond with 125 mcg and 125 mcg glycoprotein, respectively.

EFFICACY EVALUATIONS

An HIV test will be performed approximately every 3 months. Upon discretion of the investigator, additional HIV tests may be performed during unscheduled visits; participants should refrain from performing any HIV testing outside of the study protocol. Testing will be performed according to a sponsor-approved HIV testing algorithm that differentiates VISP (see below) from true HIV infection. An endpoint adjudication process will be in place to assess all serological and virological testing, in a blinded manner, on each participant in the study who, prior to study unblinding, tests positive per the sponsor-approved HIV testing.

IMMUNOGENICITY EVALUATIONS

Venous blood samples for determination of humoral immune responses will be collected from all participants (and analyzed in a subset). Humoral immune responses may be assessed by the response magnitude and frequency to the vaccine autologous Clade C gp140 and Mosaic gp140 proteins by total immunoglobulin G (IgG) binding ELISA, or alternative assays. Baseline and post-vaccination Ad26 seropositivity and titer will be assessed in a subset of participants by vector neutralization assay.

Venous blood samples for determination of cellular immune responses will be collected from participants at sites with access to sponsor approved PBMC processing facilities (and analyzed in a subset). Cellular immune responses may be assessed by the response magnitude and frequency of peripheral blood mononuclear cells generating interferon-γ ELISpot responses to cPTE Env peptide stimulation, or alternative assays.

Additional exploratory immunogenicity assessments may be performed, which may include limited genetic testing.

SAFETY EVALUATIONS

Solicited adverse events, unsolicited adverse events, AESIs, serious adverse events, MAAEs, and adverse events leading to discontinuation will be reported for all participants.

All serious adverse events and adverse events and special reporting situations, that are related to study procedures or that are related to non-investigational (concomitant) sponsor products will be reported

from the time a signed and dated informed consent form (ICF) is obtained until the end of the study/early withdrawal. Clinically relevant medical events not meeting the above criteria and occurring between signing of ICF and the moment of first vaccination will be collected on the Medical History CRF page as pre-existing conditions. Solicited adverse events, collected through a diary, will be recorded daily for each vaccination from the moment of vaccination until 7 days post-vaccination. All other unsolicited adverse events and special reporting situations will be reported for each vaccination from the moment of vaccination until 28 days post-vaccination. From the time of local approval of protocol amendment 5 onwards, TTS is considered to be an AESI. Thrombotic events and/or thrombocytopenia (defined as platelet count below the lower limit of normal (LLN) range for the testing lab) are considered to be potential AESIs. All AESIs, including potential AESIs, will be reported to the sponsor from the moment of first vaccination until 6 months after the last vaccination. Each potential AESI will be reviewed to identify a TTS case. All serious adverse events, MAAEs, and adverse events leading to discontinuation (regardless of the causal relationship) are to be reported from the moment of first vaccination for the duration of the study.

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions.

Occurrences of the following solicited administration site and systemic signs and symptoms will be collected via a diary for 7 days post-vaccination (day of vaccination and the subsequent 7 days). The diary will be used as a source document.

- Administration site: erythema, swelling (measured using the ruler supplied) and pain/tenderness.
- Systemic: fever (temperature measurement [measured at approximately the same time each day using the thermometer supplied]), fatigue, headache, nausea, myalgia, chills, arthralgia, and vomiting.

PARTICIPANT REPORTED OUTCOMES

Social impact, vaccine regimen acceptance, sexual activity, absenteeism and PrEP use will be evaluated at selected time points during the study, through questionnaires.

STATISTICAL METHODS

The primary analysis of VE will be based on the PP population[a]. The primary population for the safety analysis will be the full analysis set (FAS)[b]. For those with immunogenicity outcomes, analyses of vaccine immunogenicity and immune correlates may be based on the mITT-3[c] population, PP population, at risk immunogenicity cohort (IC-at risk)[d], and the FIS[e], Other populations may be defined in the Statistical Analysis Plan (SAP) for the purpose of exploratory (correlate) analyses.

The sample size calculations are based on the power of a 1-sided 0.025-level Wald test for comparing cumulative incidences of HIV-1 infection by the Month x visit ($24 \leq x \leq 30$) between randomized groups, in

[a] PP population: participants in the FAS population who have a negative HIV test 4 weeks post 3rd vaccination visit (ie, at the Month 7 visit), who received all planned vaccinations at the first 3 vaccination visits within the respective visit windows.

[b] FAS: all randomized participants who receive at least one vaccine administration.

[c] mITT-3 population: participants in the FAS population who have a negative HIV test 4 weeks post 3rd vaccination visit (ie, at the Month 7 Visit), who received all planned vaccinations at the first three vaccination visits. This will be an additional population for efficacy analysis, and potentially for immune correlates.

[d] IC-at risk: participants in the FAS who are selected for measurement of immune response endpoints at the primary immunogenicity timepoints and who are HIV-1 uninfected 4 weeks after the 3rd vaccination visit (ie, at the Month 7 visit).

[e] FIS: participants in the FAS who are HIV-1 uninfected 4 weeks after the 4th vaccination visit (ie, at the Month 13 visit) and who receive all planned vaccinations within the respective visit windows.

the presence of the sequential monitoring of VE. Power is computed based on simulating 10,000 efficacy studies using the R package seqDesign under the following assumptions:

- 10% annual dropout incidence in both groups;
- 5% of participants with at least one missed vaccination (excluded from PP population);
- VE=20% in the first 7 months after first vaccination;
- VE=65% from Month 7 onwards;
- 12-month uniform accrual with halved accrual during the first 3 months;
- Visits approximately every 3 months for HIV-1 diagnostic tests;
- 2% annual HIV-1 incidence in the placebo group;

Under these assumptions, a study population of 3,800 participants (randomized 1,900:1,900 to vaccine:placebo) is expected to yield a total of 78 HIV-1 infections in the PP population between the Month 7 and Month 30 visits, considered to be the TNI needed to achieve approximately 90% power for rejecting the primary H0, under an alternative VE of 65% and with a one-sided error rate of 2.5%.

Efficacy Analyses

The primary analysis of VE will evaluate the number of HIV-1 infections in the vaccine group compared to the number of HIV-1 infections in the placebo group between Month 7 and Month x (with $24 \leq x \leq 30$) in the PP population. The timing of the primary analysis will be determined by when the TNI is reached within a given follow-up period x ($24 \leq x \leq 30$). The H0 of VE, ie, VE(7-x months) ≤20% will be tested versus the H1, ie, VE(7-x months) >20%. Vaccine efficacy is defined as 1-cumulative incidence ratio (vaccine versus placebo) between Month 7 and Month x after first vaccination and is estimated by the transformation of the Nelson-Aalen estimator for the cumulative hazard function. If the lower bound of the 95% CI for VE(7-x months) is >20% (equivalently, the 1-sided p-value for testing H0: VE[7-x months] ≤20% is below 0.025), the H0 will be rejected in favor of the H1.

As a key secondary objective, the VE beyond Month 7 will be evaluated in all participants, regardless of whether they received the first three vaccinations according to the protocol-specified schedule (modified intent-to-treat-2 [mITT-2][a]). Other secondary objectives will evaluate the VE over different time intervals (eg, VE[0-x months], VE[13-x months]) and in different populations (eg, mITT, mITT-2, mITT-3, FIS).

Immunogenicity Analyses

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (actual values and changes from reference) may be calculated for continuous parameters. Frequency tabulations may be calculated for discrete parameters. Graphical representations of changes in immunologic parameters may be made as applicable.

Safety Analyses

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively.

[a] mITT-2 population: participants in the FAS who have a negative HIV test 4 weeks post 3rd vaccination visit (ie, at the Month 7 Visit).

Analyses of PRO

Data from the PRO questionnaires will be summarized using descriptive statistics. In addition, data from PRO questionnaires may be included as co-variates in the exploratory efficacy analysis.

Analyses of Health Economics Aspects (HCRU)

Health Care Resource Utilization will be described based on data collected through MAAEs and follow-up of HIV infections and complemented by description of absenteeism. Data will be summarized using descriptive statistics.

TIME AND EVENTS SCHEDULE

Time and Events Schedule for HIV-1 Negative Participants

Phase	*Scr*	*Vac*	*Post vac FU*	*Vac*	*Post vac FU*	*Vac*	*Post vac FU*			*Vac*	*Post vac FU*[a]								*Post M30 FU*[b]	*EW/ Exit*[c]
Visit #	1	2	2a[v]	3	3a[d,v]	4	4a[d,v]	5[d]	6	7	7a[d,v]	8[d]	9	10	11	12	13	14	Every 3 months post M30	
Time in months[d]		M0		M3		M6		M7[d]	M9	M12		M13[d]	M15	M18	M21	M24	M27	M30		
Visit Day[d]	D 45 to D1	D1	D9	D84	D92[d]	D168	D176[d]	D196[d]	D273	D364	D372[d]	D394[d]	D455	D546	D637	D728	D819	D910		
Visit Window			±7	±14d	±7	14/ +28d	±7	14/ +28d	14/ +28d	14/ + 42d	±7	14/ +28d	14/ +28d	14/ +28d	14/ +28d	14/ +28d	14/ +28d	14/ +28d	±28d	
Informed consent[e]	●																			
Randomization		❶																		
Test of Understanding[e]	●																			
Medical history[ff]	●																			
Demographics[gg]	●									●						●			●	
Full physical examination[f]	●																	●		
Targeted physical examination[g]		❶		❶		❶		●	●	❶		●	●	●	●	●	●			●
HIV test[h,i]	●[j]	❶		❶		❶		●	●	❶		●[k]	●	●	●	●	●	●	●	●
Concomitant medication[l]	●	❶		❶		❶		●	●	❶		●	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]	●[m]
Review of inclusion/ exclusion criteria	●	❶[n]																		
Serum pregnancy test[o]	●																			
Urine pregnancy test[o]		❶		❶		❶				❶			●[p]	●[p]	●[p]	●[p]	●[p]	●[p]	●[p]	●
Vaccination[i,q]		▲		▲		▼				▼										

Phase	*Scr*	*Vac*	*Post vac FU*	*Vac*	*Post vac FU*	*Vac*	*Post vac FU*			*Vac*	*Post vac FU*[a]								*Post M30 FU*[b]	*EW/ Exit*[c]
Visit #	1	2	2a[v]	3	3a[d,v]	4	4a[d,v]	5[d]	6	7	7a[d,v]	8[d]	9	10	11	12	13	14	Every 3 months post M30	
Time in months[d]		M0		M3		M6		M7[d]	M9	M12		M13[d]	M15	M18	M21	M24	M27	M30		
Visit Day[d]	D 45 to D1	D1	D9	D84	D92[d]	D168	D176[d]	D196[d]	D273	D364	D372[d]	D394[d]	D455	D546	D637	D728	D819	D910		
Visit Window			±7	±14d	±7	14/ +28d	±7	14/ +28d	14/ +28d	14/ + 42d	±7	14/ +28d	14/ +28d	14/ +28d	14/ +28d	14/ +28d	14/ +28d	14/ +28d	±28d	
Post vaccination observation (30 min)[r]		●		●		●				●										
Solicited AE recording[s]		●	●	●	●	●	●			●	●									●
Unsolicited AE recording[t]		❷	●	❷	●	❷	●	●		❷	●	●								●
AESI recording[u]		continuous																		●
SAE, MAAEs, and AE leading to discontinuation recording[u]		continuous																		●
Diary distribution		●		●		●				●										
Diary review[v]				●		●		●				●								
Sexual activity questionnaire[w]		●						●		●						●				●
Social impact questionnaire				●						●								●		●
Other PRO[x]		●		●		●		●	●	●		●[x]	●	●	●	●	●	●	●	●

Phase	*Scr*	*Vac*	*Post vac FU*	*Vac*	*Post vac FU*	*Vac*	*Post vac FU*			*Vac*	*Post vac FU*[a]								*Post M30 FU*[b]	*EW/ Exit*[c]
Visit #	1	2	2a[v]	3	3a[d,v]	4	4a[d,v]	5[d]	6	7	7a[d,v]	8[d]	9	10	11	12	13	14	Every 3 months post M30	
Time in months[d]		M0		M3		M6		M7[d]	M9	M12		M13[d]	M15	M18	M21	M24	M27	M30		
Visit Day[d]	D 45 to D1	D1	D9	D84	D92[d]	D168	D176[d]	D196[d]	D273	D364	D372[d]	D394[d]	D455	D546	D637	D728	D819	D910		
Visit Window			±7	±14d	±7	14/ +28d	±7	14/ +28d	14/ +28d	14/ + 42d	±7	14/ +28d	14/ +28d	14/ +28d	14/ +28d	14/ +28d	14/ +28d	14/ +28d	±28d	
Syphilis serology	●					●				●				●		●		●	●[dd]	
Chlamydia/ gonorrhea[y]	●					●				●				●		●		●	●[dd]	
Immunogenicity assays[z]		❶[cc]						●[cc]				●		●		●		●		●
Limited genetic testing[ee]		●						●												
Dried blood spot test		See footnote aa																		
PrEP Questionnaire[bb]		●		●		●			●	●			●	●	●	●	●	●	●	●
Risk reduction counseling	●	●		●		●		●	●	●		●	●	●	●	●	●	●	●	●

▲: Ad26.Mos4.HIV (5x10[10] vp/0.5 mL) or matching placebo; ▼: Ad26.Mos4.HIV is 5x10[10] vp/0.5 mL injection + Clade C gp 140 (80 mcg protein), Mosaic gp140 (75 mcg protein), adjuvanted (425 mcg aluminum) or matching placebos; ❶ pre dose; ❷ pre and post dose

AE: adverse event; AESI: adverse event of special interest; D: Day; d: days; EW: early withdrawal; FU: follow up; HCRU: Health Care Resource Utilization; M: month; SAE: serious adverse event; Scr: screening; VAC: vaccination

The COVID 19 Appendix in Section 18 provides guidance to investigators for managing study related procedures during the COVID 19 pandemic.

[a] All participants will be followed up until at least Month 30 to assess efficacy and durability of immune response.

[b] Participants who completed their Month 30 visit should return to the site every 3 months post Month 30 for an HIV test until the last participant completed the Month 30 visit or discontinued earlier. Visits post Month 30 will be scheduled relative to the Month 30 visit. At the end of the study, participants may be offered the possibility to enter a long term follow up phase or program (to collect, amongst others, additional durability data).

[c] For those participants who are unable to continue in the study, an early withdrawal/exit visit will be conducted as soon as possible.

[d] All target dates are relative to Month 0, with the exception of study site Visits 5 and 8 and follow up contact Visits 3a, 4a and 7a: if a participant is not vaccinated on the given day of vaccination, ie, Visit 2 (Day 1), Visit 3 (Day 84), Visit 4 (Day 168) and Visit 7 (Day 364), the timings of these visits, will be scheduled relative to the actual day of vaccination.

[e] The ICF should be signed before any study related activity, except for the test of understanding (TOU), which should be completed by all potential participants prior to signing the ICF.

[f] Full physical examination, including height, weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin.

[g] Targeted physical examination, including weight, vital signs, and a symptom directed evaluation by history and/or appropriate physical examination based on participant self reported symptoms or complaints.

[h] HIV testing should be performed per sponsor approved algorithm, as described in the Study Specific Procedures Binder. To avoid delays in initiation of combined antiretroviral treatment, local HIV PCR testing is allowed only in case of suspected acute HIV infection, in case of recent HIV exposure, or in case a request for sample redraw is received from the central HIV testing laboratory for confirmation of an HIV positive test. Upon discretion of the investigator, additional HIV tests may be performed during unscheduled visits; participants should refrain from performing any HIV testing outside of the study protocol.

[i] If a participant becomes HIV 1 infected during the study, no further scheduled vaccinations will be administered. The participant should follow further assessments as outlined in the Time and Events schedule for participants who become HIV 1 infected.

[j] The screening HIV test should be performed within 28 days prior to first vaccination.

[k] HIV test 13 months post 1st vaccination will be collected but is only to be analyzed in case the test at 15 months is positive and the test at 12 months was negative.

[l] The following concomitant therapies must be recorded from the first study vaccination to 1 month after the last study vaccination: analgesics/antipyretic medications and non steroidal anti inflammatory drugs, hormonal therapy, hormone based contraception, systemic corticosteroids, antihistaminics, monoclonal antibodies (mAbs), or vaccinations must be recorded from the first study vaccination to 1 month after the last study vaccination. Exception: COVID 19 vaccination must be recorded as of any time before screening until the end of the study. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening adverse events reported per protocol requirements. If applicable, HIV prevention medication should be recorded.

[m] The use of PrEP, PEP, hormonal therapy, hormone based contraception, and all COVID 19 vaccinations should be recorded. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening adverse events reported per protocol requirements.

[n] Check clinical status again before first dose of study vaccine.

[o] For participants of childbearing potential only.

[p] A urine pregnancy test is to be performed every 3 to 6 months.

[q] Participants who have been prematurely withdrawn from study vaccine administration will be encouraged to complete the visit schedule as planned with assessments per the Time and Event Schedule, including assessments of safety and HIV diagnosis. Participants who received the first 3 vaccinations but discontinue study vaccination before receiving the 4th vaccination, should continue the visit schedule as planned with assessments per the Time and Event Schedule including assessments of safety, immunogenicity and HIV diagnosis. They will also be reminded not to have HIV testing outside of the study protocol as this could lead to misdiagnosis and unblinding.

[r] Participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions.

[s] All participants will record solicited signs and symptoms in a diary for 7 days post vaccination.

[t] Unsolicited adverse events will be recorded for all participants until 28 days after each vaccination.

[u] Applicable from the time of local approval of protocol amendment 5 onwards: AESIs (including potential AESIs) are to be reported to the sponsor until 6 months after the last vaccination (see Section 12.3.4). In case of a potential AESI of TTS, a serum sample should be obtained to test for anti PF4 at the local laboratory or substitute local laboratory, if possible; repeat testing may be requested for confirmation upon sponsor discretion. A test for anti PF4 will also be performed on a stored pre vaccination sample, if possible. Serious adverse events, MAAEs, and adverse events leading to discontinuation will be recorded until the participant's last study contact.

[v] The site staff and the participant will make multiple efforts in good faith to be in contact after the last day of the reactogenicity period, or sooner if indicated, to discuss presence of any signs and symptoms of reactogenicity. Participants who self report any post vaccination reaction greater than mild are seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has resolved completely.

[w] The recall period of the questionnaire is the last month.

[x] All participants will be asked about their level of absenteeism at each visit except for Visit 2a, 3a, 4a and 7a. At Visit 8, approximately 1 month post vaccination 4, participants will be asked about the acceptance of the vaccine regimen.

[y] (1) Urine sample, (2) rectal swab, and (3) oropharyngeal swab are all required. If required by standard local procedure, the collection of a urethral swab will be considered equivalent to a urine sample.

[z] Venous blood samples for determination of humoral immune responses will be collected from all participants (and analyzed in a subset)

[aa] Blood samples will be collected for ARV detection in dried blood spot and stored at pre specified sample collection days for assessment of quantitative concentrations of tenofovir diphosphate. Additional ARV detection can be done on stored blood samples if required, as per the Study Specific Procedures Binder.

[bb] The use of PrEP at baseline and the use of PrEP and adherence to PrEP (if applicable) since their last visit will be assessed through a questionnaire. Safety monitoring for PrEP will be the responsibility of the prescribing physician.

[cc] At Visit 2 (Day 1) and Visit 5 (Month 7), venous blood samples for determination of cellular immune response will be collected from participants at sites with access to sponsor approved PBMC processing facilities (and analyzed in a subset).

[dd] Approximately every 6 months, blood samples for syphilis serology determination should be collected and a test for chlamydia/gonorrhea should be performed.

[ee] Limited genetic testing may be performed on leftover blood from samples collected for the determination of cellular immune response. No separate blood sample is needed.

[ff] Includes history and family history of immune disorders.

[gg] Demographics (eg, sex assigned at birth, participant identified gender at screening, age, male circumcision, race) will be recorded at screening. Gender identity needs to be collected at Visit 7 (Month 12), Visit 12 (Month 24), approximately Month 36 and from then onwards on an annual basis.

Time and Events Schedule for Participants Who Become HIV-1 Infected

Visit #[j]	#.X[i]	Inf1	Inf2	Early Exit Inf[b]
Time in months since diagnosis[a]		M3	M6	
Visit Day		D84	D168	
Target/allowable visit window		±28d	±28d	
HIV test	●			
HIV 1 viral load measurement	●	●	●	●
CD4+ T cell count[h]	●	●	●	●
Limited genetic testing	●			
Counseling on HIV testing/diagnosis	●			
Full physical examination[c]			●	
Pregnancy test[d]		●	●	●
Targeted physical examination	●	●		●
Concomitant medication [k]		●	●	●
AE/AESI/SAE recording[e]	●	●	●	●
Transmission risk reduction counseling	●	●	●	●
Social impact questionnaire[l]		●	●	●
Absenteeism	●	●	●	●
Immunogenicity assays[f]	●	●	●	●
Viral sequencing[g]	●	●	●	●

#.X: interim visit for the purpose of drawing samples for confirmatory HIV testing

AE: adverse event; ARV: antiretroviral; D: Day; d: days; HIV 1: human immunodeficiency virus type 1; HCRU: Health Care Resource Utilization; M: month; SAE: serious adverse event

The COVID 19 Appendix in Section 18 provides guidance to investigators for managing study related procedures during the COVID 19 pandemic.

[a] Target dates for Visit Inf1 and Inf2 are relative to the participant's diagnosis date, which is the date the initial positive HIV test result.

[b] For those participants who are unable to continue in the study, an exit visit will be conducted as soon as possible.

[c] Including assessment of HIV/acquired immunodeficiency syndrome (AIDS) related conditions.

[d] For participants of childbearing potential only.

[e] Unsolicited adverse events until 28 days after preceding vaccination, AESIs until 6 months after the last vaccination, serious adverse events and MAAEs until the last study contact. In case of a potential AESI of TTS, a serum sample should be obtained to test for anti PF4 at the local laboratory or substitute local laboratory, if possible; repeat testing may be requested for confirmation upon sponsor discretion. A test for anti PF4 will also be performed on a stored pre vaccination sample, if possible.

[f] Venous blood samples for determination of humoral immune responses will be collected from all participants and for determination of cellular immune responses from participants at sites with access to sponsor approved PBMC processing facilities. Depending on the vaccine efficacy outcome, samples may be used for the evaluation of immune markers that have a sieving effect on any breakthrough infections and for the evaluation of any immune markers that are associated with post infection control of HIV in participants, potentially including immune responses to all vaccine antigens.

[g] Blood samples for viral sequencing will be collected for all participants and may be analyzed to assess whether VE differs by phenotypic characteristics of HIV and whether there is evidence of vaccine induced immune pressure on the viral genotype, depending on the vaccine efficacy outcome.

[h] Locally performed test.

[i] To be scheduled as soon as possible after the initial positive HIV test result (Note: the request for redraw is considered as the initial positive HIV test result). This could be either a scheduled or unscheduled visit.

[j] Once the last subject has completed the Month 30 visit of the Time and Events Schedule for HIV 1 Negative Participants or has discontinued earlier, the study is considered completed. HIV infected participants still in the study at that time will be informed that they should return to the site for the Visit #.X, if not completed yet, but no further site visits will be required.

[k] All ARVs, all COVID 19 vaccinations, and all concomitant therapies administered in conjunction with new or worsening adverse events reported per protocol requirements should be reported.

[l] If, in the opinion of the investigator/site staff, the completion of the social impact questionnaire can cause undue burden to the participant, it can be omitted.

ABBREVIATIONS

Ad	adenovirus
Ad26	adenovirus serotype 26
Ad5	adenovirus serotype 5
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
API	active pharmaceutical ingredient
ART	antiretroviral therapy
ARV	antiretroviral
β-hCG	β-human chorionic gonadotropin
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
cPTE	clinical potential T cell epitopes
CRF	case report form
DAIDS	Division of Acquired Immunodeficiency Syndrome
DSMB	Data and Safety Monitoring Board
DP	drug product
DS	drug substance
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
Env	envelope
EUA	Emergency Use Authorization
EUL	Emergency Use Listing
FAS	full analysis set
FDA	Food and Drug Administration
FIH	first-in-human
Gag	group-specific antigen
gp	glycoprotein
H0	null hypothesis
H1	alternative hypothesis
HCRU	Health Care Resource Utilization
HITT	heparin-induced thrombocytopenia and thrombosis
HIV	human immunodeficiency virus
HVTN	HIV Vaccine Trials Network
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
Ig	immunoglobulin
IM	intramuscular
IRB	Institutional Review Board
IWRS	interactive web response system
LLN	lower limit of normal
MAAE	medically-attended adverse event
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT(-2)	modified intent-to-treat(-2)
Mos	Mosaic
MSM	men who have sex with men
NeF	Negative Regulatory Factor
NHP	non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OVRR	Office of Vaccines Research and Review
PBMC	peripheral blood mononuclear cell

PEP	post-exposure prophylaxis
PIMMC	potentially immune-mediated medical conditions
Pol	polymerase
PP	per-protocol
PQC	product quality complaint
PrEP	pre-exposure prophylaxis
PRO	Participant Reported Outcome
SAE	serious adverse event
SAP	Statistical Analysis Plan
SHIV	simian human immunodeficiency virus
STI	sexually transmitted infection
SUSAR	suspected unexpected serious adverse reaction
TNI	Target Number of Infections
TOU	test of understanding
TTS	thrombosis with thrombocytopenia syndrome
USFA	usual social and functional activities
VE	vaccine efficacy
Visit Inf*x*	Visit infected *x*
VISP	vaccine-induced seropositivity
VISR	vaccine-induced seroreactivity
vp	viral particle

1. INTRODUCTION

In the development of the prophylactic VAC89220 HIV-1 vaccine, the sponsor is currently evaluating the following candidate components in clinical studies: Ad26.Mos4.HIV, (aluminum phosphate-adjuvanted) Clade C gp140 and Mosaic gp140. For details see Section 14.1.

For the most comprehensive nonclinical and clinical information regarding the VAC89220 HIV-1 vaccine, see the latest version of the Investigator's Brochures and Addenda for Ad26.Mos4.HIV, Clade C gp140 and Mosaic gp140.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

Other organizations, ie, the HIV Vaccine Trials Network (HVTN), Division of AIDS (DAIDS; a division of the National Institute of Allergy and Infectious Diseases [NIAID] which is part of the National Institutes of Health [NIH]) are also involved in this study and are referred to in this protocol as "partners".

1.1. Background

1.1.1. Background on the Disease and Treatment

Human immunodeficiency virus type 1 (HIV-1) is a retrovirus that, if left untreated, can progress to acquired immunodeficiency syndrome (AIDS), a condition in which the immune system is severely compromised, leading to life-threatening conditions. The main modes of transmission of HIV-1 in the world, although varying significantly by region, are heterosexual transmission, male-to-male transmission and intravenous drug use.[34] The global prevalence of HIV-1 in 2017 is estimated at 36.9 million (range: 31.1 to 43.9 million), which is an increase from previous years, mainly explained by broader access to life-saving antiretroviral therapy (ART) and a related longer life of HIV-infected individuals. Approximately 53% of all people living with HIV have access to ART. Despite an overall decline in HIV incidence and AIDS-related deaths, the number of new infections and the cost and morbidity associated with lifelong ART remain high. Worldwide, 1.8 million (range: 1.4 to 2.4 million) people became newly infected with HIV-1 in 2017.[35] HIV infection therefore continues to be a serious and potentially life-threatening condition of major global public health interest.

A number of specific approaches are being employed or evaluated to reduce the spread of HIV-1, but no single prevention method or approach utilized to date suggests that it will be able to stop the epidemic on its own. Several methods and interventions have proved highly efficacious in reducing the risk of, and protecting against, HIV infection, including male and female condoms, the use of ARV medicines as PrEP or as PEP, voluntary male medical circumcision, sexual activity change interventions to reduce the number of sexual partners, STI testing and treatment, the use of clean needles and syringes, opiate substitution therapy (eg, methadone) and the treatment of people living with HIV to reduce viral load and prevent onward transmission (treatment as prevention). Despite the availability of this widening array of efficacious HIV prevention tools

and methods in recent years, new infections among adults globally have not decreased sufficiently.[33,36]

An effective, universal prophylactic HIV-1 vaccine could play a pivotal role in the so-called 'HIV prevention toolbox', where several HIV prevention methods will be necessary to play a significant role in controlling the spread of the infection.[33,38]

Evidence for the potential to develop a prophylactic HIV-1 vaccine comes from study RV144 (sponsored by the United States Army Surgeon General, with vaccines manufactured by Sanofi Pasteur and VaxGen). The study was conducted in more than 16,000 healthy adult Thai participants who received recombinant canarypox vector encoding group-specific antigen (Gag), polymerase (Pol), and Env proteins of HIV-1 (ALVAC-HIV [vCP1521]) vaccine followed by a recombinant gp120 subunit vaccine (AIDSVAX B/E). The vaccine afforded a modest (31%) reduction in the rate of HIV-1 acquisition.[30] In contrast to the Thai study, two Phase 3 studies of gp120 protein[11,29] and three Phase 2b/3 studies using adenovirus serotype 5 (Ad5)-vectored Gag, Pol, and Negative Regulatory Factor (Nef) HIV-1 antigens[7,16,17], failed to demonstrate protection. Recently, study HVTN 702 or Uhambo, a Phase 2b/3 evaluating the efficacy of an investigational heterologous vaccine regimen (ie, ALVAC-HIV [vCP2438] + Bivalent Subtype C gp120/MF59) based on the regimen evaluated in the RV144 clinical study but adapted to HIV-1 Clade C which is most common in southern Africa, was stopped early because the vaccine was not efficacious.[48,49]

A successful global HIV-1 vaccine will need to protect against the diverse strains and clades predominating in the target populations in different geographic regions. There is growing evidence that potent humoral responses with multiple effector functions combined with robust T cell responses will be necessary attributes of an effective HIV-1 vaccine. The HIV-1 genes expressed in the cytoplasm (eg, Gag and Pol) are primarily targeted by cytotoxic cellular immune responses, whereas the Env gp is a primary target of humoral responses.[26]

1.1.2. Background on the Study Vaccines

Nonclinical Studies

A summary of nonclinical study data available at the time of the initial protocol writing and relevant to the current study is provided below. For more information, refer to the Investigator's Brochure Editions 5 for Ad26.Mos4.HIV and Investigator's Brochure Editions 5 and Addendum 1 for and Clade C gp140 and Mosaic gp140.[21,22,20]

A regimen consisting of a 2 Ad26 vaccinations followed by two Ad26 + Clade C gp140 vaccinations was first tested in non-human primate (NHP) immunogenicity study 13-04, which showed that several differently composed heterologous Ad26/Clade C gp140 immunization schedules were immunogenic and induced comparable broad reactivity and neutralization capacity of diverse tier 1 Env pseudotyped viruses and a robust cellular immune response. This regimen was further evaluated in an NHP efficacy study (13-19/15-06), which assessed several different components and combinations thereof in the Ad26 Clade C gp140 schedule developed in 13-04. This latest study showed that a combination of vaccination with Ad26.Mos.HIV followed by

Ad26.Mos.HIV together with Clade C gp140 protein in aluminum phosphate adjuvant led to the highest level of protection observed so far with this vaccine concept. Eight/12 NHP (67%) had complete protection after the full series of 6 intrarectal challenges with Simian HIV (SHIV) SF162P3, an engineered virus consisting of the generic backbone of SIVmac239 with the envelope gene and some accessory genes derived from HIV. Env-binding antibody responses and Env-specific cellular immune responses were identified as important immunologic markers associated with vaccine-mediated protection against SHIV-SF162P3 challenges.[4]

To expand the sequence coverage of our HIV-1 vaccine strategy, an additional component (the novel Ad26.Mos2S.Env) was added to the trivalent vaccine to produce a tetravalent vaccine (Ad26.Mos4.HIV). Immunogenicity and antigenicity of a selection of novel insert combinations with the vectors under clinical development in Ad26.Mos.HIV were tested in rabbits (study 0095-14), which demonstrated that the proposed tetravalent adenovector combination shows improved Clade C pseudovirus recognition in the absence of negative effects on Clade B pseudovirus recognition and thus has the potential to substantially increase the breadth of humoral immune responses of the full vaccine regimen.

In guinea pigs, it was shown that Clade C gp140 was able to induce neutralizing antibody responses against a set of HIV-1 variants from different clades and with different neutralization sensitivities. Furthermore, it was observed that the immunogenicity of Clade C gp140 was improved by an aluminum-based adjuvant, and that these immunogenicity results were comparable in high and low absorption formulations of aluminum phosphate and aluminum hydroxide, both in terms of the binding antibody and neutralizing antibody responses induced.

Clade C gp140 was further evaluated as part of the heterologous adenovirus-based vector (Ad26)/Clade C gp140 protein immunization schedules in a rhesus monkey SHIV challenge model. The data confirmed the improved protective capacity of vaccine regimens including a Clade C gp140 boost immunization.

Mosaic gp140 induced an increased breadth of immune responses when combined with Clade C gp140 in guinea pigs, and in the context of Ad26 immunization in rabbits. Mosaic gp140 was immunogenic in NHP and was able to boost Clade C gp140-specific immune responses.

Clinical Studies

A summary of clinical study data available at the time of initial protocol writing and relevant to the current study is provided below. For more information on the clinical study results, refer to the Investigator's Brochure Editions 5 for Ad26.Mos4.HIV, Clade C gp140 and Mosaic gp140.[21,22] More information on the vaccine regimen selection for the current study is provided in Section 3.2.

Study **VAC89220HPX2004/HVTN 117** (hereafter abbreviated to HPX2004/HVTN 117), a randomized, parallel-group, placebo-controlled, double-blind Phase 1/2a study in 198 healthy HIV-uninfected adult participants is the first-in-human (FIH) study for the tetravalent Ad26.Mos4.HIV, evaluating the safety/tolerability and immunogenicity of heterologous vaccine regimens with Ad26.Mos.HIV (trivalent) or Ad26.Mos4.HIV (tetravalent) and Clade C gp140 plus adjuvant. In the Week 52 analysis (4 weeks post 3rd vaccination), all vaccine regimens were found

to be well tolerated. The most frequently reported solicited adverse events post any dose were injection site pain/tenderness, fatigue, headache, and myalgia. No deaths, no grade 4 AEs and few SAEs, Grade 3 related AEs and AEs leading to discontinuation were reported. During the vaccination period, no on-study HIV infections occurred. Overall, both vaccine regimens were immunogenic with the highest humoral and cellular responses being observed in the tetravalent group. Refer to the Investigator's Brochure Editions 6 for Ad26.Mos4.HIV, Clade C gp140 and Mosaic gp140 for more information.[46,47]

Study **VAC89220HPX2003/HVTN 118** (hereafter abbreviated to HPX2003/HVTN 118), a multi-center, randomized, parallel-group, placebo-controlled, double-blind Phase 1/2a study in 152 healthy HIV-uninfected adult participants is the FIH study for Mosaic gp 140 comparing the safety/tolerability and immunogenicity of different regimens of Ad26.Mos4.HIV together with either adjuvanted Clade C gp140 or an adjuvanted combination of Mosaic and Clade C gp140. In the Week 52 analysis (4 weeks post 4th vaccination), both vaccine regimens were found to be well tolerated. The most frequently reported solicited adverse events post any dose were injection site pain/tenderness, fatigue, headache, and myalgia. No deaths, no grade 4 AEs and few SAEs, Grade 3 related AEs and AEs leading to discontinuation were reported. During the vaccination period, no on-study HIV infections occurred. Overall, both vaccine regimens were immunogenic and favor the selection of the bivalent regimen. refer to the Investigator's Brochure Editions 6 for Ad26.Mos4.HIV, Clade C gp140 and Mosaic gp140 for more information.[46,47]

Study **VAC89220HPX2008/HVTN 705** (hereafter abbreviated to HPX2008/HVTN 705) is an ongoing, multicenter, randomized, parallel-group, placebo-controlled, double-blind Phase 2b proof-of-concept efficacy study in approximately 2,600 HIV-uninfected sexually active women aged 18 to 35 years. The study is being conducted in approximately 25 sites, with the majority of these throughout South Africa. Study participants were selected from populations at high risk of acquiring HIV infection in southern Africa settings with overall moderate to high HIV incidence. The predominant circulating HIV-1 is a Clade C virus. The study is investigating the preventive vaccine efficacy, safety, and tolerability of a heterologous regimen with 4 vaccinations consisting of tetravalent Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140, with vaccinations at Months 0, 3, 6, and 12. The primary analysis recently demonstrated that the vaccine regimen did not provide statistically significant protection against HIV infection. The vaccine efficacy over Months 7 to 24 in the per-protocol cohort did not differ significantly from zero, with a point estimate (95% confidence interval) of 25% (-10% to 49%). The regimen did not cause harm and was generally well-tolerated.[23]

Clinical Safety Experience With the Ad26.COV2.S Vaccine

Thrombosis in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome [TTS]), in some cases accompanied by internal bleeding, has been observed following vaccination with the Janssen COVID-19 (Ad26.COV2.S) vaccine. As of 31 August 2021, out of 33,584,049

doses of Ad26.COV2.S administered post-marketing, the following spontaneous reported/solicited reports of probable TTS cases were identified.[a]

- A total of 104 post-marketing events that met the Brighton TTS Case Definition Criteria Level 1 to 3.[5] This corresponds to a reporting ratio of 3.1 per million doses overall.
- A total of 67 post-marketing events that met the Centers for Disease Control and Prevention (CDC) TTS Case Definition Criteria Tier 1 to 2.[32] This corresponds to a reporting ratio 2 per million doses overall.

Reports include severe cases of venous thrombosis at unusual sites such as cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis and arterial thrombosis, in combination with thrombocytopenia. Venous thrombosis cases have also been reported at more common sites, eg, in the lower extremities. The onset of associated symptoms has usually been 1 to 4 weeks, but sometimes even later following vaccination (up to 42 days as per the American Society of Hematology 2021[2]). TTS cases have been reported mostly in women under 60 years of age although some cases of TTS have also been reported in men and in individuals older than 60 years of age. Thrombosis in combination with thrombocytopenia has been fatal in some cases. The exact pathophysiology of TTS is unclear. This event has not been observed to date with any other Janssen Ad26-based vaccines (including with Ad26.Mos4.HIV). Participants should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg pain or leg swelling, persistent abdominal pain, severe or persistent headaches, blurred vision, skin bruising or petechiae beyond the site of vaccination, changes in mental status or the occurrence of seizures.

Knowledge about TTS continues to evolve, and updates will be made as new data become available.

1.2. Benefit/Risk Section

1.2.1. Known Benefits

The clinical benefits of combinations of Ad26.Mos4.HIV and Clade C/Mosaic gp140 have yet to be established.

1.2.2. Potential Benefits

Participants may benefit from clinical testing, physical examination and high standard sexual health services; others may benefit from the knowledge that they may aid in the development of an HIV-1 vaccine. Currently, there are no effective prophylactic HIV vaccines and no efficacy can be concluded from current data. The overall benefit and risk balance for individual participants thus cannot be ascertained. Participants must be informed that this vaccine is currently being tested

[a] Probable TTS is defined as a thrombotic/thromboembolic event reported in combination with a low platelet count (thrombocytopenia).

to determine whether it is effective, and it should be assumed that it is not the case until clinical study data demonstrate its effectiveness.

1.2.3. Known Risks

Adverse drug reactions and/or adverse reactions to immunization have not yet been fully characterized. As of 8 January 2019, 2200 healthy adult participants have been enrolled in ongoing Ad26.Mos.HIV and Ad26.Mos4.HIV studies, of which 236 participants, for whom the treatment assignment is known, received at least one vaccination with Ad26.Mos4.HIV. At that cut-off date, 2250 healthy adult participants have been enrolled in ongoing Clade C gp140 and Clade C gp140 in combination with Mosaic gp140 studies, of which 93 participants, for whom the treatment assignment is known, received 250 mcg glycoprotein Clade C gp140 + Mosaic gp140. The available nonclinical and clinical data for the study vaccines support the conclusion that the vaccines have an acceptable safety profile with no emerging significant safety concerns to date. As with any experimental product, the safety profile of the vaccines or of the vaccine regimen cannot be fully defined until more clinical data are available.

1.2.4. Potential Risks

The following potential risks for Ad26.Mos4.HIV and Clade C/Mosaic gp140 will be monitored during the study and are specified in the protocol and/or the Study-Specific Procedures Binder:

Risks Related to Vaccination

In general, IM injection may cause local itching, warmth, pain, tenderness, erythema/redness, induration/swelling, arm discomfort or bruising of the skin at vaccine administration sites. Participants may exhibit general signs and symptoms associated with administration of a vaccine, or injection with placebo, including fever, chills, rash, myalgia, nausea/vomiting, headache, dizziness, arthralgia, general itching, and fatigue. These side effects will be monitored but are generally short-term and do not require treatment.

Syncope can occur in association with administration of injectable vaccines. Syncope can be accompanied by falls. Procedures should be in place to avoid falling injury. If syncope develops, participants should be observed until the symptoms resolve. Fear of injection might lead to fainting and fast breathing.

Participants may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, urticaria or even anaphylaxis. Severe reactions are rare. Participants with a known allergy, or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine products (including any of the constituents of the study vaccine) will be excluded from the study.

Risks Related to Aluminum

Aluminum is one of the most common metals found in nature and is present in air, food, and water. Aluminum salts, such as aluminum hydroxide, aluminum phosphate, and aluminum potassium sulphate have been used safely in vaccines for more than 70 years. A few studies reported an association between vaccines containing aluminum adjuvants and persistent nodules at the

injection site, at an estimated rate of 0.03% to 0.83%.[39,40,41,42] Two studies examining infant exposures to aluminum from both diet and vaccines concluded that aluminum adjuvants at the levels included in vaccines are well below the calculated body burden.[43,44] A 2017 review found that current data do not support a causal relationship between aluminum-containing vaccines and a variety of autoimmune disorders.[45]

Risks Related to Vaccine-induced Seropositivity

Risks related to vaccine-induced seropositivity (VISP) are discussed in Section 9.2.

Pregnancy and Contraception

No preclinical developmental or reprotoxicity studies have yet been performed with Ad26.Mos.HIV, Ad26.Mos4.HIV, Clade C gp140 or Mosaic gp140. However, a combined embryo-fetal and pre- and postnatal development study has been conducted in rabbits with an Ad26 vector in combination with another insert (Ad26ZEBOV, as part of a 2-dose vaccine regimen with MVA-BN-Filo). In this study, there was no maternal or developmental toxicity observed during premating and gestation period.

The sponsor is planning to conduct a combined embryo-fetal and pre- and postnatal development study including Ad26.Mos4.HIV and a combination of aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140 in parallel with the Phase 3 HPX3002 study.

Since the effect of the study vaccines on a fetus or nursing baby is unknown, participants of childbearing potential are required to agree to practice adequate contraception measures for sexual intercourse from at least 21 days before the first vaccination until at least 90 days after the last vaccination (see Section 4.1).

Risks from Blood Draws

As with all clinical studies requiring blood sampling, there are risks associated with venipuncture and multiple blood sample collection. Blood drawing may cause pain, tenderness, bruising, bleeding, dizziness, vaso-vagal response, syncope, and, rarely, infection at the site where the blood is taken. The total blood volume to be collected is considered to be an acceptable amount of blood over this time period from the population in this study (see Section 16.1).

Risks of genetic testing

The genetic testing could indicate risks for certain diseases, which could potentially lead to discrimination of or other problems for the participant. However, the results are for exploratory research purposes only and will not be provided to the participant.

Unknown Risks

There may be other risks that are not known. If any significant new risks are identified, the investigators and participants will be informed.

Participants may believe that this vaccine provides protection against acquiring HIV infection, and therefore practice riskier sexual activity. Participants must be informed that this vaccine is currently being tested to determine whether it is efficacious, and it should be assumed that it is not the case until clinical study data demonstrate efficacy. The overall benefit and risk balance for individual participants thus cannot be ascertained.

In previous HIV-efficacy studies utilizing Ad5, increased HIV-1 infection was observed in vaccine recipients as compared with placebo recipients. The mechanism for this possible increase in HIV-1 acquisition risk remains unclear, but a longstanding hypothesis suggested that activation of vector-specific $CD4^+$ T cells at mucosal surfaces following Ad5 vaccination potentially results in increased targets for HIV-1 infection. However, a recent study demonstrated no long-term changes in the activation state of mucosal CD4+ or CD8+ T cells after Ad5-vectored vaccination, regardless of baseline Ad5 serostatus.[10] Ad26 is substantially different from Ad5 in seroprevalence and immunology, biology, and protective efficacy in NHP.

1.2.5. Overall Benefit/Risk Assessment

Based on the available data and proposed safety measures, the overall benefit/risk assessment for this clinical study is considered acceptable for the following reasons:

- Safety data from the ongoing clinical studies revealed no significant safety issues (see Section 1.1.2).
- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 4) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study:

  In general, safety evaluations will be performed at scheduled visits during the study, as indicated in the Time and Events Schedule.

  After each vaccination, participants will remain in the clinic for a certain period and will be closely observed by study staff. Necessary emergency equipment and medications must be available in the clinic to treat severe allergic reactions. Participants will use a diary to document solicited administration site and systemic signs and symptoms. Details are provided in Section 9.1.1.

  The investigator or the designee will document unsolicited adverse events, SAEs, MAAEs and (potential) adverse events of special interest (AESIs) as indicated in Section 12.3.1.

  Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until a clinically stable endpoint is reached.
- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:

  The NIAID HIV Vaccine DSMB (further referred to as DSMB) will serve as an independent DSMB for this study and will monitor data on an ongoing basis to ensure the

continuing safety of the participants and will formally monitor the efficacy endpoints (see Section 11.4). The sponsor's HPX3002/HVTN 706 safety review team may initiate DSMB review for any single event or combination of multiple events which, in their professional opinion, could jeopardize the safety of the participants or the reliability of the data.

Participants will discontinue study vaccine for the reasons included in Section 10.2.

Contraindications to vaccination are included in Section 10.3.

If acute illness (excluding minor illnesses such as diarrhea or mild upper-respiratory tract infection) or fever (body temperature ≥38.0°C) occur at the scheduled time for vaccination, vaccination will be temporarily contraindicated. However, the participant may be vaccinated later, within the window allowed for the scheduled vaccination (see Section 10.3).

1.3. Overall Rationale for the Study

The proposed Phase 3 clinical study VAC89220HPX3002/HVTN 706 (hereafter referred to as HPX3002/HVTN 706) will aim to demonstrate the efficacy of a heterologous HIV-1 vaccine regimen consisting of Ad26.Mos4.HIV and a combination of aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

An overview of the objectives and endpoints is provided in Table 1.

Table 1: Objectives and Endpoints

Objectives		Endpoints	
Primary			
1	To evaluate the VE of a heterologous vaccine regimen utilizing Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140 for the prevention of HIV-1 infection in HIV-1 seronegative cis-gender men and transgender individuals having sex with cis-gender men and/or transgender individuals.	1	Confirmed HIV-1 infections diagnosed between Month 7 and Month x (with 24≤x≤30) visits in the PP population.
Secondary			
1	To evaluate the safety and reactogenicity of a heterologous vaccine regimen utilizing Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140 for the prevention of HIV-1 infection in HIV-1 seronegative cis-gender men and transgender individuals having sex with cis-gender men and/or transgender individuals.	1	• Reactogenicity: Solicited administration site and systemic adverse events for 7 days after each vaccination • Unsolicited adverse events for 28 days after each vaccination • AESIs for 6 months after the last vaccination • MAAEs for the entire duration of the study • Serious adverse events for the entire duration of the study • Discontinuations from the study or vaccination due to adverse events
2	To evaluate VE at other timepoints and in other analysis populations.	2	Confirmed HIV-1 infections over different time intervals (eg, VE[0-x months], VE[13-x months]) and in different populations (eg, mITT, mITT-2, mITT-3, FIS).
3	To evaluate VE by and adjusting for potential (baseline) confounders.	3	Potential confounders include but are not limited to: demographic characteristics, baseline Ad26 seropositivity status and titer, sexual risk behavior, and PrEP use.
Exploratory			
1	To evaluate whether VE differs by phenotypic characteristics of HIV, such as neutralization sensitivity, and whether there is evidence of vaccine-induced immune pressure on the viral phenotype.	1	Confirmed HIV-1 infection diagnosed after Day 1 through Month 30 and inferred transmitted viral isolate(s) phenotype(s) from HIV-1–infected mITT participants at the earliest available post-infection timepoint, and possible subsequent visits.

2	To evaluate whether VE differs by genotypic characteristics of HIV, such as signature site mutations, and whether there is evidence of vaccine-induced immune pressure on the viral sequences.	2	Confirmed HIV-1 infection diagnosed after Day 1 through Month 30 and inferred transmitted viral sequence(s) genotype(s) from HIV-1–infected mITT participants at the earliest available post-infection timepoint, and possible subsequent visits, using sieve analysis methods.
3	To evaluate vaccine effects on virologic and immunologic outcomes among participants that become HIV-1–infected during the study, accounting for ARV use.	3	HIV-1 viral load and $CD4^+$ count over a 6-month period after diagnosis. The frequency and magnitude of HIV-1 cellular (participants at sites with access to sponsor approved PBMC processing facilities) and humoral immune responses in participants that become HIV-1–infected during the study.
4	To evaluate immune correlate(s) of risk of HIV-1 infection and/or correlates of VE.	4	Magnitude and/or frequency of immune responses to vaccination in HIV-1 infected vaccine recipients (cases) relative to a subset of HIV-1 uninfected vaccine recipients (controls) and placebo cases and controls, as relevant. The association of immune response(s) that are identified as being associated with VE in Study VAC89220HPX2008/HVTN 705 (further referred to as HPX2008/HVTN 705), in HIV-1 infected vaccine recipients (cases) relative to a subset of HIV-1 uninfected vaccine recipients (controls) and placebo cases and controls, as relevant.
5	To evaluate the occurrence of VISP following vaccination with heterologous vaccine regimen utilizing Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140.	5	The frequency of confirmed VISP, determined utilizing a pre-specified diagnostic algorithm to distinguish HIV- 1 infection from VISP (refer to the Study-Specific Procedures Binder for more information) at different time points following vaccination.
6	To describe PROs.	6	Social impact and vaccine regimen acceptance, sexual activity, absenteeism and PrEP use collected through questionnaires completed by study participants.
7	To describe HCRU over the study period.	7	Collection of MAAEs, level of absenteeism and follow-up of HIV infections throughout the study.
8	To evaluate the immune responses elicited by the vaccine regimen.	8	The frequency and magnitude of HIV-1-specific cellular and humoral immune responses.

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

This study is designed to test the primary hypothesis of VE in the PP population:

H0: VE(7-x months) ≤20% versus H1: VE(7-x months) >20%, with 24≤x≤30.

If the lower bound of the 95% CI for VE(7-x months) is >20% at the primary analysis, the corresponding H0 will be rejected.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multi-center, randomized, parallel-group, placebo-controlled, double-blind, Phase 3 study to demonstrate efficacy of a heterologous prophylactic HIV-1 vaccine regimen consisting of Ad26.Mos4.HIV and a combination of aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140. Safety, reactogenicity and immunogenicity will also be evaluated. The study population will include healthy adults considered to be at increased risk of acquiring HIV-1 infection. A target of 3,800 participants, consisting of HIV-1-uninfected cis-gender men and transgender individuals having sex with cis-gender men and/or transgender individuals, aged ≥18 to ≤60 years, will be randomized in a 1:1 ratio to the study vaccine or placebo. Randomization will be stratified by site. All efforts will be made to ensure that the study population includes good representation of the population at the highest risk of HIV infection in terms of race, ethnicity, gender identity and age. Participants will receive IM doses of study vaccine or placebo at 4 time points: Ad26.Mos4.HIV or placebo will be given at Months 0 (Day 1) and 3; Ad26.Mos4.HIV together with a co-formulation of aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140, or placebo will be given at Months 6 and 12 (see Table 2). Sample size re-assessment may be performed based on blinded study data or external study data (eg, Phase 2b Study HPX2008/HVTN 705). The target number of HIV-1 infections may be re-assessed based on external study data (eg, Phase 2b Study HPX2008/HVTN 705) only.

Table 2: Vaccination Schedule

Group	N	Month 0	Month 3	Month 6	Month 12
1	1,900	Ad26.Mos4.HIV	Ad26.Mos4.HIV	Ad26.Mos4.HIV + Clade C gp140, Mosaic gp140, adjuvanted	Ad26.Mos4.HIV + Clade C gp140, Mosaic gp140, adjuvanted
2	1,900	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo

Total dose of Ad26.Mos4.HIV is $5x10^{10}$ viral particles (vp)/0.5 mL injection.
Clade C gp140, Mosaic gp140, adjuvanted: adjuvanted protein formulation with a dosage strength of 80 mcg Clade C protein, 75 mcg Mosaic protein and 425 mcg aluminum (as aluminum phosphate adjuvant). Note: previously the dose of Clade C gp140 and/or Mosaic gp140 was reported as mcg of glycoprotein: 125 mcg Clade C gp140 and 125 mcg Mosaic gp140 glycoprotein correspond with 80 mcg and 75 mcg of protein, respectively.

The study comprises of a screening period of 45 days, a 12-month vaccination period and a follow-up period of at least 18 months after the fourth vaccination (until Month 30) in participants who remain HIV-1 negative or up to 6 months after diagnosis of HIV-1 infection in participants who become HIV-1 infected. Participants who completed their Month 30 visit will be followed for HIV infection, MAAEs and serious adverse events until the end of the study (ie, when the last participant completed the Month 30 visit or discontinued earlier). At the end of the study, participants may be offered the possibility to enter a long-term follow-up phase or program (to collect, amongst others, additional durability data).

After vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions. In addition, participants will record solicited signs and symptoms in a diary for 7 days post-vaccination. Unsolicited adverse events will be recorded for all participants until 28 days after each preceding vaccination. From the time of local approval of protocol amendment 5 onwards, TTS is considered to be an AESI. Thrombotic events and/or thrombocytopenia (defined as platelet count below the lower limit of normal (LLN) range for the testing lab) are considered to be potential AESIs. All AESIs, including potential AESIs, will be reported to the sponsor from the moment of first vaccination until 6 months after the last vaccination. Each potential AESI will be reviewed to identify a TTS case. Serious adverse events, MAAEs, and adverse events leading to discontinuation will be collected for all participants until the end of the study. For details on reporting period of unsolicited adverse events, MAAEs, and serious adverse events, see Section 9.4. In addition, physical examinations, which includes vital sign measurements, and pregnancy testing will be performed.

An HIV test will be performed approximately every 3 months. Upon discretion of the investigator, additional HIV tests may be performed during unscheduled visits; participants should refrain from performing any HIV testing outside of the study protocol. Blood samples will be collected at specific visits for determination of humoral immune responses (all participants) and for determination of cellular immune responses (at selected sites). Participants will complete PRO questionnaires, including a social impact questionnaire, a sexual activity questionnaire and a questionnaire on the use of PrEP and questions with regard to the level of absenteeism and the vaccine regimen acceptance. For details, see the Time and Events Schedule.

If a participant becomes HIV-infected during the study (confirmed HIV test), the participant will remain in the study but no further scheduled vaccinations will be administered. Participants will be followed-up until up to 6 months after the diagnosis and will be referred to a local clinic for medical treatment and follow-up on their HIV-1 infection as soon as possible after the diagnosis of the infection. Assessments during the 6-month study follow-up will be performed according to the Time and Events Schedule for Participants Who Become HIV-1 Infected.

The sponsor and its partners are committed to ensuring that all study participants receive access to the highest standard of prevention, which may include, but is not limited to, HIV testing, risk reduction counseling, provision of male condoms and lubricants, access to management of STIs, and appropriate referrals for PrEP and PEP according to national and/or local guidelines. Note: potential participants choosing to use PrEP will not be eligible for participation in the study as, due to the high effectiveness of PrEP, these individuals are not considered to be at increased risk of HIV acquisition. However, once enrolled in the study and having received their first vaccination, a participant who changes his/her mind regarding PrEP use is permitted to take PrEP according to the site PrEP plan and will continue to receive further vaccinations. In case of PrEP use during the study, safety monitoring for PrEP will be the responsibility of the prescribing physician. HIV testing should be performed within the study to avoid unblinding due to VISP elicited by the vaccine. Participants should refrain from HIV testing outside of the study protocol. As part of the study protocol, blood samples will be collected for ARV detection in dried blood spot and stored at pre-specified sample collection days for assessment of quantitative concentrations of tenofovir

diphosphate. Additional ARV detection can be done on stored blood samples if required, as per the Study Specific Procedures Binder. The use of PrEP and adherence to PrEP (if applicable) will be monitored by means of a questionnaire which will be completed by all participants on Day 1 and approximately every 3 months.

An independent DSMB will monitor data on an ongoing basis to ensure the continuing safety of the participants and will formally monitor the efficacy endpoints (see Section 11.4). The DSMB responsibilities, authorities, and procedures will be documented in its charter.

The COVID-19 Appendix in Section 18 provides guidance to investigators for managing study-related procedures during the COVID-19 pandemic.

3.2. Study Design Rationale

Vaccines and Dose Selection Rationale

The sponsor and its partners has evaluated and are evaluating different candidate HIV-1 vaccine components in different clinical studies, results of which formed the basis of the vaccine regimen selection for the the Phase 3 study HPX3002/HVTN 706.

Based on immunologic responses observed in the Phase 1/2a study HIV-V-A004, a regimen of vaccination with the Ad26.Mos.HIV vaccine at Months 0 (Day 1) and 3 and vaccination with the Ad26.Mos.HIV vaccine and aluminum phosphate-adjuvanted Clade C gp140 at Months 6 and 12 has been selected over other regimens. The pre-clinical NHP study NHP 13-19/15-06 (in which the vaccination regimens reflect to a large extent the regimens in the HIV-V-A004 clinical study) indicated that this vaccination regimen showed the highest per exposure risk reduction (94%), which was associated with 67% complete protection after a series of 6 weekly intrarectal SHIV challenges.[4]

Based on the magnitude of immunologic responses observed in the Phase 1 study HIV-V-A003 and in the Phase 1/2a study HIV-V-A004, a 250-mcg glycoprotein dose of aluminum phosphate-adjuvanted Clade C gp140 has been selected over a 50-mcg glycoprotein dose.

Based on interim (Month 7 [Week 28; 4 weeks post 3rd vaccination], approximately 60 participants) results of the Phase 1/2a study HPX2004/HVTN 117 showing better immunogenicity for Clade C and other clades, the tetravalent Ad26.Mos4.HIV was selected for evaluation in the Phase 2b proof-of-efficacy study HPX2008/HVTN 705. Consequently, a heterologous regimen with the tetravalent Ad26.Mos4.HIV and a 250-mcg dose of aluminum phosphate-adjuvanted Clade C gp140 is being evaluated in the ongoing Phase 2b study HPX2008/HVTN 705. This study is being performed in female participants in sub-Saharan Africa where circulating viruses are predominantly of subtype (Clade) C. The primary analysis results of HPX2004/HVTN 117, including Month 7 data of all participants confirm the choice of the tetra- over the trivalent Ad26 vaccine.[21,22] Therefore, the Ad26.Mos4.HIV will be used for the proposed Phase 3 efficacy study HPX3002/HVTN 706.

Based on the primary analysis of HPX2003/HVTN 118 and HPX2004/HVTN 117, the combination of aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140 was selected for inclusion in the 3rd and 4th vaccinations over the Clade C gp140 alone. In line with the bivalent nature of the Env and Gag-Pol encoding Ad26 vectors, a bivalent mixture of gp140 proteins, which have complementary sequences, is anticipated to provide better coverage of the circulating strains of HIV-1 globally, than either component alone. The favorable safety profile of Clade C gp140 was maintained by replacing half of the Clade C gp140 dose with Mosaic gp140, while maintaining the same total glycoprotein dose of 250 mcg (corresponding to a total protein dose of 155 mcg). Peak immune responses post 3rd vaccination were highly comparable between the 2 regimens and similar levels of Clade C-specific humoral and cellular responses were observed, demonstrating that a region-specific vaccine is not needed. The immune responses induced by the combination of Clade C gp140 and Mosaic gp140 show broad Env-specific binding and functional humoral responses, as well as high frequencies of Env-specific T cell responses and improved Clade B Env binding antibody responses without compromising Clade C Env binding antibody responses. In addition, a combination of Clade C and Mosaic gp140 is preferred due to the efficient manufacturability of Mosaic gp140, which results in higher yields compared to Clade C gp140, thereby contributing to a continuous vaccine supply.

This last step of the final regimen selection was based on the Month 7 (Week 28; 4 weeks post 3rd vaccination) results of HPX2003/HVTN 118. The Month 13 (Week 52; 4 weeks post 4th vaccination) analysis results of HPX2003/HVTN 118 strengthened the original choice of the combination of aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140 over the Clade C gp140 alone.

Blinding, Control, Study Phase/Periods, Treatment Groups

A placebo control will be used to establish the frequency in clinical endpoints that may occur in the absence of active vaccine. Randomization will be used to minimize bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. In addition, randomization will be stratified by site. Blinded vaccination will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

The independent DSMB will monitor data on a 6-monthly basis to ensure the continuing safety of the participants enrolled in this study. The independent DSMB will review unblinded data.

4. PARTICIPANT POPULATION

Screening for eligible participants will be performed within 45 days before administration of the first study vaccination.

The inclusion and exclusion criteria for enrolling participants in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate HPX3002/HVTN 706 safety review team

representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

4.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Each potential participant must pass the TOU (see Attachment 2), indicating understanding of the purpose, procedures and potential risks and benefits of the study, after reading the ICF and after the investigator or designee has provided detailed information on the study and has answered the potential participant's questions. Each participant must subsequently sign the ICF, indicating the willingness to participate in the study.

2. Potential participant is ≥18 to ≤60 years old on the day of signing the ICF.

3. Criterion modified per Amendment 1

   3.1 Criterion modified per Amendment 3

   3.2 Individual is either:

   - Cis-gender man having sex with cis-gender men and/or transgender individuals, OR
   - Transgender woman having sex with cis-gender men and/or transgender individuals, OR
   - Transgender man having sex with cis-gender men and/or transgender women (transgender man having sex exclusively with transgender men is excluded), OR
   - Gender non-conforming individual having receptive or insertive anal and/or vaginal condomless intercourse,

   AND who is considered by the site staff to be at increased risk for HIV-1 infection. The potential participants must in the last 6 months have had:

   - Any condomless receptive anal or vaginal sex (not included is condomless anal sex within a mutually monogamous relationship ≥12 months if the partner is HIV negative or living with HIV and virally suppressed), OR
   - Rectal or urethral gonorrhea or chlamydia or incident syphilis, OR
   - Any stimulant use or any other drug and/or substance which in the local context may be associated with increased HIV transmission (eg, cocaine, amphetamine), OR
   - 5 or more sex partners

Refer to the Study-Specific Procedures Binder for further guidance and screening tool on the sexual risk evaluation.

4. Criterion modified per Amendment 1

   4.1 Criterion modified per Amendment 3

   4.2 Criterion modified per Amendment 4

   4.3 Potential participant has a negative test result for HIV-1 and HIV-2 infection ≤28 days prior to first vaccination.

5. Potential participant must be healthy based on medical history, physical examination, and vital sign measurement performed at screening.

6. Potential participant is willing/able to adhere to the prohibitions and restrictions specified in the protocol and study procedures.

7. Criterion modified per Amendment 1

   7.1 Criterion modified per Amendment 3

   7.2 Contraceptive use by participants assigned female at birth and who have not had sexual reassignment surgery should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

   Before randomization, participants who were assigned female at birth must be either (as defined in Attachment 1):

   a. Not of childbearing potential

   b. Of childbearing potential and practicing an acceptable highly effective method of contraception when engaging in receptive vaginal sexual intercourse and agrees to remain on such a method of contraception from 21 days prior to the first vaccination until 90 days after the last dose of study vaccine. Acceptable highly effective contraceptive methods based on the Clinical Trial Facilitation Group guidance are included in Attachment 1:

8. Criterion modified per Amendment 1

   8.1 Criterion modified per Amendment 3

   8.2 All participants of childbearing potential (as defined in Attachment 1) must:

   a. Have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening

   b. Have a negative urine β-hCG pregnancy test immediately prior to each study vaccine administration

9. Criterion was deleted per Amendment 1

4.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Criterion modified Amendment 1

   1.1 Potential participant shares needles during injection of drugs or any other substance.

2. Criterion modified Amendment 1

   2.1 Potential participant has any clinically significant acute or chronic medical condition that in the opinion of the investigator would preclude participation (including, but not limited to: history of seizure disorders, bleeding/clotting disorder, autoimmune disease, active malignancy, poorly controlled asthma, active tuberculosis or other systemic infections). In case of questions, the investigator should contact the HPX3002/HVTN 706 safety review team. An isolated seizure with clear etiology or febrile seizures during childhood are not exclusionary.

3. Criterion modified Amendment 1

   3.1 Criterion modified per Amendment 3

   3.2 Criterion modified per Amendment 5

   3.3 Potential participant has had surgery requiring hospitalization (defined as inpatient stay for longer than 24 hours or overnight stay) within the 4 weeks before screening, or will not have fully recovered from surgery requiring hospitalization, or has surgery (planned before enrollment) requiring hospitalization planned 28 days before or after planned administration of the first or subsequent study vaccination(s) that would interfere with protocol assessments (as per the investigator's judgement and after HPX3002/HVTN 706 safety review team consultation).

4. Potential participant has had a psychiatric condition or alcohol or drug abuse problems (including hospitalization or periods of work disability) that in the opinion of the investigator would interfere with protocol compliance and thus would preclude participation.

5. Criterion modified per Amendment 4

   5.1 Potential participant received or plans to receive:

   a. licensed live attenuated vaccines - within 28 days before or after planned administration of the first or subsequent study vaccination[s]. For details regarding COVID-19 vaccines, see bullet c and d below.

   b. other licensed (not live) vaccines - within 14 days before or after planned administration of the first or subsequent study vaccination[s]. For details regarding COVID-19 vaccines, see bullet c and d below.

c. Recombinant viral vectored COVID-19 vaccines or live attenuated COVID-19 vaccines, either licensed or authorized for emergency use (eg, Emergency Use Authorization [EUA], Emergency Use Listing [EUL] or similar program) within 28 days before or after planned administration of the first or subsequent study vaccination[s].

d. Other COVID-19 vaccines than the ones specified in bullet c (eg, mRNA vaccines, protein-based vaccines) either licensed or authorized for emergency use (eg, EUA, EUL or similar program) within 14 days before or after planned administration of the first or subsequent study vaccination[s]

6. Criterion modified per Amendment 1

6.1 Criterion modified per Amendment 3

6.2 Potential participants choosing to use PrEP.

Notes:

- Once participants are enrolled and received their first vaccination, and they change their mind regarding PrEP usage, they will be allowed to take PrEP according to the site PrEP plan and will continue to receive further vaccinations.

- The use of long acting PrEP is disallowed from 24 months prior to Day 1.

7. Criterion modified per Amendment 1

7.1 Potential participant has used investigational research agents within 28 days of randomization. For experimental vaccines, see exclusion criterion 8. For HIV-related monoclonal antibodies (mAbs), see exclusion criterion 9.

8. Criterion modified per Amendment 1

8.1 Criterion modified per Amendment 4

8.2 Potential participant is a recipient of a HIV-vaccine candidate at any time, or a recipient of other experimental vaccine(s) within the last 12 months prior to Day 1. For participants who received an experimental vaccine (except HIV vaccine) more than 12 months prior to Day 1, documentation of the identity of the experimental vaccine must be provided to the HPX3002/HVTN 706 safety review team, who will determine eligibility on a case-by-case basis.

Exceptions: Participants can be included if the vaccine received (except HIV vaccine) was subsequently licensed or authorized for emergency use (eg, EUA, EUL, or similar program) (see exclusion criterion 5). Participants with proof of having received only placebo can also be included. Participants who are currently still in an interventional study of such a licensed/emergency use-authorized vaccine are to be excluded from the current study (see exclusion criterion 10).

9. Criterion modified per Amendment 1

   9.1 Potential participant has received an HIV-related mAb, whether licensed or investigational, within the last 12 months prior to Day 1. For participants who received an HIV-related mAb more than 12 months prior to Day 1, documentation of the identity of the mAb must be provided to the HPX3002/HVTN 706 safety review team, who will determine eligibility on a case-by-case basis.

10. Criterion modified Amendment 1

    10.1 Potential participant is currently in, or plans participation in, another interventional study during the study period. Participation in an observational study is allowed with prior approval of the HPX3002/HVTN 706 safety review team.

11. Potential participant has been in receipt of blood or Ig products in the past 3 months.

12. Criterion modified per Amendment 1

    12.1 Potential participant has known allergy or history of anaphylaxis or other serious adverse reactions to vaccines.

    Note: Potential participants should inform the doctor/staff of prior history of any allergic reaction to any injection or vaccine. If the answer is yes, more in-depth questioning will be conducted in an attempt to ascertain the specific vaccine, type of vaccine, excipients used in such a vaccine, etc

13. Potential participant has a history of any chronic/recurrent conditions that require regular/recurrent use of oral/parenteral corticosteroids or other immunomodulators/immunosuppressors. Ocular, topical or inhaled steroids are allowed.

14. Potential participant is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site or an employee of the sponsor or its partners.

15. Criterion modified per Amendment 2

    15.1 Pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 90 days after the last dose of study vaccination.

16. Criterion added per Amendment 5

    16.1 History of TTS or heparin-induced thrombocytopenia and thrombosis (HITT)

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study vaccine is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 9.1.3 describes options for retesting. Section 17.5, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential participants must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8 PRESTUDY AND CONCOMITANT THERAPY for details regarding prohibited and restricted therapy during the study.

2. Criterion modified per Amendment 1:

   2.1. Participants in the study will not be able to donate blood, blood products, eggs (ova, oocytes) or sperm during the time of the study due to the potential confusion with VISP at blood banks or sperm banks. Furthermore, participants may be excluded from donating blood, eggs or sperm in the future upon disclosure of their participation in a viral-vectored vaccine study and the potential of a positive HIV screening test result due to VISP.

3. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (Section 4.1 and Section 4.2, respectively). For the surgeries mentioned in exclusion criterion 3, it will be per investigator's judgement whether the surgery would interfere with protocol assessments during the study. The safety review team will be available for consultation, where appropriate.

5. STUDY VACCINE ALLOCATION AND BLINDING

Study Vaccine Allocation

Procedures for Randomization and Stratification

Participants will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using permuted blocks and will be stratified by study site. Based on this randomization code, the study vaccine/placebo will be packaged and labeled for each participant.

Central randomization will be implemented in this study. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study vaccine/placebo vial for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

The study participants, study-site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and investigator will be blinded to study vaccine allocation until the end of the study (see Section 10.1). The sponsor and its partners will be blinded to study

vaccine allocation until the primary analysis when the last participant has reached their Month x visit (with 24≤x≤30).

The pharmacist with primary responsibility for vaccine preparation (see Section 14.3) will not be blinded to the study vaccine. In order to preserve blinding, he/she will place an overlay on the syringes. Administration of study vaccine to the participants will be performed by a blinded qualified healthcare provider from the study site.

The investigator will not be provided with randomization codes during the study. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the treatment assignment will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding. Participants who discontinue vaccination early will be reminded that no HIV testing should be performed outside the study protocol to avoid unblinding.

Under normal circumstances, the blind should not be broken by the investigator until the end of the study and the electronic data capture (eDC) database is finalized unless it is essential for the timely management of the participant. In this case, the investigator may determine the identity of the treatment by contacting the IWRS. While the responsibility to break the code in emergency situations resides solely with the investigator, it is recommended that the investigator contacts the HPX3002/HVTN 706 safety review team if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its partners will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor and its partners must be informed as soon as possible. The date and reason for the unblinding must be documented by the IWRS, in the appropriate section of the case report form (CRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their treatment assignment unblinded due to safety reasons should continue to return for safety and immunogenicity evaluations and efficacy (see Section 10.2), but will be withdrawn from further study vaccine administration.

6. DOSAGE AND ADMINISTRATION

Participants will be vaccinated at the study site according to the schedule detailed in Section 3.1. For description of the vaccinations, see Section 14.1.

Each participant will receive doses of study vaccine or placebo at four time points according to randomization, on Month 0 (Day 1), 3, 6, and 12, administered by IM injection, preferably into the deltoid muscle. In case an alternative site is needed, please refer to the Study Specific Procedures Binder. For visits with only one injection (ie, at Month 0 [Day 1] and 3), preferably the deltoid of the non-dominant upper arm is used. When 2 injections are to be given at one visit (ie, at Month 6

and 12), it is required to use a different deltoid for each injection. Two injections in the same deltoid are allowed only if medically indicated.

For information on vaccination windows, see Section 9.1.2. Every effort should be made to follow the vaccination schedule per the protocol. Vaccinations should generally not be administered outside the predefined visit window (see Section 9.1.2). If a participant cannot be vaccinated within the predefined window, the HPX3002/HVTN 706 safety review team can determine on a case-by-case basis if the participant can still be vaccinated. Note that cases of out of window vaccination due to per protocol allowed COVID-19 vaccination (see Section 8) should be notified to the sponsor and do not need safety review team approval. There should be a time interval of at least 28 days between study vaccinations.

Table 3: Description of Study Products

Test articles	Ad26.Mos4.HIV	Clade C gp140, Mosaic gp140, aluminum phosphate	Placebo
Description	See Section 14.		
Dose/delivery (0.5 mL injection)	$5x10^{10}$ vp	80 mcg Clade C protein*, 75 mcg Mosaic protein*, adjuvanted with aluminum phosphate (425 mcg aluminum)	0.9% saline
Frequency	Month 0 (Day 1), 3, 6, and 12	Month 6 and 12	Month 0 (Day 1) and 3 (1 injection), Month 6 and 12 (2 injections)
Route of administration	IM in deltoid	IM in deltoid	IM in deltoid
Delivery method	Refer to the Study-Specific Procedures Binder for details.		

Gp: glycoprotein; HIV: human immunodeficiency virus; IM: intramuscular; vp: viral particle
* 80 mcg Clade C gp140 and 75 mcg Mosaic gp140 of protein correspond with 125 mcg and 125 mcg glycoprotein, respectively.

7. TREATMENT COMPLIANCE

Study vaccines will be administered as an IM injection by blinded qualified study-site personnel at the study site. Details of each administration will be recorded in the CRF (including date and time of injection and deltoid used for injection). For blinding procedures, see Section 5.

8. PRESTUDY AND CONCOMITANT THERAPY

The following prestudy specific therapies administered up to 1 month before the first vaccination must be recorded at screening: analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, systemic corticosteroids, antihistaminics, mAbs, or vaccinations. Any COVID-19 vaccination must also be recorded at screening, regardless of how long before screening the vaccination took place.

The following concomitant therapies must be recorded from the first dose of study vaccine to 1 month after the last study vaccination: analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs, hormonal therapy, hormone-based contraception, systemic corticosteroids, antihistaminics, mAbs, or vaccinations. Exception: Any COVID-19 vaccination

must be recorded until the end of the study. In addition, any HIV prevention medication should be recorded. The use of PrEP, PEP, hormonal therapy and hormone-based contraception should be recorded at each visit, except for the follow-up contact Visits 2a, 3a, 4a and 7a). All other concomitant therapies should also be recorded if administered in conjunction with new or worsening adverse events reported per protocol requirements outlined in Section 12.3.1. If a participant becomes HIV-1 infected during the study, use of ARVs should also be recorded.

Use of any experimental medication (including experimental vaccines other than the study vaccines) during the study is not allowed.

The use of long acting PrEP is disallowed from 24 months prior to Day 1 until after the first vaccination.

Vaccination with licensed live attenuated vaccines (for details on COVID-19 vaccines, see below) within 28 days before or after planned administration of the first or subsequent study vaccination(s) is prohibited. Other licensed vaccines (eg, tetanus, hepatitis A, hepatitis B, rabies, for details on COVID-19 vaccines, see below) should be given at least 14 days before or after administration of first or subsequent study vaccination(s) in order to avoid potential confusion of adverse reactions and potential immune interference. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

Vaccination with COVID-19 vaccines that have been either licensed or authorized for emergency use (eg, EUA, EUL, or similar program) must take priority over the study vaccine. The interval between study vaccination and administration of a recombinant viral vectored COVID-19 vaccine or a live attenuated COVID-19 vaccine should be at least 28 days. The interval between study vaccination and administration of other types of COVID-19 vaccines (eg, mRNA vaccines, protein-based vaccines) should be at least 14 days.

Treatment with HIV-related mAbs, whether licensed or investigational, during the study is disallowed.

Chronic or recurrent use of immunomodulators/suppressors, eg, cancer chemotherapeutic agents or systemic corticosteroids, is prohibited (after discussion with the HPX3002/HVTN 706 safety review team) starting from 1 month before the planned administration of the first dose of study vaccine until 1 month after the last vaccination. If participants require these medications, they will be withdrawn from the study vaccine administration (See Section 10.2). Note: Ocular, topical or inhaled steroids are allowed.

For participants who become HIV infected, all ARVs and all concomitant therapies administered in conjunction with new or worsening adverse events reported per protocol requirements should be reported.

The HPX3002/HVTN 706 safety review team must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy (HIV testing; refer to the Study-Specific Procedures Binder for more information) immunogenicity and safety measurements applicable to this study.

Evaluation of the safety/tolerability of the vaccine regimens will include physical examinations by clinical staff, vital signs assessments and signs and symptoms following vaccinations. Additional unscheduled study visits may be required if in the investigator's opinion, further clinical or laboratory evaluation is needed.

Participants will be provided with a thermometer (to measure body temperature), ruler (to measure local administration site reactions), and participant diary to record body temperature and solicited administration site and systemic signs and symptoms.

The diary includes instructions on how to capture the data and grading scales to assess severity of the signs and symptoms. The study staff is responsible for providing appropriate training to the participant to avoid missing or incorrect data (refer to Study-Specific Procedures Binder). If a participant misses a vaccination, the diary covering the period after the missed vaccination does not have to be filled in.

Venous blood samples will be collected for humoral immunogenicity testing (all participants; analyzed in a subset) and for cellular immunogenicity testing (participants at sites with access to sponsor approved PBMC processing facilities; analyzed in a subset).

To determine VE, venous blood samples will be collected for HIV testing. HIV testing should be performed per the sponsor-approved algorithm as described in the Study Specific Procedures Binder.

9.1.2. Visit Windows

The maximum screening period is 45 days, except for HIV testing which needs to be performed within 28 days prior to first vaccination.

The timings of the visits will be determined relative to the actual day of the first vaccination. For the study visits, following windows will be allowed:

- Visit 2a: (Day 9) ± 7 days[#]
- Visit 3: Month 3 (Day 84) ± 14 days
- Visit 3a: (Day 92)* ± 7 days[#]
- Visit 4: Month 6 (Day 168) -14/+28 days
- Visit 4a: (Day 176)* ±7 days[#]
- Visit 5: Month 7 (Day 196)* -14/+28 days

- Visit 6: Month 9 (Day 273) -14/+28 days
- Visit 7: Month 12 (Day 364) -14/+42 days
- Visit 7a: (Day 372)* ±7 days[#]
- Visit 8: Month 13 (Day 394)* -14/+28 days
- Visit 9: Month 15 (Day 455) -14/+28 days
- Visit 10: Month 18 (Day 546) -14/+28 days
- Visit 11: Month 21 (Day 637) -14/+28 days
- Visit 12: Month 24 (Day 728) -14/+28 days
- Visit 13: Month 27 (Day 819) -14/+28 days
- Visit 14: Month 30 (Day 910) -14/+28 days

* If a participant is not vaccinated on the given day of vaccination, ie, Visit 3 (Day 84), Visit 4 (Day 168) and Visit 7 (Day 364), the timings of the study site Visits 5 and 8 and follow-up contact Visits 3a, 4a and 7a, will be scheduled relative to the actual day of vaccination.

[#] The site staff and the participant will make multiple efforts in good faith to be in contact after the last day of the reactogenicity period, or sooner if indicated, to discuss presence of any signs and symptoms of reactogenicity. Participants who self-report any post-vaccination reaction greater than mild are seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has resolved completely.

Every effort should be made to follow the vaccination schedule per the protocol. Vaccinations should generally not be administered outside the prespecified window. If a participant cannot be vaccinated within the predefined window, the HPX3002/HVTN 706 safety review team can determine on a case-by-case basis if the participant can still be vaccinated. Note that cases of out of window vaccination due to per protocol allowed COVID-19 vaccination (see Section 8) should be notified to the sponsor and do not need safety review team approval. There should be a time interval of at least 28 days between study vaccinations.

The allowed time window for the follow-up visits scheduled every 3 months post Month 30 is ± 28 days. Visits post Month 30 will be scheduled relative to the Month 30 visit.

For participants who become HIV-1 infected, the timings of the follow-up visits will be determined relative to the date of diagnosis, which is the date of the initial positive HIV test result. Following time windows will be allowed:

- Visit #.X as soon as possible after the initial positive HIV test result. This could be either a scheduled or unscheduled visit.
- Visit Inf1: Month 3 (Day 84) ± 28 days
- Visit Inf2: Month 6 (Day 168) ± 28 days

9.1.3. Screening Phase (Day -45 to Month 0)

Only healthy volunteers negative for HIV infection and complying with the inclusion and exclusion criteria specified in Section 4, Participant Population, will be included into the study. The investigator or designee will provide detailed information on the study to the potential

participants and will obtain written informed consent prior to each participant's enrollment in the study. All the procedures described in the Time and Events Schedule, except for the TOU, will only take place after written informed consent has been obtained.

Screening may be conducted in part via a protocol team (cross-functional) and Institutional Review Board (IRB)/Institutional Ethics Committee (IEC)-pre-approved non-study-specific screening consent process, but only if the relevant pre-screening tests match the per protocol screening tests and are within 45 days (28 days for HIV test) prior to first vaccination. However, no study-specific procedures, other than screening assessments, will be performed until the potential participant has signed the study-specific ICF. The study-specific ICF date will be entered into the CRF. The non-study-specific ICF will be considered source data.

Each potential participant must pass the TOU (see Section 16.1 and Attachment 2), indicating that he or she understands the purpose of, and procedures required for the study, after reading the informed consent and after the investigator or designee has provided detailed information on the study and has answered the potential participant's questions. Each participant must subsequently sign the ICF, indicating that he or she is willing to participate in the study.

The following evaluations will be performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Demographics (eg, sex assigned at birth, participant-identified gender at screening, age, male circumcision, race) and Medical history (Note in addition to medical history to determine eligibility requirements, history and family history of immune disorders will be recorded)
- Full physical examination, including height, weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin
- Review of prestudy medications as specified in Section 8
- Counseling on avoidance of HIV infection
- Review of inclusion/exclusion criteria
- HIV testing (including pre- and post-HIV-test counseling). The screening HIV test should be performed within 28 days prior to first vaccination
- Participants of childbearing potential: serum β-hCG pregnancy testing

General eligibility for this clinical study will be dependent on results of the medical assessment. After medical history and physical examination data have been reviewed for completeness and adherence to inclusion/exclusion criteria, the potential participant can be deemed to be eligible for the study. Eligible participants will be contacted and scheduled for vaccination (Visit 2) within 45 days from signing ICF.

At screening, blood samples for syphilis serology determination will be collected and the presence of chlamydia/gonorrhea will be tested using (1) a urine sample, (2) a rectal swab, and (3) an oropharyngeal swab. If required by standard local procedure, the collection of a urethral swab will

be considered equivalent to a urine sample. However, potential participants with STIs will not be excluded from the study.

Potential participants with vital signs not meeting eligibility criteria on the screening visit may have one repeat testing during the screening period if the abnormality is not clinically significant and may be a testing aberrancy. The screening visit may be split into multiple days/visits.

All serious adverse events and adverse events and special reporting situations, that are related to study procedures or that are related to non-investigational sponsor products will be recorded on the CRF, from the time a signed and dated ICF is obtained until the end of the study/early withdrawal, together with information about concomitant medications as specified in Section 8.

If a potential participant is a screen failure, but at some point in the future is expected to meet the participant eligibility criteria, the potential participant may be rescreened on one occasion only. Potential participants who are rescreened will be assigned a new participant number, undergo the informed consent process, and then restart a new screening phase. In case a potential participant is rescreened, there is no need to repeat the STI tests (syphilis, chlamydia and gonorrhea), unless the STI test results were performed more than 3 months prior to the planned first vaccination or unless clinically indicated. Previous STI test results can be used provided these are not older than 3 months. If the previous STI test was performed more than 3 months prior to the first vaccination or if clinically indicated, the STI testing needs to be repeated.

9.1.4. Vaccination

Visit 2/Randomization/Vaccination 1

After re-check of inclusion/exclusion criteria (including concomitant medication), a targeted, symptom-directed physical examination (including weight measurement and vital sign measurement), and a urine pregnancy test (for participants of childbearing potential), eligible participants will be randomized as described in Section 5.

If medical status and/or physical examination suggest(s) significant changes have occurred since screening, the clinically relevant screening assessments, if applicable, will be repeated and the Month 0 (Day 1) visit rescheduled, provided that the rescheduled visit is within 45 days of the initial screening assessment.

Blood samples for HIV testing and humoral (pre-dose; all participants) and cellular (pre-dose; at sites with access to sponsor approved PBMC processing facilities) immunogenicity assays will be collected.

Participants will be provided with a thermometer, ruler, and participant diary to measure and record solicited signs and symptoms. Solicited adverse events will be recorded daily for 7 days post-vaccination. Pre-and post-dose unsolicited adverse events will be recorded for 28 days post-vaccination in all participants. AESIs will be recorded from first vaccination onwards until 6 months after the last vaccination. Serious adverse events, MAAEs and adverse events leading to

vaccine or study discontinuation will be collected for all participants, together with information about concomitant medications as specified in Section 8.

Study vaccine will be prepared by the unblinded site pharmacist, who will place an overlay on the syringes (to preserve blinding) and will send it to the clinic. Administration of study vaccine to the participant will be performed by a blinded qualified healthcare provider from the study site.

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions (see Section 9.4), and vital signs measurement will be repeated.

A sexual activity questionnaire and a questionnaire on the use of PrEP will be completed. In addition, the level of absenteeism since screening will be collected.

Counseling related to avoidance of HIV infection will be provided to all participants.

Visit 3/Vaccination 2

Procedures for Visit 3 will include the following:

- A targeted physical examination as described for Visit 2
- Completion of the social impact questionnaire
- Collection level of absenteeism since Visit 2
- An HIV test (pre-dose)
- Recording of concomitant medication, adverse events, including AESIs, serious adverse events and MAAEs as described for Visit 2
- Distribution of diary
- HIV risk reduction counseling
- Completion of a questionnaire on the use of and, if applicable, adherence to PrEP
- Blood for dried blood spots will be collected for participants who have their visit on pre-specified calendar days (may differ per site)
- A urine pregnancy test must be performed before vaccination for participants of childbearing potential, and results must be available and negative prior to vaccination.
- Review of solicited signs and symptoms recorded in the diary will be completed and solicited adverse events will be documented.

Visit 4/Vaccination 3

Procedures for Visit 4 will include the following:

- A targeted physical examination as described for Visit 2
- Collection level of absenteeism since Visit 3
- An HIV test (pre-dose)
- Recording of concomitant medication, adverse events, including AESIs, serious adverse events and MAAEs as described for Visit 2
- Distribution of diary
- Syphilis serology and chlamydia/gonorrhea test as described for Visit 1
- HIV risk reduction counseling
- Completion of a questionnaire on the use of and, if applicable, adherence to PrEP
- Blood for dried blood spots will be collected for participants who have their visit on pre-specified calendar days (may differ per site)
- A urine pregnancy test must be performed before vaccination for participants of childbearing potential, and results must be available and negative prior to vaccination.
- Review of solicited signs and symptoms recorded in the diary will be completed and solicited adverse events will be documented.

Visit 7/Vaccination 4

Procedures for Visit 7 will include the following:

- A targeted physical examination as described for Visit 2
- An HIV test (pre-dose)
- Recording of concomitant medication, adverse events, including AESIs, serious adverse events and MAAEs as described for Visit 2
- Distribution of diary
- Syphilis serology and chlamydia/gonorrhea test as described for Visit1
- HIV risk reduction counseling
- Completion of the sexual activity questionnaire and social impact questionnaire

- Collection level of absenteeism since their last visit
- Completion of a questionnaire on the use of and, if applicable, adherence to PrEP.
- Blood for dried blood spots will be collected for participants who have their visit on pre-specified calendar days (may differ per site).
- A urine pregnancy test must be performed before vaccination for participants of childbearing potential, and results must be available and negative prior to vaccination.
- Recording of gender identity

9.1.5. Post-vaccination Follow-up Phase

Participants who have been prematurely withdrawn from study vaccine administration will be encouraged to complete the visit schedule as planned with assessments per the Time and Event Schedule, including assessments of safety and HIV diagnosis. Participants who received the first 3 vaccinations but discontinue study vaccination before receiving the 4th vaccination, should continue the visit schedule as planned with assessments per the Time and Event Schedule including assessments of safety, immunogenicity and HIV diagnosis. They will also be reminded not to have HIV testing outside of the study protocol as this could lead to misdiagnosis and unblinding.

Visits 2a, 3a, 4a and 7a

The site staff and the participant will make multiple efforts in good faith to be in contact after the last day of the reactogenicity period, or sooner if indicated, to discuss the presence of any signs and symptoms of reactogenicity. Clinic staff will follow new or unresolved reactogenicity symptoms present at the last day of the reactogenicity assessment period to resolution. Participants are instructed to contact the clinic for events that arise during the period between vaccination and the next scheduled visit. In general, a participant who self-reports any postvaccination reaction greater than mild is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has resolved completely.

Visits 5 and 6/Post-Vaccination 3 Follow-up

Visit 5 is a clinic visit which will include a targeted, symptom-directed physical examination (including weight measurement and vital signs measurement) and HIV testing. Unsolicited AEs (if applicable), AESIs, SAEs, MAAEs and adverse events leading to study discontinuation will be recorded for all participants, together with information about concomitant medications as described in Section 8. Review of solicited signs and symptoms recorded in the diary will be completed and solicited adverse events will be documented. Counseling related to avoidance of HIV infection will be provided to all participants. A sexual activity questionnaire will be completed. The level of absenteeism since their last visit will be recorded. Samples for humoral (all participants) and cellular (at sites with access to sponsor approved PBMC processing facilities) immunogenicity assays will be collected.

Visit 6 is a clinic visit which will include a targeted physical examination, HIV testing, recording of AESIs, serious adverse events, MAAEs and adverse events leading to study discontinuation, recording of concomitant medication, and HIV risk reduction counseling as described above for Visit 5. The level of absenteeism since their last visit will be recorded. Participants will complete a questionnaire on the use of and, if applicable, adherence to PrEP and blood for dried blood spots will be collected for participants who have their visit on pre-specified calendar days (may differ per site).

Visits 8 to 14/Post-Vaccination 4 Follow-up

Visit 8 is a clinic visit which will include a targeted, symptom-directed physical examination (including weight measurement) and vital signs measurement. Review of solicited signs and symptoms recorded in the diary will be completed and solicited adverse events will be documented. AESIs, serious adverse events, MAAEs and adverse events leading to study discontinuation and concomitant medications (see Section 8) will be recorded for all participants. Counseling related to avoidance of HIV infection will be provided to all participants. A sample for HIV testing will be collected but will only be analyzed in case the test at Month 15 (Visit 9) is positive and the test at Month 12 (Visit 7) is negative. Blood samples for humoral (all participants) immunogenicity assays will be collected. A urine pregnancy test (participants of childbearing potential) will be performed. The level of absenteeism since their last visit will be recorded. In addition, participants will be questioned about the vaccine regimen acceptance (see Section 9.5).

Visit 9 to 14 are clinic visits that will include a targeted physical examination (full physical examination at Visit 14), recording of serious adverse events, MAAEs and adverse events leading to study discontinuation and HIV reduction counseling as described above for Visit 8. AESIs are to be collected up to Visit 10 (6 months after the last vaccination). Samples for HIV testing will be collected at each visit. The level of absenteeism since their last visit will be recorded. The use of PrEP, PEP, hormonal therapy, hormone-based contraception, and all COVID-19 vaccinations should be recorded at each visit. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening adverse events reported per protocol requirements. Participants will complete a questionnaire on the use of and, if applicable adherence to PrEP and blood for dried blood spots will be collected for participants who have their visit on pre-specified calendar days (may differ per site).

In addition:

- If applicable, unsolicited AEs will be recorded at Visit 8
- A urine pregnancy test should be performed every 3 to 6 months
- Blood samples for syphilis serology determination will be collected and tests for chlamydia/gonorrhea will be performed at Visit 10, 12 and 14.
- Blood samples for humoral (all participants) immunogenicity assays will be collected at Visit 10, 12 and 14.

- A sexual activity questionnaire will be completed at Visit 12.
- A social impact questionnaire will be completed at Visit 14.
- Gender identity will be recorded at Visit 12.

9.1.6. Post-M30 Follow-up Phase

Participants who complete their Month 30 visit will return to the site every 3 months for an HIV test until the last participant has completed the Month 30 visit or discontinued earlier. Visits post Month 30 will be scheduled relative to the Month 30 visit. At approximately Month 36 and from then onwards approximately on an annual basis, gender identity should be recorded. Upon discretion of the investigator, additional HIV tests may be performed during unscheduled visits; participants should refrain from performing any HIV testing outside of the study protocol. Serious adverse events, MAAEs and adverse events leading to study discontinuation will be recorded. The use of PrEP, PEP, hormonal therapy, hormone-based contraception, all COVID-19 vaccinations, and all other concomitant therapies administered in conjunction with new or worsening adverse events reported per protocol requirements will be recorded. A urine pregnancy test is to be performed every 3 to 6 months. The level of absenteeism since their last visit will be recorded. Approximately every 6 months, blood samples for syphilis serology determination should be collected and tests for chlamydia/gonorrhea should be performed.

9.1.7. Visits for Participants who Become HIV-1 Infected During the Study

If a participant has a positive HIV test during the study, the participants will have a visit (Visit #.X, scheduled or unscheduled visit as soon as possible after the initial positive test) to perform a confirmatory HIV test, viral load measurement, and $CD4^+$ cell count (tested locally). In addition, a blood sample for limited genetic testing will be collected. Counseling on HIV testing and diagnosis and transmission reduction will be provided, and a targeted physical examination will be performed. In addition, the level of absenteeism since their last visit will be recorded. Blood samples for immunogenicity assays (humoral immune response from all participants and cellular response from participants at sites with access to sponsor approved PBMC processing facilities) and viral sequencing will be collected and may be analyzed when required. Solicited and unsolicited adverse events will be recorded, if visit is within the 7 and 28 days post-vaccination window, respectively. AESIs will be recorded until 6 months after last vaccination. Serious adverse events, MAAEs and events leading to study discontinuation will be recorded for all participants until the end of the study.

The study staff will receive a report confirming the HIV-1 diagnosis. Participants with a negative HIV test may continue study vaccinations as planned. The participant with confirmed HIV-1 will remain in the study but no further scheduled vaccinations will be administered. These participants will be referred to a local clinic for medical treatment and follow-up on their HIV-1 infection as soon as possible after the diagnosis of the infection and will have 2 additional follow-up visits (Visit Inf1 and Visit Inf2 approximately at Month 3 and Month 6 after the initial positive HIV test result, respectively). At these visits, procedures will be the same as for Visit #.X, except that no HIV test will be performed, no blood sample for limited genetic testing will be collected,

concomitant medication (all ARVs, all COVID-19 vaccinations, and all concomitant therapies administered in conjunction with new or worsening adverse events reported per protocol requirements should be reported.) will be recorded, at the Visit Inf2, a full physical examination, including assessment of HIV/AIDS-related conditions will be performed and a social impact questionnaire will be completed at Visits Inf1 and Inf2 . However, if, in the opinion of the investigator/site staff, the completion of the social impact questionnaire can cause undue burden to the participant, it can be omitted. Clear documentation on the rationale should be taken up in the source document. A urine pregnancy test (participants of childbearing potential) will be performed at each visit.

Once the last subject has completed the Month 30 visit of the Time and Events Schedule for HIV-1 Negative Participants or has discontinued earlier, the study is considered completed. HIV infected participants still in the study at that time will be informed that they should return to the site for the Visit #.X, if not completed yet, but no further site visits will be required.

9.1.8. Early Withdrawal/Exit Visit

In the event of early withdrawal from the study, an exit visit will be conducted as soon as possible. The following procedures will be performed: a targeted symptom-directed physical examination (including weight and vital signs measurement), recording of any adverse events (solicited and unsolicited adverse events or AESIs, if applicable, and MAAEs and serious adverse events for all participants), blood sampling for immunogenicity (humoral immune response), and HIV testing. The use of PrEP, PEP, hormonal therapy, hormone-based contraception, and all COVID-19 vaccinations should be recorded. All other concomitant therapies should also be recorded if administered in conjunction with new or worsening adverse events reported per protocol requirements. A sexual activity questionnaire and social impact questionnaire will be completed. In addition, the level of absenteeism since their last visit will be recorded. HIV risk reduction counseling will be provided to all participants and participants will complete a questionnaire on the use of and, if applicable, adherence to PrEP. A urine pregnancy test (participants of childbearing potential) will be performed.

In the event of withdrawal from participants who become HIV-1 infected during the follow-up, an exit visit will be conducted as soon as possible. Procedures will be similar as for Visit Inf1 specified in Section 9.1.7.

9.2. Efficacy Evaluations

An HIV test will be performed approximately every 3 months (see Time and Events schedule). To avoid delays in initiation of combined antiretroviral treatment, local HIV PCR testing is allowed only in case of suspected acute HIV infection, in case of recent HIV exposure, or in case a request for sample redraw is received from the central HIV testing laboratory for confirmation of an HIV positive test. Upon discretion of the investigator, additional HIV tests may be performed during unscheduled visits; participants should refrain from performing any HIV testing outside of the study protocol. Testing will be performed according to a sponsor-approved HIV-1-testing algorithm that differentiates VISP (see below) from true HIV-1 infection. An endpoint adjudication process will be in place to assess all serological and virological testing, in a blinded

manner, on each participant in the study who, prior to study unblinding, tests positive per the sponsor-approved HIV testing.

If a participant has a confirmed positive HIV test during the study, the participant will remain in the study but no further scheduled vaccinations will be administered. The study staff will receive a report confirming the diagnosis. Confirmed HIV-1 infection should not be recorded as (serious) adverse event. The participants will be provided counseling, will be referred for medical treatment and, if applicable, will be informed about observational studies monitoring participants with HIV infection. Further assessments, including HIV-1 viral load measurements, $CD4^+$ T cell count, and viral sequencing (samples taken in all participants and analyzed to assess whether VE differs by genotypic characteristics of HIV and whether there is evidence of vaccine-induced immune pressure on the viral genotype, depending on the vaccine efficacy outcome) will then be performed according to the Time and Events Schedule for Participants Who Become HIV-1 Infected.

VISP

In general, HIV-uninfected participants in preventative HIV-vaccine studies may develop HIV-specific antibodies as a result of an immune response to the candidate HIV-1 vaccine, referred to as VISP (also known as VISR). These antibodies may be detected in common HIV-serologic tests, causing the test to appear positive even in the absence of actual HIV infection. Vaccine-induced seropositivity may become evident during the study or after the study has been completed.

In a preliminary analysis from study HIV-V-A004, using commercially available 4th generation ELISA test kits, VISP developed in a high percentage of the participants starting after the 1st vaccination and increasing to >90% at all subsequent vaccination time points. The full duration of VISP is not yet clear but VISP persisted to Week 96 (96%) and Week 120 (92%). The collection of VISP data is continuing during the long-term extension of the HIV-V-A004 study and in specific other Janssen-sponsored clinical studies to clarify the exact incidence of VISP and its duration.

Study participants have to be made aware of the risk of VISP. Study sites must ensure that study participants understand the social risk of a positive test if it is conducted by an insurance company, employer, government agency, blood bank, or other institution that is unaware of the characteristics of the HIV vaccines or that the participant is or has been enrolled in an HIV-1 vaccine study.

The current study will utilize a diagnostic algorithm to distinguish HIV-1 infection from VISP. More information is provided in the Study-Specific Procedures Binder. Should an HIV-Ab test give a positive result for a particular participant during the study, the central lab will carry out a follow-up testing algorithm either to exclude or confirm HIV infection. Further details of this algorithm are given in the Study-Specific Procedures Binder.

To avoid possible unblinding as a result of positive HIV testing due to VISP, participants should not donate blood, blood products or sperm during the study. Participants should also refrain from performing any HIV testing outside of the study protocol as this could lead to misdiagnosis and unblinding. Blood donation options for those participants who wish to resume blood donation after the study will be explained at the final study follow-up visit.

In the case of VISP, if, either during the study or after the end of the study, a participant requires an HIV test outside the study (eg, to obtain a travel visa or insurance, or for medical reasons), they should contact the site. The sponsor or its designee can issue a written statement giving details on VISP and on the testing algorithm to be followed. If requested by a participant, HIV testing will be available to confirm their HIV status upon discretion of the investigator. Preferably, the frequency of HIV testing should not exceed once every 3 months. It is highly preferable that this repeat HIV testing will be performed through the site. After the study, testing for a particular participant will be available as long as VISP is present for this participant.

In addition to providing testing, participants will always receive pre- and post-test HIV counseling. In participants who become HIV-infected, samples for viral sequencing will be collected. These samples will only be analyzed upon discretion of the study responsible virologist.

9.3. Immunogenicity Evaluations

Venous blood samples for determination of humoral responses to vaccination will be collected from all participants (and analyzed in a subset) at the time points indicated in the Time and Events Schedules. Humoral immune response may be assessed by the response magnitude and frequency to the vaccine autologous Clade C gp140 and Mosaic gp140 proteins by total IgG binding ELISA, or alternative assays. At baseline and post-vaccination, Ad26 seropositivity status and titer will be assessed in a subset of participants by vector neutralization assay.

Venous blood samples for determination of cellular immune responses to vaccination will be collected from a subset of participants at sites with access to sponsor approved PBMC processing facilities (and analyzed in a subset) at the time points indicated in the Time and Events Schedules. Cellular immune responses may be assessed by the response magnitude and frequency of peripheral blood mononuclear cells generating interferon-γ ELISpot responses to cPTE Env peptide stimulation, or alternative assays.

Depending on the vaccine efficacy outcome, samples may be used for the evaluation of immune markers that have a sieving effect on any breakthrough infections and for the evaluation of any immune markers that are associated with post-infection control of HIV, potentially including immune responses to all vaccine antigens. These additional tests may include limited genetic testing.

The collected blood per the Time and Events Schedules, will be sufficient to allow for exploratory immune analyses. Additional exploratory immunogenicity assessments may be performed for the purposes of more fully characterizing the immune responses elicited by vaccination and/or, if any vaccine-associated change in HIV acquisition is identified, identifying immunologic responses which are associated with vaccination and the rate of HIV acquisition.

Note: Participant samples with high levels of biotin can interfere with immunoassays utilizing interaction of biotin with streptavidin.

9.4. Safety Evaluations

Details regarding the independent DSMB are provided in Section 11.9.

Any clinically significant abnormalities that are considered related to vaccination persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached (see Section 12.3.2).

All adverse events and laboratory data will be graded for severity according to the criteria presented in Section 12.1.3.

Adverse Events

All serious adverse events and adverse events and special reporting situations, that are related to study procedures or that are related to non-investigational concomitant sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/early withdrawal. Clinically relevant medical events not meeting the above criteria and occurring between signing of ICF and the moment of first vaccination will be collected on the Medical History CRF page as pre-existing conditions.

Solicited adverse events, collected through a diary, will be recorded daily for each vaccination from the moment of vaccination until 7 days post-vaccination.

All other unsolicited adverse events and special reporting situations will be reported for each vaccination from the moment of vaccination until 28 days post-vaccination. Unsolicited adverse events with the onset date outside the timeframe defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded as such.

From the time of local approval of protocol amendment 5 onwards, TTS is considered to be an AESI (see Section 12.3.4). Thrombotic events and/or thrombocytopenia (defined as platelet count below the LLN range for the testing lab) are considered to be potential AESIs. All AESIs, including potential AESIs, will be reported to the sponsor from the moment of first vaccination until 6 months after the last vaccination. Each potential AESI will be reviewed to identify a TTS case.

All serious adverse events, MAAEs, and adverse events leading to discontinuation (regardless of causal relationship) are to be reported from the moment of first vaccination for the duration of the study, which may include contact for safety follow-up. The HPX3002/HVTN 706 safety review team will review the safety information during the conduct of the study. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All AEs will be followed until resolution or until clinically stable.

Medically-attended adverse events (MAAEs) are defined as adverse events with medically attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Potentially immune-mediated medical conditions (PIMMCs) and new onset of chronic diseases will be collected as part of the MAAEs. Adverse events identified during a routine study visit will not be considered MAAEs. STIs (including HIV-2 infection) are associated with an increased likelihood to acquire HIV infection. Note that

an STI identified from study visit testing, for which a participant receives subsequent medical intervention, fulfils the criteria of an MAAE.

Based on regulatory feedback, special attention will be put on PIMMC that are reported as MAAEs. These events will be collected and analyzed. A list of PIMMCs defined for this study is presented in Attachment 3.

For solicited adverse events, the following applies.

Solicited Adverse Events

Solicited adverse events are used to assess the reactogenicity of the study vaccine and are predefined local (at the administration site) and systemic events for which the participant is specifically questioned, and which are noted by participants in their diary.

After each vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions. In addition, participants will record solicited signs and symptoms in a diary for 7 days post-vaccination. These participants will be provided with a diary and instructions on how to complete the diary (Section 9.1.1). The study staff will transcribe the information provided by the participant into the relevant sections of the CRF. After review and verbal discussion of the initial paper diary entries with the participant, the investigator will complete his/her own assessment in the relevant sections of the CRF. Once a solicited sign or symptom from a diary is considered to be of severity Grade 1 or above, it will be recorded as a solicited adverse event. For grading of solicited adverse events, see Section 12.1.3. For solicited adverse events, the investigators will document them in the clinic note, followed by entry into the CRF.

Solicited Administration Site Adverse Events

Participants will be asked to note in the diary occurrences of pain/tenderness, erythema and swelling at the study vaccine administration site daily for 7 days post-vaccination (day of vaccination and the subsequent 7 days). The extent (largest diameter) of any erythema, and swelling should be measured (using the ruler supplied) and recorded daily.[12,25]

Solicited Systemic Adverse Events

Participants will be instructed on how to record daily temperature using a thermometer provided for home use. Participants should record the temperature in the diary in the evening of the day of vaccination, and then daily for the next 7 days approximately at the same time each day. If more than one measurement is made on any given day, the highest temperature of that day will be used in the CRF.

Fever is defined as endogenous elevation of body temperature ≥38° C, as recorded in at least one measurement.[27]

Participants will also be instructed on how to note daily in the diary signs and symptoms for 7 days post-vaccination (day of vaccination and the subsequent 7 days) of the following events: fatigue, headache, nausea, myalgia, chills, arthralgia, and vomiting.

Clinical Laboratory Tests

No blood samples for safety laboratory testing will be collected. However, clinical laboratory assessments to be performed are as follows:

- Serum (at screening; local laboratory) and Urine (at time points indicated in the Time and Events Schedule) pregnancy testing for participants of childbearing potential only.
- HIV testing (see Section 9.2 and Study-Specific Procedures Binder; screening test: local laboratory, other HIV testing: central laboratory)
- Syphilis, chlamydia, and gonorrhea (local laboratory)
- Dried blood spot test (central laboratory)
- In case of HIV infection: HIV viral load (central laboratory) and $CD4^+$ cell count (local laboratory)
- In case of a potential AESI of TTS (see Section 12.3.4.1), a serum sample should be obtained to test for anti-PF4 at the local laboratory or substitute local laboratory, if possible; repeat testing may be requested for confirmation upon sponsor discretion. A test for anti-PF4 will also be performed on a stored pre-vaccination sample, if possible.

Vital Signs (Oral or Tympanic Temperature, Pulse/Heart Rate, Blood Pressure)

Vital sign measurements will be performed at time points specified in the Time and Events Schedule.

Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Physical Examination

Full physical examination, including vital sign measurements, will be carried out at screening, Month 30 and 6 months after HIV-1 diagnosis, as applicable. At all other study visits, a targeted, symptom-directed exam will be performed as indicated by the investigator based on any clinically relevant issues, clinically relevant symptoms, and medical history. Symptom-directed physical examination may be repeated if deemed necessary by the investigator. Height will be measured at screening. Weight will be measured at every study visit.

Physical examinations will be performed by the investigator or designated medically-trained clinician. Any screening or baseline abnormality should be documented in the medical history page of the CRF.

9.5. Participant Reported Outcomes

Social impact, sexual activity, absenteeism, vaccination regimen acceptance, and PrEP use will be evaluated over the study period, until the end of follow up, through questionnaires completed under

confidentiality by the study participants. Replies to questionnaires will be assessed in the following groups:

1. In vaccine and placebo recipients,
2. In participants who become HIV-1 infected in comparison to non-infected participants,
3. In VISP positive and negative study participants,
4. In participants who are using PrEP or not during the course of the study, if applicable.

For the full questionnaires, refer to the Study Specific Procedures Binder.

9.5.1. Social Impact Measured Using Questionnaire

Participants in prophylactic HIV-vaccine clinical studies may experience problems with personal relationships, employment, education, health care, housing, health, disability or life insurance, travel, and immigration.[1] In relation to a participant's family, friends, and/or colleagues, the social impact could manifest in one or more ways, resulting in social conflicts and stigmatization, for example:

1. The investigational vaccine is thought to be harmful to the participant's health, including a belief that it might cause HIV infection.
2. The participant is perceived as HIV-infected or at high risk.
3. Repercussions from VISP.

For these reasons, participants will complete a social impact questionnaire at the time points specified in the Time and Events Schedule, to evaluate any potential consequences of the participant's enrollment in the study.

9.5.2. Sexual Activity Questionnaire

In order to collect information to assess the level of risk of HIV infection throughout the study, participants will complete a sexual activity questionnaire, at the time points specified in the Time and Events Schedule. The recall period for this questionnaire is the last month.

9.5.3. Questionnaire on the Use of PrEP

Information with regard to the use of and, if applicable, adherence to PrEP will be collected for all participants by means of a questionnaire. The questionnaire will be completed at the time points specified in the Time and Events Schedule.

9.5.4. Other Participant Reported Outcomes

At each visit (except for Visit 2a and Visit 3a), participants will be questioned on their level of absenteeism, defined as health-related productivity loss due to sick-leave, since their last visit at which absenteeism was recorded.

In addition, at Visit 8, 1 month post-vaccination 4, participants will be asked how they perceived their experience with this HIV vaccination.

9.6. Sample Collection and Handling

The actual dates and time of sample collection must be recorded in the laboratory requisition form.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Study-Specific Procedures Binder that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Study-Specific Procedures Binder.

10. PARTICIPANT COMPLETION/DISCONTINUATION OF STUDY VACCINATION/ WITHDRAWAL FROM THE STUDY

10.1. Completion

The study will be considered completed when the last participant completed the Month 30 visit or discontinued earlier. Participants will continue the study until the last participant has completed the Month 30 visit or discontinued earlier.

At the end of the study, participants may be offered the possibility to enter a follow-up phase or program.

10.2. Discontinuation of Study Vaccination/Withdrawal from the Study

Discontinuation of Study Vaccination

Participants will be withdrawn from study vaccine administration for the reasons listed below. These participants must not receive any additional dose of study vaccine but should continue the visit schedule as planned with assessments per the Time and Event Schedule including assessments of safety and HIV diagnosis. Participants who received the first 3 vaccinations but discontinue study vaccination before receiving the 4th vaccination, should continue the visit schedule as planned with assessments per the Time and Event Schedule including assessments of safety, immunogenicity and HIV diagnosis. Additional unscheduled visits may be performed for safety/reactogenicity reasons, if needed. In case of questions, the investigator is encouraged to contact the HPX3002/HVTN 706 safety review team.

- Unblinding due to safety reasons
- Pregnancy
- Confirmed HIV-1 or HIV-2 infection
- Any related adverse event, worsening of health status or intercurrent illnesses that, in the opinion of the investigator, required discontinuation from study vaccine
- Anaphylactic reaction following vaccination
- Serious adverse event or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine

- Chronic or recurrent use of systemic immunomodulators/suppressants, eg, cancer chemotherapeutic agents (after discussion with the HPX3002/HVTN 706 safety review team)
- Use of HIV-related mAbs
- From the time of local approval of protocol amendment 5 onwards: participant previously experienced TTS or HITT.

Withdrawal From the Study

Each participant has the right to withdraw from the study at any time for any reason without affecting the right to treatment by the investigator. The investigator should make an attempt to contact participants who did not return for scheduled visits or follow-up. Although the participant is not obliged to give reason(s) for withdrawing prematurely, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the participant's rights.

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Repeated failure to comply with protocol requirements
- Decision by the sponsor or the investigator to stop or cancel the study
- Decision by local regulatory authorities or IRB/IEC to stop or cancel the study

If a participant is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the participant and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study vaccine assigned to the withdrawn participant may not be assigned to another participant. Participants who are vaccinated and withdraw will not be replaced. If a participant withdraws early from the study, assessments for early withdrawal should be obtained (see Section 9.1.8).

Participants who wish to withdraw consent from participation in the study will be offered a single exit visit for safety follow-up (prior to formal withdrawal of consent). They have the right to refuse.

10.3. Contraindications to Vaccination

The following events constitute a temporary contraindication to study vaccination. If any of these events occur at the scheduled time for vaccination, the vaccination can be rescheduled (as long as this is in agreement with the allowed windows (see Section 9.1.2):

- Acute illness at the time of vaccination. This does not include minor illnesses, such as diarrhea or mild upper-respiratory tract infection.
- Fever (body temperature ≥38.0°C) at the planned time of vaccination.

If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the HPX3002/HVTN 706 safety review team should be contacted for further guidance.

10.4. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor and its partners or under the authority of the sponsor. A general description of the statistical methods is outlined below. Specific details will be provided in the SAP.

11.1. Participant Information

For all participants, descriptive statistics of demographic (eg, sex assigned at birth, participant-identified gender at screening, age, height, weight, male circumcision, body mass index [BMI], and race) and other baseline characteristics (eg, medical history, including history and family history of immune disorders, concomitant diseases, Ad26 baseline serostatus) will be provided by vaccination group.

11.2. Analysis Populations

The following study populations or analysis sets are used for addressing the study objectives. This terminology is used throughout this protocol and SAP. The following sets and populations will include all vaccinated participants with respect to the vaccine actually administered.

1. Full Analysis Set (FAS): all randomized participants who receive at least one vaccine administration. This will be the primary population for the safety analysis.

2. Modified Intent-to-Treat (mITT) Population: participants in the FAS who are HIV-1 negative on the date of first vaccination.

3. Modified Intent-to-Treat-2 (mITT-2) Population: participants in the FAS who have a negative HIV test 4 weeks post 3rd vaccination visit (ie, at the Month 7 Visit).

4. Per-Protocol (PP) Population: participants in the FAS population who have a negative HIV test 4 weeks post 3rd vaccination visit (ie, at the Month 7 Visit), who received all planned vaccinations at the first three vaccination visits within the respective visit windows. This will be the primary population for the efficacy analysis.

5. Modified Intent-to-Treat-3 (mITT-3): participants in the FAS population who have a negative HIV test 4 weeks post 3rd vaccination visit (ie, at the Month 7 Visit), who received all planned

vaccinations at the first three vaccination visits, irrespective whether within or outside the respective visit windows. This will be an additional population for efficacy analysis, and potentially for immune correlates.

6. Full Immunization Set (FIS): participants in the FAS who are HIV-1 uninfected 4 weeks after the 4th vaccination visit (ie, at the Month 13 Visit) and who receive all planned vaccinations within the respective visit windows.

7. At risk Immunogenicity Cohort (IC-at risk): participants in the FAS who are selected for measurement of immune response endpoints at the primary immunogenicity timepoints and who are HIV-1 uninfected 4 weeks after the 3rd vaccination visit (ie, at the Month 7 Visit).

The analyses of safety will be performed on the FAS. The primary analysis of VE will be based on the PP population. Secondary analyses of VE will be based on the mITT, mITT-2, and mITT-3 population, and the FIS. For those with immunogenicity outcomes, analyses of vaccine immunogenicity and immune correlates may be based on PP, mITT-3, IC-at risk and the FIS. Other populations may be defined in the SAP for the purpose of exploratory (correlate) analyses.

11.3. Sample Size Determination

This study is designed to test the primary hypothesis of VE in the PP population:

H0: VE(7-x months) ≤20% versus the H1: VE(7-x months) >20%, with 24≤x≤30 (See Section 11.5.1.1).

If the lower bound of the 95% CI for VE(7-x months) is >20% at the primary analysis, the corresponding H0 will be rejected.

The sample size calculations are based on the power of a 1-sided 0.025-level Wald test for comparing cumulative incidences of HIV-1 infection by the Month x visit (24≤x≤30) between randomized groups, in the presence of the sequential monitoring of VE. Power is computed based on simulating 10,000 efficacy trials using the R package seqDesign[14,24] under the following assumptions:

- 10% annual dropout incidence in both groups;
- 5% of participants with at least one missed vaccination (excluded from PP population);
- VE 20% in the first 7 months after first vaccination;
- VE 65% from Month 7 onwards;
- 12-month uniform accrual with halved accrual during the first 3 months;
- Visits approximately every 3 months for HIV-1 diagnostic tests;
- 2% annual HIV-1 incidence in the placebo group;

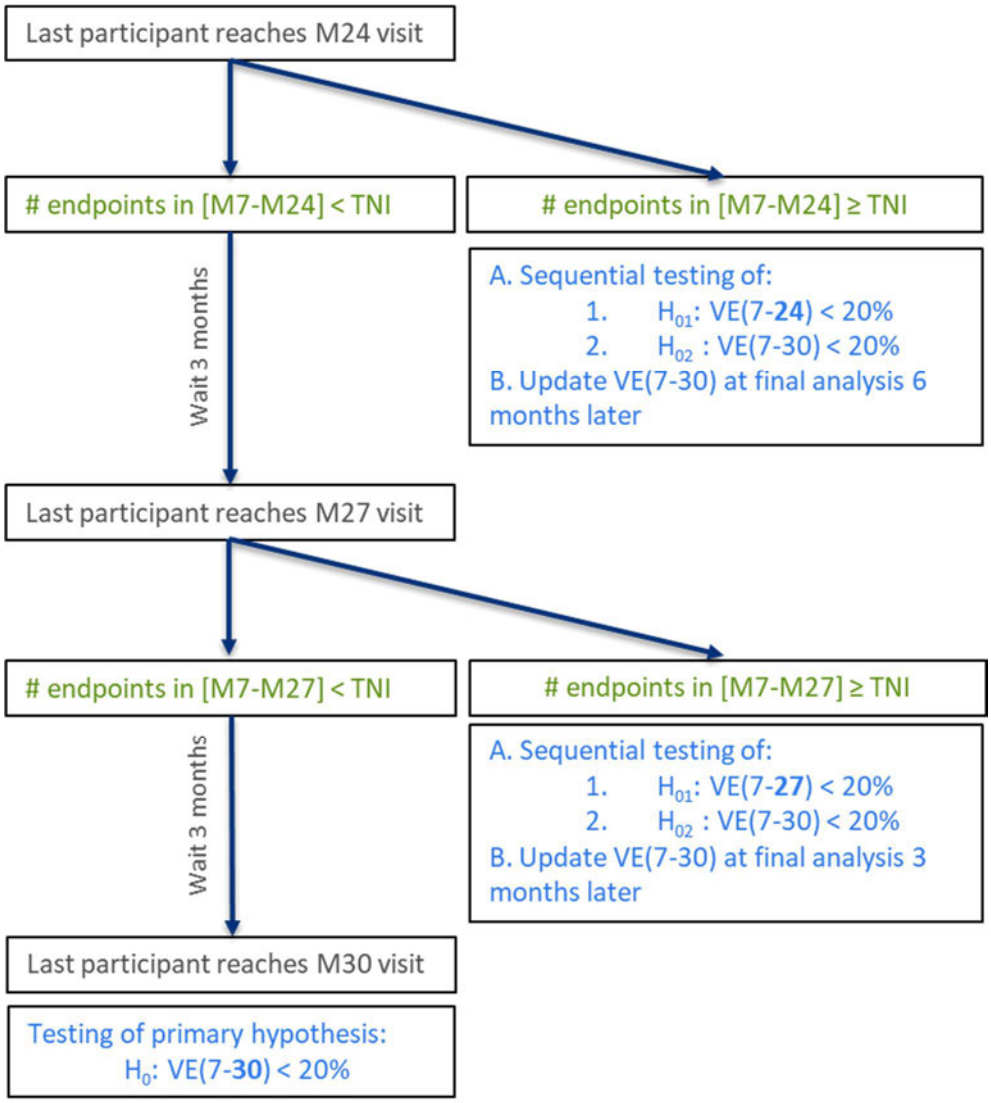
Under these assumptions, a study of 3,800 participants (randomized 1,900:1,900 to vaccine:placebo) is expected to yield a total of 78 HIV-1 infections in the PP population between

the Month 7 and Month 30 visits, considered to be the TNI needed to achieve approximately 90% power for rejecting the primary H0, under an alternative VE of 65% and with a one-sided error rate of 2.5%.

The timing of unblinding and conducting the primary analysis and the definition of the primary efficacy endpoint will be determined by when the TNI is reached within a given follow-up period x ($24 \leq x \leq 30$) for each participant. In practice, when the last participant has reached his/her Month 24 visit (or discontinued earlier), it will be assessed whether the TNI has been obtained within the period of Month 7-Month 24. If at that time the number of HIV-1 infections between Month 7 and Month 24 is greater than or equal to the TNI, the primary analysis may be conducted using VE(7-24 months) as the primary efficacy endpoint. Only if this primary H0 is rejected, VE(7-30 months) will be tested as secondary hypothesis, using a fixed sequence testing strategy, without adjustment for the Type-I error, and using all available durability data between Month 24 and Month 30. If the number of infections between Month 7 and Month 24 is less than the TNI, the study will continue for 3 months until the last participant has reached their Month 27 visit. The same procedure is repeated as described above, using all available HIV-1 infections between Month 7 and Month 27 and with VE(7-27 months) as the primary efficacy endpoint. If the number of infections between Month 7 and Month 27 is less than the TNI, the study will continue for 3 months until the last participant has reached his final study visit at Month 30. At that point, the primary analysis will be conducted regardless of whether the TNI has been reached, using VE(7-30 months) as only efficacy endpoint.

The statistical strategy is schematically presented in Figure 1.

Figure 1: Primary Efficacy Testing – Schematic Overview



H0: null hypothesis; M: month; TNI: Target Number of Infections; VE: vaccine efficacy

Note that investigators and participants will remain blinded with regards to their treatment assignment, at least until the last participant has reached the Month 30 visit or discontinued earlier.

Both the study's sample size as well as the TNI may be adjusted during the study, but prior to unblinding, to ensure sufficient power at the time of the primary analysis. Whereas adjustment of the sample size may be based on internal (but sponsor-blinded) study data (through monitoring of the pooled HIV-1 incidence) as well as on external study data (eg, Phase 2b HPX2008/HVTN 705), any adjustment of the TNI will solely be driven by data external to this study (eg, Phase 2b HPX2008/HVTN 705). Full details on the possible sample-size reassessment will be described in the DSMB Charter and the SAP.

To cope with the dynamic environment of the development, approval and uptake of other prophylactic methods, such as PrEP (which would result in lower than expected annual incidence rates and thus lower study power), an estimated annual incidence rate in the control group of 2% was used to size this study.

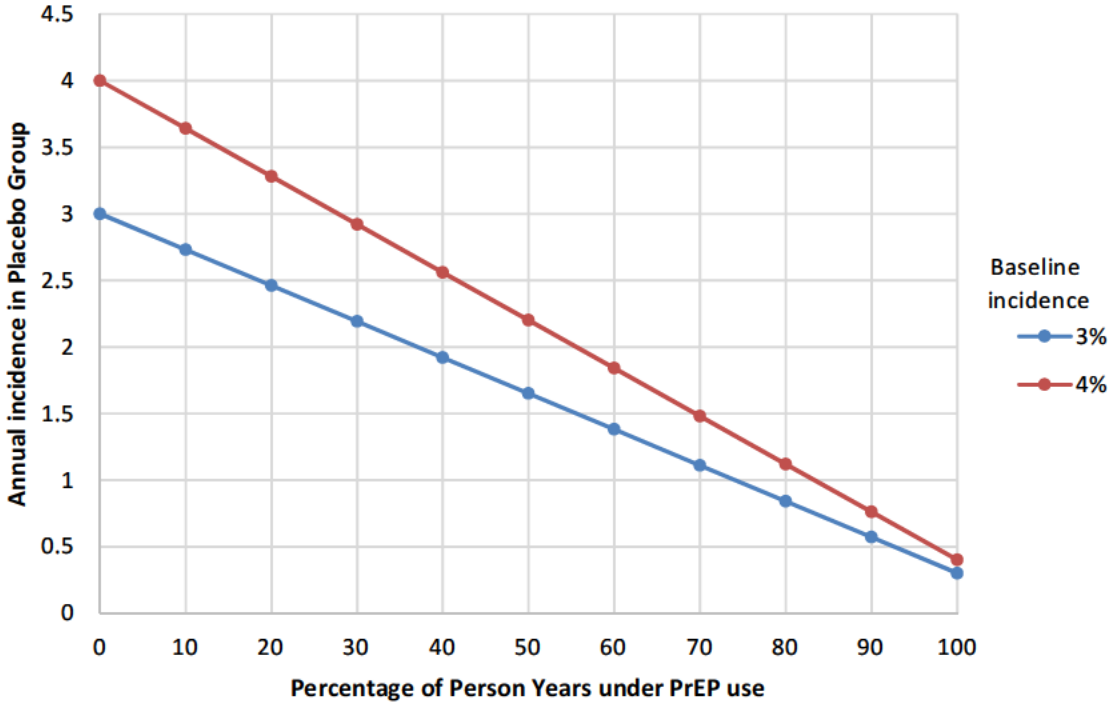
Under the study assumptions as described above, the study will also have approximately 80% power for the secondary efficacy endpoint VE(0-x months), assessing VE in the mITT population and accounting for all HIV-1 infections starting from Month 0 (Day 1).

Rationale for the HIV-1 Incidence Assumptions

This study will recruit a large population of highest-risk MSM and transgender individuals who have sex with men from many regions. In 2011, 62% of estimated new HIV diagnoses in the United States were attributed to male-to-male sexual contact; 39% of these MSM were black or African American.[9] Lifetime risk was 1 in 68 for males and 1 in 253 for females. Lifetime risk for men was 1 in 22 for blacks, 1 in 51 for Hispanic/Latinos, and 1 in 140 for whites. By risk group, the highest risk was among MSM (1 in 6) and the lowest was among male heterosexuals (1 in 524). Most of the states with the highest lifetime risk were in the South.[19] Recent data from clinical studies show placebo incidence rates in high risk MSM of 6.6% in the Ipergay study (France, Canada)[28], 3.9% in the iPrEX study for high risk MSM (USA, Brazil, Peru, Ecuador, South Africa and Thailand)[15], HVTN 505 yielded annual incidence rates of 2.3% in circumcised MSM and TG (USA)[18]. To help identify the study participants pre-trial assessments and data will be collected regarding incidence in potential sites.

The assumption of 2% annual HIV-1 incidence in the placebo group accommodates background PrEP use by assuming incidence is decreased by the person-years at risk during which PrEP is used, the efficacy of PrEP during PrEP use and the adherence to PrEP use. Figure 2 shows the impact of assumed PrEP use and adherence on annual HIV-1 incidence in the placebo group when the initial incidence (in the absence of PrEP) is 3% or 4% and the efficacy of PrEP is assumed to be 90%.

Figure 2: Impact of Assumed PrEP use and Adherence on Annual HIV-1 Incidence in the Placebo Group



HIV-1: human immunodeficiency virus type 1; PrEP: pre-exposure prophylaxis

Based on the assumption of 3% annual incidence in the absence of PrEP and, about 35% of person-years at risk during PrEP use and 90% PrEP efficacy during use would provide us with the assumed 2% annual placebo incidence rate.

A total sample size of 3,800 participants, as based on the efficacy endpoints, will also provide enough power for assessing safety of the vaccine regimen. The probability of observing at least one adverse event occurring at a rate of 1/100 is >99.9% with approximately 1,900 vaccinees. The probability of observing at least 1 adverse event occurring at a rate of 1/1,000 is 85% with approximately 1,900 participants. If no events will be observed for a specific (serious) adverse event, then the Bayesian posterior probability that the adverse event rate is below 1/1,000 equals 95% for 1,900 participants and would provide us with 95% confidence that the true incidence is no more than 0.16%.

11.4. Study Monitoring

The study will be formally monitored. This may lead to a modification or termination of the study. The set of monitoring rules will include monitoring for potential harm, non-efficacy and operational futility. Monitoring rules applied in the current simulations are preliminary and subject to finetuning based on operating characteristics but will be formally finalized prior to study start and fully documented in the SAP and DSMB charter. The sequential monitoring to be applied to this study will follow the principles as discussed in Gilbert et al.[14] Monitoring of the VE and underlying HIV-1 incidence will occur through the study's DSMB. A summary of the monitoring rules for vaccine efficacy, as used in the current simulations, is provided in Table 4 below.

Eventually, the monitoring rules as agreed with the independent DSMB and described in the DSMB charter will take priority over the ones presented below.

Table 4: Summary of interim monitoring of VE

Monitoring Outcome	Hypotheses	Testing Approach	Size	Monitoring Plan	Timing of analyses
Potential Harm	H_0: VE(0-30) ≥0% vs. H_1: VE(0-30) <0%	Exact 1-sided binomial test of the proportion of infections assigned to the vaccine group	1-sided alpha=0.05	Near-constant 1-sided p-value cut-off controlling FWER at alpha=0.05	After every mITT infection starting at the 10th total until the first non-efficacy analysis
Non-Efficacy	H_0: VE(0-30) ≥50% vs. H_1: VE(0-30) <50% and H_0: VE(7-30) ≥50% vs. H_1: VE(7-30) <50%	Wald Test	1-sided alpha=0.025	Unadjusted 95% CIs for VE(0-30) and VE(7-30): lower bounds <0% and upper bounds <50%	6-monthly starting at 40 mITT infections and then through the primary analysis

CI: confidence interval; FWER: family-wise error rate; H_0: null hypothesis; H_1: alternative hypothesis; mITT: modified intent-to-treat; VE: vaccine efficacy; vs.: versus

11.5. Efficacy Analysis

The primary efficacy analysis will be performed when all participants have reached the Month x (with 24≤x≤30) visit or discontinued earlier and the TNI has been reached in the study. Refer to Figure 1 for more information on the timing and strategy of statistical testing.

11.5.1. Vaccine Efficacy Analysis

The primary analysis of VE will evaluate the number of HIV-1 infections in the vaccine group compared to the number of HIV-1 infections in the placebo group between Month 7 and Month x (with 24≤x≤30) in the PP population. The H0 of VE will be tested VE(7-x months) ≤20% versus the H1 VE(7-x months) >20%. Vaccine efficacy is defined as 1-cumulative incidence ratio (vaccine versus placebo) between Month 7 and Month x after first vaccination and is estimated by the transformation of the Nelson-Aalen estimator for the cumulative hazard function. If the lower bound of the 95% CI for VE(7-x months) is >20% (equivalently, the 1-sided p-value for testing H0: VE[7-x months] ≤20% is below 0.025), the H0 will be rejected in favor of the H1.

11.5.1.1. Primary Vaccine Efficacy Analysis: HIV-1 Infection

The primary analysis will be done in the PP population, where participants who become HIV-1 infected or who drop out before Month 7 or who have not received all of the first three vaccinations within the specified time window, will be excluded from the analysis. The date of HIV-1 diagnosis will be the draw date of the first sample that leads to a positive test result by the study protocol's diagnostic algorithm. Dropouts will be censored at the time of their last HIV-1 negative test. To evaluate the primary VE endpoint, the number of HIV-1 infections in the vaccine group will be compared to the number of HIV-1 infections in the placebo group between Month 7 and x months since the first vaccination (with 24≤x≤30). The vaccine effect will be assessed using a ratio of

cumulative incidences of HIV-1 infection between Month 7 and x (vaccine versus placebo), estimated using the transformed Nelson-Aalen cumulative hazard function estimator and tested via a Wald test.

11.5.1.2. Secondary/Exploratory Vaccine Efficacy Analyses

As a key secondary objective, the VE beyond Month 7 will be evaluated in all participants, regardless of whether they received the first three vaccinations according to the protocol-specified schedule (mITT-2 population, see Section 11.2 for definition). Other secondary objectives will evaluate the VE over different time intervals (eg, VE[0-x months], VE[13-x months]) and in different populations (eg, mITT, mITT-2, mITT-3, FIS), using similar methods as described above. Cox proportional hazards model will also be used for estimating VE(7-x months), measured by one minus the hazard ratio (vaccine versus placebo) and for testing whether the VE(7-x months) differs from 20%.

To account for potentially confounding factors, subgroup and covariate-adjusted analyses will be performed. These subgroups/covariates will include PrEP use, baseline Ad26 seropositivity status and titers, presence of risk factors for HIV infection, and other baseline demographic factors. Efforts will be made to estimate vaccine efficacy in complete absence of PrEP use in a counterfactual framework.

In addition, an exploratory analysis that employs Bayesian methods will be conducted to evaluate VE.[13] The prior to be used for this analysis will be a robust, meta-analytic one based on pre-specified weighting of the external Phase 2b data (study HPX2008/HVTN 705) as informative prior and a non-informative prior.[31] Details of pre-specified weights and priors will be specified in the SAP.

If VE is established, an attempt will be made to identify correlates of increased risk of HIV-1 infection as well as correlates of VE, best individual-level classifiers of HIV infection and to assess mediators of vaccine efficacy. To this extent, appropriate statistical methodology will be applied or developed, and will be described in a (separate) SAP for correlate identification. If significant VE is observed, a pre-specified case-control study of immune responses elicited by vaccination in active vaccine recipients will be performed to identify vaccine-induced correlates of protection and/or risk. Both single parameter and combinations of multiple immunologic parameter models will be explored. The presence of time-dependent correlates of protection will be examined in addition to single time point immune responses, including the peak immune response after the primary vaccination series, or the time point most closely preceding the diagnosis of HIV-1 infection. To further ascribe immune correlates of protection and/or specifically of VE, placebo case and control samples will also be included in a secondary stage of analysis.

11.6. Safety Analysis

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively. All safety analyses will be tabulated by vaccination group (active vaccine, placebo) and based on the FAS.

Tabulations will be presented by time of occurrence relative to the preceding vaccination (7 days for solicited adverse events and 28 days for unsolicited adverse events, 6 months after last vaccination for AESIs).

Baseline for all safety parameters will be defined as the last evaluation done before the first dose of study vaccine.

11.6.1. Reactogenicity: Solicited Adverse Events

The number and percentage of participants experiencing each type of solicited adverse event will be tabulated by severity and vaccination group, and the percentages will be displayed graphically by group. For a given solicited adverse event, each participant's adverse event will be counted once under the maximum severity for each vaccination dose.

11.6.2. Unsolicited Adverse Events, AESIs, MAAEs and Serious Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Tables will show, by vaccination group, the number and percentage of participants experiencing an adverse event within a system organ class or within a preferred term category by severity and by relationship to study vaccine. All reported adverse events and events-related diary information with onset or worsening within 28 days after each vaccination (ie, treatment-emergent adverse events) will be included in the analysis. For each adverse event, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by vaccine group. A participant with multiple adverse events within a category will be counted once under the maximum severity and by causal relationship to study vaccine. Formal statistical testing comparing groups is not planned since interpretation of differences must rely heavily upon clinical judgement. Parallel analyses will include all AESIs, serious adverse events and adverse events leading to participant withdrawal or early discontinuation of study vaccine(s).

For this study events of interest are PIMMCs. PIMMCs that are recorded as MAAEs will be collected and analyzed.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue treatment due to an adverse event, or who experience a serious adverse event or an AESI.

Summaries and listings may be provided separately for adverse events with onset outside the above defined timeframe and that were reported pre-dose at the moment of subsequent vaccinations.

11.6.3. Other Safety Parameters

Vital Signs

The percentage of participants with values beyond pre-specified limits will be summarized.

Physical Examination

Physical examination findings will not be tabulated separately. Clinically relevant findings will be reported as adverse event and will be tabulated and listed as adverse events. BMI will be calculated using the recording of height at screening.

11.6.4. Other Parameters

Participant Reported Outcomes

Data from the social impact questionnaire, sexual activity questionnaire, the questionnaire on the use of PrEP and the level of absenteeism and vaccine regimen acceptance will be summarized using descriptive statistics:

1. In vaccine and placebo recipients,
2. In participants who become HIV-1 infected in comparison to non-infected participants,
3. In VISP positive and negative study participants,
4. In participants who are using PrEP or not during the course of the study, if applicable.

In addition, data may be included as co-variates in the exploratory efficacy analysis.

Health Economics Aspects (HCRU)

Health Care Resource Utilization will be described based on data collected through MAAEs and follow-up of HIV infections, and complemented by description of absenteeism.

1. Data will be summarized using descriptive statistics:In vaccine and placebo recipients,
2. In participants who become HIV-1 infected in comparison to non-infected participants,
3. In VISP positive and negative study participants,
4. In participants who are using PrEP or not during the course of the study, if applicable.

11.7. Reasons for Vaccination Discontinuation and Early Study Termination

The number and percentage of participants who discontinue vaccination and who terminate the study early will be tabulated by vaccination group. The reason for discontinuation will be included.

11.8. Immunogenicity Analysis

Data from quantitative assays may be summarized (tabulated/graphically presented per timepoint available) by vaccination group: N, geometric means and corresponding 95% CIs, percentage positive responses/responders (if available).

Qualitative endpoints may be summarized by tabulating the frequency of positive responses for each assay by group at each timepoint that an assessment is performed.

Descriptive statistics (actual values and changes from reference) may be calculated for continuous parameters. Frequency tabulations may be calculated for discrete parameters. Graphical representations of changes in immunologic parameters may be made as applicable.

No formal hypothesis on immunogenicity will be tested. The analysis of immunogenicity may be done on the immunogenicity populations as defined above.

11.9. Independent Data and Safety Monitoring Board

The NIAID HIV vaccine DSMB will serve as an independent DSMB for this study and will monitor data on a 6-monthly basis to ensure the continuing safety of the participants enrolled in this study. The independent DSMB will review unblinded data as indicated below. After the review, the independent DSMB will make recommendations to the sponsor about potential modifications to the study. The independent DSMB will also monitor the study progression.

An independent statistical support group, appointed by the sponsor, and not involved in the study, will be unblinded to treatment assignment and provide all necessary data to the independent DSMB. The independent DSMB will consist of at least four clinical and vaccine experts, at least one independent statistician, one ethicist, and one community representative. All independent DSMB responsibilities, authorities, and procedures (data to be provided, meeting frequency, type of meetings) will be specified in the DSMB Charter and the details on the analyses will be provided in the SAP. An independent DSMB meeting will start with an open (blinded to treatment assignment with attendance of sponsor study representatives) followed by a closed (unblinded to treatment assignment) session. No sponsor representative will be involved in the closed sessions. The unblinded, closed DSMB report including evaluations of HIV infections will be shared with the FDA Center for Biologics Evaluation and Research (CBER)/Office of Vaccines Research and Review (OVRR). To ensure the blinding of the study team, an independent regulatory expert will act as an intermediary between the DSMB and CBER/OVRR. Further details are described in the DSMB charter.

In case of serious safety issues, the independent DSMB will be informed immediately by the sponsor.

11.10. Endpoint Adjudicator(s)

The diagnostic criteria for HIV-1 infection outside the setting of a vaccine trial are well accepted. However, definitive diagnosis of HIV-1 infection in the context of having received an HIV vaccine that is even partially effective may be more difficult. Specifically, if the immune responses elicited by vaccination are capable of completely suppressing viral replication, or if vaccination alters the normal serological response upon exposure to HIV-1, standard diagnostic tests may be more difficult to assess.

Therefore, an endpoint adjudicator(s) and/or designees will assess all serological and virological testing, in a blinded manner, on each participant in the study who, prior to study unblinding tests positive per the sponsor-approved HIV testing algorithm.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in

conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting Adverse Events, AESIs, MAAEs and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events, AESIs, MAAEs or serious adverse events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined administration site and systemic events for which participants are specifically questioned and which are noted in their diary (see Section 9.1.1).

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the participant is specifically not questioned in the participant diary.

AESIs

For details, see Section 12.3.4.

Medically-attended Adverse Events

Medically-attended adverse events (MAAEs) are adverse events with medically attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the medicinal product. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: For time period of sponsor's adverse event collection, see Section 12.3.1.

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study product and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Ad26.Mos4.HIV, Clade C gp140, and Mosaic gp140, the expectedness of an adverse event will be determined by whether or not it is listed in the respective Investigator's Brochures.

Adverse Event Associated With the Use of the Vaccine

An adverse event is considered associated with the use of the vaccine if the attribution is related by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Causality of adverse events should be assessed by the investigator based on the following:

Related: there is a reasonable possibility* that the adverse event may be related to the study agent. This suggests that the adverse event is more likely to be related than not related to the study product(s).

Unrelated: there is not a reasonable possibility* that the adverse event is related to the study agent. The choice suggests that the adverse event is more likely to be related to another cause rather than the study products.

* There is evidence to suggest a causal relationship between the study product and the adverse event.

By definition, all solicited adverse events at the administration site will be considered related to the study vaccine administration.

12.1.3. Severity Criteria

For severity grading of solicited administration site adverse events the following applies (differences with the DAIDS table are indicated in strikethrough and bold/underlined):

Table 5: Grading of Solicited Administration Site Adverse Events

	Grade 1: MILD	Grade 2: MODERATE	Grade 3: SEVERE	Grade 4: POTENTIALLY LIFE-THREATENING
~~Injection~~**Administration-related** Site Pain or Tenderness **(proximal to the injection site)**	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform USFA[a]	Pain or tenderness causing inability to perform basic self-care function OR hospitalization indicated
~~Injection~~**Administration-related** Site Erythema or Redness AND ~~Injection~~**Administration** -related Site ~~Induration or~~ Swelling	2.5 to <5 cm in diameter OR 6.25 to <25 cm^2 surface area ~~AND Symptoms causing no or minimal interference with USFA~~	≥5 to <10 cm in diameter OR ≥25 to <100 cm^2 surface area ~~OR Symptoms causing greater than minimal interference with USFA~~	≥10 cm in diameter OR ≥100 cm^2 surface area OR secondary infection OR phlebitis OR sterile abscess OR drainage ~~OR Symptoms causing inability to perform USFA~~	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

[a] USFA: usual social and functional activities. Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc

All adverse events, including solicited systemic adverse events, and laboratory data, if applicable, will be coded for severity using the Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1, July 2017 and its addenda (the DAIDS addenda grading tables for microbicides studies will be used for the grading of genito-urinary disorders, STIs, uterine bleeding and pregnancy complications although this is not a microbicide study). Laboratory reference ranges will be applied according to the participant's sex at birth. Details for solicited systemic adverse events are provided in Table 6. For the full DAIDS grading table, refer to the Study Specific Procedures Binder.

Table 6: Grading of Solicited Systemic Adverse Events

	Grade 1: MILD	Grade 2: MODERATE	Grade 3: SEVERE	Grade 4: POTENTIALLY LIFE-THREATENING
Fever (non-axillary temperatures only)	38.0 to <38.6°C OR 100.4 to <101.5°F	≥38.6 to <39.3°C OR ≥101.5 to <102.7°F	≥39.3 to <40.0°C OR ≥102.7°F to <104.0°F	≥40.0°C OR ≥104.0°F
Fatigue or Malaise	Symptoms causing no or minimal interference with USFA[a]	Symptoms causing greater than minimal interference with USFA	Symptoms causing inability to perform USFA	Incapacitating symptoms of fatigue or malaise causing inability to perform BSCF[b]
Myalgia (generalized)	Muscle pain causing no or minimal interference with USFA	Muscle pain causing greater than minimal interference with USFA	Muscle pain causing inability to perform USFA	Disabling muscle pain causing inability to perform BSCF
Headache	Symptoms causing no or minimal interference with USFA	Symptoms causing greater than minimal interference with USFA	Symptoms causing inability to perform USFA	Symptoms causing inability to perform BSCF OR hospitalization indicated OR headache with significant impairment of alertness or other neurologic function
Nausea	Transient (<24 hours) or intermittent AND no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Vomiting	Transient or intermittent AND no or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Chills	Symptoms causing no or minimal interference with USFA	Symptoms causing greater than minimal interference with USFA	Symptoms causing inability to perform USFA	NA
Arthralgia	Joint pain causing no or minimal interference with USFA	Joint pain causing greater than minimal interference with USFA	Joint pain causing inability to perform USFA	Disabling joint pain causing inability to perform BSCF

[a] Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

[b] Basic self-care functions. Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant.

12.2. Special Reporting Situations

Safety events of interest on a sponsor study vaccine that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study vaccine
- Suspected abuse/misuse of a sponsor study vaccine
- Accidental or occupational exposure to a sponsor study vaccine
- Medication error involving a sponsor product (with or without participant/patient exposure to the sponsor study product, eg, name confusion)
- AESIs

Participant-specific special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

Solicited adverse events, unsolicited adverse events, AESIs, serious adverse events and adverse events leading to vaccine discontinuation will be reported for all participants.

All serious adverse events and adverse events and special reporting situations, that are related to study procedures or that are related to non-investigational sponsor products will be reported from the time a signed and dated ICF is obtained until the end of the study/withdrawal. Clinically relevant medical events not meeting the above criteria and occurring between signing of ICF and the moment of first vaccination will be collected on the Medical History CRF page as pre-existing conditions.

Solicited adverse events, collected through a diary, will be recorded daily for each vaccination from the moment of vaccination until 7 days post-vaccination.

All other unsolicited adverse events and special reporting situations will be reported for each vaccination from the moment of vaccination until 28 days post-vaccination. Unsolicited adverse events with the onset date outside the timeframe defined above (>28 days after previous study vaccination), which are ongoing on the day of the subsequent vaccination, should be recorded as such.

From the time of local approval of protocol amendment 5 onwards, TTS is considered to be an AESI. Thrombotic events and/or thrombocytopenia (defined as platelet count below the LLN range for the testing lab) are considered to be potential AESIs. All AESIs, including potential AESIs, will be reported to the sponsor from the moment of first vaccination until 6 months after the last vaccination. Each potential AESI will be reviewed to identify a TTS case.

All serious adverse events, MAAEs, and adverse events leading to discontinuation (regardless of the causal relationship) are to be reported from the moment of first vaccination for the duration of the study. The HPX3002/HVTN 706 safety review team will review the safety information during the conduct of the study. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All AEs will be followed until resolution or until clinically stable.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

The investigator will monitor and analyze study data including all adverse event data as they become available and will make determinations regarding the severity of the adverse experiences and their relation to study vaccine. Adverse events will be deemed either related to study vaccine or not related to study vaccine, according to Section 12.1.2.

The investigator or designee must review both collected solicited events and other adverse event CRFs to ensure prompt and complete identification of all events that require expedited reporting as serious adverse events or as other serious and unexpected events.

All per-protocol collected adverse events, regardless of seriousness, severity, or presumed relationship to study product, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper-respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number

- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by email (facsimile [fax] is acceptable if email is not an option for the site).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study product or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a participant in a study during the entire study period, whether or not the event is expected or associated with the study product, is considered a serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy in participants or partners of participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further vaccination.

Follow-up information regarding the outcome of the pregnancy will be required. Any postnatal sequelae in the infant will be collected, if possible.

12.3.4. Adverse Events of Special Interest

Adverse Events of Special Interest (AESIs) (including potential AESIs) are significant AEs that are judged to be of special interest because of clinical importance, known or suspected class effects, or based on nonclinical signals. AESIs (including potential AESIs) will be carefully monitored during the study by the sponsor.

AESIs (including potential AESIs) must be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious AEs) or causality following the procedure described above for SAEs.

AESIs (including potential AESIs) must be reported using the AESI checkbox in the eCRF using the eCRF completion guidelines.

Specific requirements for the AESI are described below.

12.3.4.1. Thrombosis with Thrombocytopenia Syndrome

As described in Section 1.1.2, TTS has been observed following vaccination with Janssen COVID vaccine and is considered to be an AESI in this study. TTS is a syndrome characterized by a combination of both a thrombotic event and thrombocytopenia.[2,5]

Because this syndrome is rare and not completely understood, all cases of thrombosis and/or thrombocytopenia will be considered a potential case of TTS and should be reported to the sponsor within 24 hours of awareness using the SAE form (even in cases that are not considered ‘serious’). Each potential AESI will be reviewed to identify a TTS case. A Charter will describe the roles and responsibilities of the Committee appointed to perform this review. A potential TTS case is defined as:

- Thrombotic events: suspected deep vessel venous or arterial thrombotic events as detailed in Attachment 4,

  and/or

- Thrombocytopenia, defined as platelet count below LLN for the testing lab

Symptoms, signs, or conditions suggestive of a thrombotic event or thrombocytopenia should be recorded and reported as a potential AESI even if the final or definitive diagnosis has not yet been determined, and alternative diagnoses have not yet been eliminated or shown to be less likely. Follow-up information and final diagnoses, if applicable, should be submitted to the sponsor as soon as they become available.

In the event of thrombocytopenia, study site personnel should report the absolute value for the platelet count and the reference range for the laboratory test used.

For either a thrombotic event or thrombocytopenia, a serum sample should be obtained to test for anti-PF4 at the local laboratory or substitute local laboratory, if possible; repeat testing may be requested for confirmation upon sponsor discretion. A test for anti-PF4 will also be performed on a stored pre-vaccination sample, if possible.

AESIs (including potential AESIs) will require enhanced data collection and evaluation. Every effort should be made to report as much information as possible about the event to the sponsor in a reasonable timeframe.

If an event meets the criteria for an SAE (Section 12.1.1), it should be reported using the same process as for other SAEs.

Treatment and Follow-up Recommendation

The medical management of thrombotic events with thrombocytopenia is different from the management of isolated thromboembolic diseases. Study site personnel and/or treating physicians should follow available guidelines for treatment of thrombotic thrombocytopenia (eg, American Society of Hematology 2021[2]; British Society of Haematology 2021[6]; CDC 2021[8]). The use of heparin may be harmful and alternative treatments may be needed. Consultation with a hematologist is strongly recommended.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY PRODUCT INFORMATION

14.1. Physical Description of Study product(s)

The candidate components of the VAC89220 HIV-1 vaccine supplied for this study are formulated as follows:

Ad26.Mos4.HIV

Ad26.Mos4.HIV is a tetravalent vaccine composed of four pre-mixed recombinant, replication-incompetent serotype 26 adenoviruses, in a 1:1:1:1 vp ratio:

- Ad26.Mos1.Gag-Pol: serotype 26 adenovirus encoding for Mosaic 1 HIV-1 Gag and Pol proteins, manufactured in PER.C6® cells (JNJ-55471494).
- Ad26.Mos2.Gag-Pol: serotype 26 adenovirus encoding for Mosaic 2 HIV-1 Gag and Pol proteins, manufactured in PER.C6® cells (JNJ-55471520).
- Ad26.Mos1.Env: serotype 26 adenovirus encoding for Mosaic 1 HIV-1 Env protein, manufactured in PER.C6® cells (JNJ-55471468).
- Ad26.Mos2S.Env: serotype 26 adenovirus encoding for Mosaic 2S HIV-1 Env protein, manufactured in PER.C6® cells (JNJ-64219324).

The Ad26.Mos4.HIV vaccine is supplied as a colorless to slightly yellowish/brownish, clear to slightly opalescent solution, practically free from particles. The recommended storage condition of the Ad26.Mos4.HIV vaccine is 2°C to 8°C at the clinical site. The vaccine will be provided in individual dosage vials at a concentration of $1x10^{11}$ vp/mL, for IM injection. Refer to the most recent version of the Investigator's Brochure for a list of excipients.

Clade C and Mosaic gp140 HIV Bivalent Vaccine, Recombinant

The Clade C and Mosaic gp140 HIV bivalent vaccine, recombinant (JNJ-65184340) contains following active pharmaceutical ingredients:

- Clade C gp140 drug substance (DS) is a trimeric, recombinant HIV-1 Env gp140 of Clade C, produced on a PER.C6® cell line.
- Mosaic gp140 DS is a trimeric, recombinant HIV-1 Env gp140 engineered to contain motifs of multiple HIV-1 variants produced on a PER.6® cell line.
- Aluminum phosphate adjuvant.

The bivalent drug product (DP) is a vaccine with a dosage strength of 80 mcg Clade C protein and 75 mcg Mosaic protein and 425 mcg aluminum (as aluminum phosphate adjuvant) based on 0.5 mL delivery volume. Note: previously the dose of Clade C gp140 and/or Mosaic gp140 was reported as mcg of glycoprotein: 125 mcg Clade C gp140 and 125 mcg Mosaic gp140 glycoprotein corresponds with 80 mcg and 75 mcg of protein, respectively. The DP white to off-white suspension for IM injection (or essential free of foreign particles). The DP is to be stored at 2 to 8°C. Refer to the most recent version of the Investigator's Brochure for a list of excipients.

Placebo

Placebo consisting of sterile 0.9% Saline for Injection will be supplied (as commercially available).

Study vaccines will be manufactured and provided under the responsibility of the sponsor.

14.2. Packaging and Labeling

All study vaccines were manufactured and packaged in accordance with Current Good Manufacturing Practice. All study vaccines will be packaged and labeled, and all placebo repackaged and relabeled under the responsibility of the sponsor.

No study vaccine can be repacked or relabeled without prior approval from the sponsor.

Further details for study vaccine packaging and labeling can be found in the Study-Specific Procedures Binder.

14.3. Preparation, Handling, and Storage

See the Study-Specific Procedures Binder for guidance on study product preparation, handling, and storage.

Study vaccine must be stored upright in a secured location at controlled temperature with no access for unauthorized personnel. In the event that study vaccine is exposed to temperatures outside the specified temperature ranges, all relevant data will be sent to the sponsor to determine if the affected study vaccine can be used or will be replaced. The affected study vaccine must be quarantined and not used until further instruction from the sponsor is received.

A site pharmacist will prepare all doses for administration and will provide it to the clinic. In order to preserve blinding, the pharmacist will place an overlay on the syringes. Administration of study vaccine to the participants will be performed by a blinded qualified healthcare provider from the study site.

14.4. Vaccine Accountability

The investigator is responsible for ensuring that all study vaccine received at the site is inventoried and accounted for throughout the study. The study vaccine administered to the participant must be documented on the intervention accountability form. All study vaccine will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study product containers.

Study product must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study vaccine must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study vaccine will be documented on the Investigational Product Destruction Form. When the study site is an authorized destruction unit and study product supplies are destroyed on-site, this must also be documented on the Investigational Product Destruction Form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for vaccine accountability purposes.

Study vaccine should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study vaccine will be supplied only to participants in the study. Study vaccine may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study product from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochures for Ad26.Mos.HIV and Clade C gp140 and Mosaic gp140
- Study-Specific Procedures Binder*
- Sample ICF
- Participant diary
- TOU
- Social Impact Questionnaire
- Sexual Activity Questionnaire
- Questionnaire on the use of PrEP
- Ruler (to measure diameter of any erythema and swelling)
- Thermometer
- Participant wallet cards
- Recruitment tools, as applicable

* The Study-Specific Procedures Binder consists of:

Study Procedures Manual

Guidance documents for identification of risk behavior

Guidance document for PrEP

Laboratory Manual

IWRS Manual

eDC Guidelines

etc

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only potential participants who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

From screening to the final study visit, the total blood volume to be collected from each participant will be approximately 590 mL (maximum). In case a participant becomes HIV-1 infected, from visit #.X to the final study visit, additionally approximately 420 mL (maximum) will be taken. The total blood volume to be collected is within the US Department of Health and Human Services Office for Human Research Protections, and US Food and Drug Administration (FDA) guidelines of 550 mL in any 8-week period.

Janssen scientists and operational staff are committed to adhering to all local and national guidance as well as Good Participatory Practice[37], which dictates broad and meaningful stakeholder engagement (including but not limited to Community Advisory Boards) for input into the planning, conduct, and follow-up of research to address all pertinent stakeholder issues including the local cultural and linguistic needs of the communities where the research occurs.

Test of Understanding

The TOU (see Attachment 2) is a short assessment of the potential participant's understanding of key aspects of the study. The test will help the study staff to determine how well potential participants understand the study and their requirements for participation.

Each potential participant must pass the TOU, indicating that he or she understands the purpose of, and procedures required for the study, after reading the informed consent and after the investigator or designee has provided detailed information on the study and has answered the potential participant's questions. Each participant must subsequently sign the ICF, indicating that he or she is willing to participate in the study.

Potential participants are allowed to retake the test twice to achieve the passing score (≥90%) required for participation in the study. Further information and counseling will be provided by the study team member after each missed question.

Any potential participant not capable of understanding the key aspects of the study, and their requirements for participation, should not be enrolled.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor/partners have received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants

- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study product
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the potential participant can read and/or understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor and its partners

personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access, which includes permission to obtain information about their HIV status. It also denotes that the participant agrees to allow his or her study clinician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor and its partners personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory research is not conducted under standards appropriate for the return of data to participants. Exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand vaccines, to understand differential vaccine responders, and to develop tests/assays related to vaccines, and may include DNA/RNA testing. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 10.4, Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

17.2. Protocol Amendments

Neither the investigator nor the sponsor or its partners will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate protocol representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the protocol representative must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.3. Regulatory Documentation

17.3.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.3.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study product to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.4. Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor/partner study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

The investigator must also complete a participant screening log, which reports on all participants who were seen to determine eligibility for inclusion in the study.

17.5. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study product administration information; and date of study completion and reason for early discontinuation of study product or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor/partner. If the electronic source system is utilized, references made

to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

Participant- and investigator-completed scales and assessments designated by the sponsor/partner will be recorded and will be considered source data. The participant's diary used to collect information regarding solicited signs and symptoms after vaccination will be considered source data.

17.6. Case Report Form Completion

Case report forms are prepared and provided by the sponsor/partner for each participant in electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor/partner.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.7. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.8. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.9. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.10. Study Completion/Termination

17.10.1. Study Completion/End of Study

The study is considered completed with the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor and its partners (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.10.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study product development

17.11. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be

respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.12. Use of Information and Publication

If applicable, study results will be communicated to the study participants through the study sites and/or community representatives prior to general public disclosure (eg, at a conference).

All information, including but not limited to information regarding VAC89220 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of VAC89220, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multi-center) data and information without approval from the investigator. The investigator has the right to publish study-site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor and its partners for review at least 21 days before submission for publication or presentation. At the request of the sponsor and/or partners, such submission may be delayed up to 60 days. Expedited

reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multi-center study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multi-center study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multi-center study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by applicable law.

18. COVID-19 APPENDIX: GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks, and may lead to a pause (after agreement between the sponsor and the study site).

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff and to maintain oversight of delegated trial activities.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible as a remote visit, a home visit, or delayed until such time that on-site visits can be resumed.[a] At each contact, participants will be interviewed to collect safety data. Key endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF). Any deviations to study procedures occurring due to the COVID-19 pandemic need to be properly captured in the clinical trial management system (or CRF), with the prefix "COVID-19-related" (including actual visit date) and will be summarized in the clinical study report.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to applicable guidance documents and regulations. If a participant has tested positive for SARS-CoV-2, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

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[a] An on-site visit is defined as a visit during which the participant and the qualified and blinded site staff are both present in person at the study site.

A remote visit is defined as a visit during which there is no direct in-person physical presence between the participant and the qualified and blinded site staff (telephone or video call).

A home visit is defined as a visit during which the participant and the qualified and blinded site staff are both present at the participants' home.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

The following emergency provisions are meant to ensure participant safety on study while site capabilities are compromised by COVID-19-related restrictions. When restrictions are lifted, sites should revert to the original protocol conduct as soon as feasible and in accordance with local guidance and regulations and in agreement with the institutions and the investigator's assessment of the safety of site staff and study participants. The sponsor has developed a specific process allowing activity to resume on a site-by-site basis when deemed safe to do so based on a risk assessment.

Screening

- During COVID-19-related pauses, all screening activities and enrollment of new participants are stopped to safeguard well-being of individuals. Participants who are in screening at this time, will be classified as screen failures, which will be captured in the CRF using the pre-fix 'COVID-19-related'. When screening activities can be resumed, these participants will be allowed to be rescreened. Although protocol Section 9.1.3 states that potential participants who fail screening can be rescreened only once, the COVID-19-related screen failure will not be counted in this respect.

Vaccination Visits

- During COVID-19-related pauses, study vaccine administration is put on hold. At the next possible on-site visit, the study vaccine may be administered. Vaccination outside of the window can be assessed on a case-by-case basis following approval and recommendations from the safety review team and will be documented as 'COVID-19-related'.

Other Study Visits and Assessments

- When site visits are not possible, sites should collect the assessments via remote visits or via home visits (if possible and if the participant allows and provides consent to it). For participants having received one or more vaccinations, post-vaccination visits can be conducted remotely with the main objective to collect safety and reactogenicity data, if possible. The actual visit date and the type of visit (ie, remote or home visit) should be captured in the eCRF according to the eCRF completion guidelines.
- Procedures that can't be performed in case of remote visits (eg, blood/urine sampling, swabbing), including missed assessments related to efficacy endpoints (in-study HIV testing and sampling for immunogenicity testing), should be documented as protocol deviations and labelled as "missed due to COVID-19". The protocol deviations need to be captured in the source document.
- Reactogenicity assessment should be discussed during the remote visits. Diary reconciliation by the investigator will be done at the next possible on-site visit or at a home visit if possible and agreed by the participant. At the end of the study, all diaries should be on site for final reconciliation and filed in participants' folders.

Sample Management

- If a site is experiencing a disruption in shipment of specimens from their Site Processing Lab to the centralized HIV diagnostic testing laboratory(ies) due to the COVID-19 pandemic-related challenges, the Site Processing Lab should hold that specimen at the proper temperature for later per-protocol testing and the Clinical Research Site should collect an additional specimen for HIV-1 PCR RNA testing at a local laboratory. The site should collect the specimen appropriate to local lab requirements for this purpose. Locally performed rapid test, enzyme immunoassay (EIA), or chemiluminescence microparticle immunoassay (CMIA) should NOT be used due to potential risk of unblinding to clinical staff. Local HIV-1 PCR RNA testing will be used only for clinical management of the participants and will not replace the in-study HIV diagnostics testing for protocol endpoints. The local testing result should be recorded in the source document. Sites should continue to collect all specimens that are required per the Specimen Collection Table SSP (including specimens for HIV diagnostics testing).

Source Data Verification/Monitoring

- In case on-site monitoring visits are not possible, the site monitor may contact the investigator to arrange monitoring visits and activities remotely (in accordance with site and local requirements). Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

Site Audits

- During the COVID-19 pandemic and at the impacted sites, study site GCP audits with direct impact/engagement from the investigator and study site personnel may not be conducted in order to comply with national, local, and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study related documents may take place with limited impact/engagement if possible.

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Attachment 1: Definition of Individual of Childbearing Potential and List of Acceptable Highly Effective Contraceptive Methods

Definition of Individual of Childbearing Potential

Individual of Childbearing Potential

A participant is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Individual Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal participant experiences menarche) or the risk of pregnancy changes (eg, a participant who is not heterosexually active becomes active), a participant must begin a highly effective method of contraception, as described throughout the inclusion criteria.

List of Highly Effective Contraceptive Methods

Highly effective contraceptive methods, based on the CTFG guidance, for this study include:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)[a]
2. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectible, implantable)[a,b]
3. Intrauterine device (IUD)[a,b]
4. Intrauterine hormone-releasing system (IUS)[a,b]
5. Bilateral tubal occlusion[a,b]
6. Vasectomized partner[b,c]
7. Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action

[a] Contraception methods that in the context of the CTFG guidance are considered highly effective.

[b] Contraception methods that in the context of the CTFG guidance are considered to have low user dependency.

[c] Vasectomised partner is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCP study participant and that the vasectomised partner has received medical assessment of the surgical success.

Attachment 2: Test of Understanding[a]

Please read each question and answer whether the statement is **True** or **False**.

True ☐	False ☐	1. There is a 50% chance (1 chance out of 2) that you will receive a placebo vaccine in this study.
True ☐	False ☐	2. The experimental vaccine you may receive in this study is proven to protect against HIV.
True ☐	False ☐	3. You will need to come to the clinic for scheduled visits for at least the next two and a half years.
True ☐	False ☐	4. The vaccines in this study can give you HIV.
True ☐	False ☐	5. One purpose of this study is to determine if the experimental vaccine prevents HIV infection -
True ☐	False ☐	6. Participants in this study will have access to measures to prevent HIV infection and other sexually transmitted infections
True ☐	False ☐	7. Because the experimental vaccine may turn some of the standard tests for HIV infection positive, some people may incorrectly think that study participants are infected with HIV (false-positive).
True ☐	False ☐	8. We will not test you for HIV infection during the study.
True ☐	False ☐	9. You should avoid performing tests for HIV infection outside the study as this could cause misdiagnosis and interfere with clinical follow-up.
True ☐	False ☐	10. A participant in this study may experience side effects after vaccination.
True ☐	False ☐	11. You may withdraw from the study at any time if you choose or your participation may be stopped if the study team decides it is in your best interest.

[a]Adaptations to the TOU are allowed for local purposes, after IRB/IEC and sponsor approval.

Attachment 3: List of Potentially Immune-mediated Medical Conditions

The list below contains relevant examples but might not be an exhaustive list.

Gastrointestinal disorders	**Blood disorders**
Celiac disease Crohn disease Ulcerative colitis Ulcerative proctitis	Antiphospholipid syndrome Autoimmune aplastic anemia Autoimmune hemolytic anemia Autoimmune neutropenia Autoimmune pancytopenia Autoimmune thrombocytopenia Pernicious anemia
Liver disorders	**Metabolic disorders**
Autoimmune cholangitis Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis	Addison's disease Autoimmune thyroiditis (including Hashimoto thyroiditis) Diabetes mellitus type I Grave's or Basedow's disease
Musculoskeletal disorders	**Neuroinflammatory disorders**
Antisynthetase syndrome Idiopathic inflammatory myopathies, including dermatomyositis Mixed connective tissue disorder Polymyalgia rheumatica Polymyositis Psoriatic arthropathy Relapsing polychondritis Rheumatoid arthritis, and associated conditions including juvenile chronic arthritis and Still's disease Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis Systemic lupus erythematous and associated conditions Systemic scleroderma (Systemic sclerosis), including diffuse systemic form and CREST syndrome	Acute disseminated encephalomyelitis, including site-specific variants (eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis) Cranial nerve disorders, including paralyses/paresis (eg, Bell's palsy) Guillain-Barré syndrome, including Miller Fisher syndrome and other variants Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy Multiple sclerosis Myasthenia gravis, including Lambert-Eaton myasthenic syndrome Narcolepsy Optic neuritis
Skin disorders	**Vasculitides**
Alopeci areata Autoimmune bullous skin diseases, including pemphigus, pemphigoid, and dermatitis herpetiformis Cutaneous lupus erythematosus Erythema nodosum Lichen planus Localized scleroderma (Morphea) Psoriasis Sweet's syndrome Vitiligo	Large vessel vasculitis including giant cell arteritis such as Takayasu's arteritis and temporal arteritis Medium sized and/or small vessels vasculitis including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and antineutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Others
Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
Autoimmune myocarditis/cardiomyopathy
Goodpasture syndrome
Idiopathic pulmonary fibrosis
Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy)
Raynaud's phenomenon
Sarcoidosis
Sjörgen's syndrome
Stevens-Johnson syndrome

Attachment 4: Thrombotic Events to be Reported as Potential AESIs

At the time of protocol amendment 5 writing, the list of thrombotic events to be reported to the sponsor as potential AESIs is provided below. Further guidance may become available on thrombotic events of interest.

- MedDRA PTs for large vessel thrombosis and embolism

  Aortic embolus, aortic thrombosis, aseptic cavernous sinus thrombosis, brain stem embolism, brain stem thrombosis, carotid arterial embolus, carotid artery thrombosis, cavernous sinus thrombosis, cerebral artery thrombosis, cerebral venous sinus thrombosis, cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, mesenteric artery embolism, mesenteric artery thrombosis, mesenteric vein thrombosis, splenic artery thrombosis, splenic embolism, splenic thrombosis, thrombosis mesenteric vessel, visceral venous thrombosis, hepatic artery embolism, hepatic artery thrombosis, hepatic vein embolism, hepatic vein thrombosis, portal vein embolism, portal vein thrombosis, portosplenomesenteric venous thrombosis, splenic vein thrombosis, spontaneous heparin-induced thrombocytopenia syndrome, femoral artery embolism, iliac artery embolism, jugular vein embolism, jugular vein thrombosis, subclavian artery embolism, subclavian vein thrombosis, obstetrical pulmonary embolism, pulmonary artery thrombosis, pulmonary thrombosis, pulmonary venous thrombosis, renal artery thrombosis, renal embolism, renal vein embolism, renal vein thrombosis, brachiocephalic vein thrombosis, vena cava embolism, vena cava thrombosis, truncus coeliacus thrombosis

- MedDRA PTs for more common thrombotic events

  Axillary vein thrombosis, deep vein thrombosis, pulmonary embolism, MedDRA PTs for acute myocardial infarction*, MedDRA PTs for stroke*

Source: Shimabukuro T. CDC COVID-19 Vaccine Task Force. Thrombosis with thrombocytopenia syndrome (TTS) following Janssen COVID-19 vaccine. Advisory Committee on Immunization Practices (ACIP). April 23, 2021. https://www.cdc.gov/vaccines/acip/meetings/slides-2021-04-23.html.

*Vaccine Adverse Event Reporting System (VAERS) Standard Operating Procedures for COVID-19 (as of 29 January 2021) https://www.cdc.gov/vaccinesafety/pdf/VAERS-v2-SOP.pdf

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD by delegation

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	28-Feb-2023 17:06:36 (GMT)	Document Approval