Janssen Vaccines & Prevention B.V.*

Clinical Protocol

A randomized, parallel-group, placebo-controlled, double-blind Phase 1/2a study in healthy HIV-uninfected adults to assess safety/tolerability and immunogenicity of 2 different prime/boost regimens: priming with tetravalent Ad26.Mos4.HIV and boosting with tetravalent Ad26.Mos4.HIV and either Clade C gp140 plus adjuvant OR a combination of Mosaic and Clade C gp140 plus adjuvant

IPCAVD-012/ HVTN 118

Protocol VAC89220HPX2003 Amendment 6; Phase 1/2a

JNJ-55471468, JNJ-55471494, JNJ-55471520, JNJ-55471585, JNJ-64219324, JNJ-64219311, JNJ-65184340

These compounds are being investigated in Phase 1/2a clinical studies.
US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).
IND: 016263

* Janssen Vaccines & Prevention B.V. (formerly known as Crucell Holland 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.

Status: Approved
Date: 27 October 2021
EDMS number: EDMS-ERI-112499463, 14.0

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	29 Feb 2016
Amendment 1	02 Dec 2016
Amendment 2	12 Feb 2018
Amendment 3	6 Feb 2020
Amendment 4	23 July 2020
Amendment 5	21 May 2021
Amendment 6	This document

Amendments below are listed beginning with the most recent amendment.

Amendment 6 (This document)

The overall reason for the amendment: Upon request of the Center for Biologics Evaluation and Research (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.

Rationale: 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.

TIME AND EVENTS SCHEDULE FOR THE LATE BOOST EXTENSION
9.3 Safety Evaluations
12.3.3.2 Thrombosis with Thrombocytopenia Syndrome

Rationale: 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:

- 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.

ABBREVIATIONS AND DEFINITIONS
1.1.2.3 Clinical Safety Experience With the Ad26.COV2.S Vaccine
12.3.3.2 Thrombosis with Thrombocytopenia Syndrome
REFERENCES

Rationale: For consistency with the definitions of thrombocytopenia of the CDC, Brighton Collaboration and Medicines and Healthcare products Regulatory Agency, which do not include symptomatology, 'symptomatic thrombocytopenia' was replaced by 'thrombocytopenia' in the definition of TTS in this protocol.

SYNOPSIS
1.2.5 Overall Benefit/Risk Assessment
3.1 Overview of Study Design
9.3 Safety Evaluations
12.3.1 All AEs
12.3.3.2 Thrombosis with Thrombocytopenia Syndrome

Rationale: The reference to the Brighton Collaboration case definition of thrombotic events and thrombocytopenia was updated.

REFERENCES

Rationale: 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.

12.3.3 Adverse Events of Special Interest

Rationale: Clarified that TTS is reported using the SAE form and not a separate or different AESI specific form.

12.3.3.2 Thrombosis with Thrombocytopenia Syndrome

Rationale: For consistency with a request from an ethics committee in one of the other studies of the HIV Vaccine program, it was clarified that any postnatal sequelae in an infant will be collected if possible.

12.3.4 Pregnancy

Rationale: The background section of the protocol has been updated with a summary of the HPX2008/HVTN 705 results.

1.1.2.2 Current Studies
REFERENCES

Rationale: Clarified that a blood draw will be needed for the central HIV testing. The footnote stating 'no extra blood required' has been removed. As a result, the overall blood volume throughout the late boost extension phase was updated.

TIME AND EVENTS SCHEDULE FOR THE LATE BOOST EXTENSION
9.1.1 Overview
16.1 Study-specific Design Considerations

Amendment 5 (21 May 2021)

The overall reason 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.

Rationale: 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. A potential TTS/AESI is defined as thrombotic events or symptomatic thrombocytopenia.

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Attachment 5: Thrombotic Events to be reported as Potential AESIs

Rationale: Participants planning to receive the late boost study vaccination are allowed to receive a COVID-19 vaccine that has been either licensed or authorized for emergency use (eg, EUA, EUL or similar program). However, an exclusion criterion is added for the late boost vaccination that specifies the time interval that should be respected between late boost study vaccination and COVID-19 vaccination. An exclusion criterion is also added for the late boost vaccination, specifying that concomitant participation in an interventional study with COVID-19 vaccines is not allowed.

ABBREVIATIONS AND DEFINITIONS
4.5 Inclusion Criteria, Exclusion Criteria and Prohibitions and Restrictions for the Late Boost Vaccination
8 PRESTUDY AND CONCOMITANT MEDICATION

Rationale: For participants planning to receive the late boost study vaccination, COVID-19 vaccination is to be recorded as of any time before signing of the ICF addendum until the end of the study for a participant.

TIME AND EVENTS SCHEDULE FOR THE LATE BOOST EXTENSION
8 PRESTUDY AND CONCOMITANT MEDICATION
9.1.10 Late Boost Vaccination

Rationale: To ensure alignment with Janssen internal Standard Operation Procedures, the process for protocol clarification communications was added.

17.1 Protocol Clarification Communications

Rationale: For clarification, the IND number is added to the title page.

Title page

Amendment 4 (23 July 2020)

The overall reason for the amendment: In this amendment, it is clarified that if a visit of the LTE and late boost extension phases can't be scheduled within the allowed window, it will be assessed on a case-by-case basis whether this visit can still be performed. In addition, all post late boost vaccination visits have been made relative to the time of the boost vaccination. 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 the subjects and site staff during the pandemic. These measures will not be described in the body of the protocol but rather outlined in an appendix (Section 18). Furthermore, the Time and Events Schedule has been updated to reflect all assessments described for the exit visit as mentioned in the protocol body and the outdated storage conditions of the Ad26.Mos4.HIV vaccine have been removed.

Rationale: It is clarified that if a visit of the LTE and late boost extension phases can't be scheduled within the allowed window, it will be assessed on a case-by-case basis upon discussion between investigator and sponsor whether this visit can still be performed. In addition, all post late boost vaccination visits have been made relative to the time of the boost vaccination for consistency in immunological assessments. A clarification has been added to interpret 1 month as 30 days, and 1 week as 7 days; hence, the visit window for visit 22a ought to be interpreted as -28 days/+120 days.

TIME AND EVENTS SCHEDULE FOR THE LONG-TERM EXTENSION PHASE (FROM WEEK 72 ONWARDS, GROUP 1 AND GROUP 2)
TIME AND EVENTS SCHEDULE FOR THE LATE BOOST EXTENSION
9.1.2 Visit Windows
9.1.10 Late Boost Vaccination

Rationale: A COVID-19 Appendix has been added to provide guidance to investigators for managing study-related procedures during the COVID-19 pandemic. For health and safety reasons, subjects may not be able to come to the study site for scheduled procedures.

TIME AND EVENTS SCHEDULE
3.1 Overview of Study Design
9.1.2 Visit Windows
18 COVID-19 APPENDIX: GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

Rationale: The Time and Events Schedule for the late boost extension has been updated to include a symptom-directed physical examination and vital signs measurements for the exit visit.

TIME AND EVENTS SCHEDULE FOR THE LATE BOOST EXTENSION

Rationale: The storage conditions for Ad26.Mos4.HIV mentioned in the protocol are outdated. Therefore, the details have been removed from the protocol. A sentence has been added to clarify that the study vaccine storage conditions are also mentioned on the clinical label.

14.1 Physical Description of Vaccines
14.3 Preparation, Handling, and Storage

Rationale: The Confidentiality Statement was revised and the statement 'CONFIDENTIAL – FOIA Exemptions Apply in U.S.' was added to the running footer, to comply with an update from Janssen's Legal department.

Title page

Amendment 3 (6 Feb 2020)

The overall reason for the amendment: In this amendment, an optional late boost extension to the long term extension (LTE) phase of the study is introduced to assess the impact of a late boost vaccination administered approximately 3 years after the 4th vaccination of the primary vaccination series on the immunologic responses as well as to assess the safety of such late boost vaccination. Eligible subjects will be randomized (3:1 ratio) to receive vaccination with Ad26.Mos4.HIV together with Clade C gp140 and Mosaic gp140 or placebo.

Rationale: The goal of this protocol amendment is to include an optional extension to the LTE phase of the study. Subjects enrolled in the LTE phase will be offered participation in this extension and if eligible, consenting subjects will be randomized (3:1 ratio) in a blinded fashion to receive a late boost vaccination with Ad26.Mos4.HIV together with a co-formulation of aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140 (gp140 HIV bivalent vaccine, further referred bivalent gp140) or placebo. The late boost vaccination will be administered at Week 192 (-4 weeks/+4 months [Visit 22a], ie, approximately 3 years after the 4th vaccination of the primary vaccination series). The goal is to evaluate the impact of a late boost vaccination on the quantity (including magnitude and breadth) and quality of the immune response (humoral and cellular) as well as the safety of such late boost vaccination.
Data from the current clinical study HPX2003 and ongoing study HPX2004 have been added to the protocol where relevant to demonstrate the acceptable overall benefit/risk profile for the late boost vaccination.

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3.1 Overview of Study Design
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12.3.3 HIV Infection
14.1 Physical Description of Vaccines
14.3 Preparation, Handling, and Storage
16.1 Study-specific Design Considerations
16.2.3 Informed Consent
REFERENCES

Rationale: The section describing the risks related to aluminum has been aligned with updated template language.

1.2.4 Potential Risks
REFERENCES

Rationale: It is clarified that subjects may be excluded from donating blood following vaccination in the study due to vaccine induced seropositivity (VISP) for as long as VISP persists, as the screening HIV tests most often used on donated blood (ELISA) will often be positive.

4.3 Prohibitions and Restrictions

Rationale: Due to a typographical error the HPX2003 protocol amendment 2 states that subjects in Group 3 of the study will not be informed of their treatment assignment until after the Week 72 eDC database lock. However, given the three-arm design of the study and the inclusion of both active groups in the LTE, it is impossible to inform participants if they qualify for the LTE phase (ie, if the subject is randomized to Group 1 or Group 2) without unblinding those randomized to Group 3 (placebo). Subjects randomized to Group 3 are informed of their treatment assignment when the subject reaches the Week 72 visit, or as soon as possible following Week 72 upon sponsor unblinding at the Week 28 analysis. The protocol has been adjusted accordingly.

5 TREATMENT ALLOCATION AND BLINDING

Amendment 2 (12 Feb 2018)

The overall reason for the amendment: In this amendment, a Long-term Extension (LTE) phase was introduced to assess the durability of immunologic responses up to approximately 3 years after the end of the main study.

Rationale: To assess the durability of the immune responses, an LTE phase of approximately 3 years was introduced for subjects randomized to Group 1 or Group 2, who have received all 4 vaccinations and are negative for HIV infection at the end of the main study. The vaccination regimens of Group 1 and Group 2 (including Ad26.Mos4.HIV and either Clade C gp140 alone or combined with Mosaic gp140) form the basis for the regimens that will likely be evaluated in future studies.

SYNOPSIS
TIME AND EVENTS SCHEDULE
TIME AND EVENTS SCHEDULE FOR THE LONG-TERM EXTENSION PHASE (FROM WEEK 72 ONWARDS, GROUP 1 AND GROUP 2)
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1.2.4 Potential Risks
1.3 Overall Rationale for the Study
2.1 Objectives and Endpoints
3.1 Overview of Study Design
4.1 Inclusion Criteria for the Main Study
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12.3.3 HIV Infection
16.1 Study-specific Design Considerations
16.2.3 Informed Consent

Rationale: It was clarified that subjects are not eligible for participation in the study if they received an experimental vaccine (other than a prophylactic or therapeutic HIV vaccine candidate) within the last 12 months prior to the Day 1 visit (Vaccination 1).
4.2 Exclusion Criteria for the Main Study 8 PRESTUDY AND CONCOMITANT MEDICATION
Rationale: It was indicated that microscopic reflex testing will not be carried out in the event of abnormal urinalysis tests that are considered by the investigator to have a menstrual origin.
TIME AND EVENTS SCHEDULE 9.3 Safety Evaluations
Rationale: A definition of the per protocol immunogenicity population was added to exclude subjects with major protocol deviations from the immunogenicity population.
11.2 Analysis Populations 11.4 Immunogenicity Analyses
Rationale: It was clarified that a (remote) safety follow-up communication 24-72 hours post-vaccination is not required if the vaccination was missed.
TIME AND EVENTS SCHEDULE 9.1.5 Post-vaccination Follow-up Phase
Rationale: It was clarified that subjects who have been prematurely withdrawn from study vaccine administration will be encouraged to complete the post-vaccination follow-up visits of the last vaccination received and a 12 and 24 weeks follow-up visit after the last vaccination received.
TIME AND EVENTS SCHEDULE 10.2 Discontinuation of Study Treatment/Withdrawal from the Study
Rationale: For subjects who withdraw from the study, options regarding the use of optional research samples which were collected are added.
10.2 Discontinuation of Study Treatment/Withdrawal from the Study
Rationale: Minor clarifications and corrections.

1.1.2.1 Prototypes and Similar Vaccines	A typographical error was corrected.
1.2.4 Potential Risks	Update of text on risks related to vaccination for consistency throughout the company's vaccine studies.
1.2.5 Overall Benefit/Risk Assessment 9.3 Safety Evaluations	Administrative change.
SYNOPSIS 3.1 Overview of Study Design	Duration of the main study has been corrected from 76 to 78 weeks (6-week screening + 72 weeks main study).
5 TREATMENT ALLOCATION AND BLINDING	Administrative change.
TIME AND EVENTS SCHEDULE 9.1.1 Overview	Added clarification on time points for review of diary.
9.3 Safety Evaluations 12 AE REPORTING	Added clarification of collection of symptoms in diary.
9.4.3 VISP	It was indicated that the central lab will carry out a follow-up testing algorithm in response to a positive result in an HIV-Ab test.

9.4.4 Social Impact	It was indicated that more details regarding completion of the social impact questionnaire can be found in the Study Procedures Manual.
10.2 Discontinuation of Study Treatment/Withdrawal from the Study	It was clarified that subjects who are vaccinated and who withdraw will not be replaced.
11.8 Data Review Committee	It was clarified that DRC reviews blinded data but can request unblinded data.
11.9 Study Holding Rules	Clarification of footnote 4 of Table 3.
12 AE REPORTING	Removal of redundant instructional text.
12.3.2 SAEs	Administrative change.
12.3.4 Pregnancy	Administrative change.
Attachment 4	It was clarified that adaptations to the social impact questionnaire are allowed for local purposes, after IRB and sponsor approval.
17.3 Subject Identification, Enrollment, and Screening Logs	Administrative change.
17.11 Use of Information and Publication	Administrative changes.

Amendment 1 (02 Dec 2016)

The overall reason for the amendment: Removal of mucosal sampling from the optional study procedures. Changes in the inclusion criteria to align with updated company policies regarding standard contraceptive use in vaccine studies.

Rationale: The optional mucosal sampling assessments have been removed from the protocol. Assessment of mucosal immune responses will be performed later in the clinical development program.

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1.2.5. Overall Benefit/Risk Assessment
2.1. Objectives and Endpoints
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9.1.6. Second Year Follow-up Phase
9.2. Immunogenicity Evaluations
9.3. Safety Evaluations
9.5. Sample Collection and Handling
12.3.4. Pregnancy

Rationale: Changes in the contraceptive requirement in the inclusion criteria to align with updated company policies regarding standard contraceptive use in vaccine studies.

4.1. Inclusion Criteria

Rationale: Change in the approach for collection of specimens to assess vector shedding (optional procedure). Frequency of specimen collection has been updated to align with Health Authority guidance.

Time and Events Schedule
TIME AND EVENTS SCHEDULE FOR OPTIONAL VECTOR SHEDDING ASSESSMENT
3.1. Overview of Study Design
9.1.2 Visit Windows
9.1.3. Screening Phase (Week -6 to 0)
9.1.8. Vector Shedding Evaluations
9.5. Sample Collection and Handling

Rationale: The HIV RNA test at baseline has been deleted, since evaluation of VISP is not relevant at this timepoint. Clarification of HIV testing to include local and central HIV testing.

ABBREVIATIONS
Time and Events Schedule
9.3. Safety Evaluations
9.4.1. HIV Testing
12.3.3. HIV Infection

Rationale: From 1 Jun 2016 onwards, the name of Crucell Holland B.V. has been changed to Janssen Vaccines & Prevention B.V.

Title page

Rationale: Subject's diary should be reviewed at the first opportunity to collect the most reliable AE information and discuss diary data. Therefore diary should be reviewed at Visit 9, one week after third study vaccination. Visit 9 is an additional safety follow-up after the FIH administration of Mosaic gp140 at Visit 8. If the 7-day diary observation period is not completed at Visit 9, the diary will be returned at the subsequent Visit 10.

Time and Events Schedule
9.1.5. Post-vaccination Follow-up Phase

Rationale: Minor clarifications

Title page	Addition of HVTN study number.
Time and Events Schedule	Simplification in TES on weight measurement being predose at vaccination visits
4.2. Exclusion Criteria	Corrected reference to Criteria 10 and 12.
9.3. Safety Evaluations	Added language that laboratory test ranges will be applied according to subject's sex at birth.
12.2. Situations Requiring Special Notification	Clarification on the process for notifying the sponsor of new HIV infection.

Rationale: Minor corrections

Time and Events Schedule and 9.1.2. Visit Windows	Addition of specification on visit window for the visit one week post-vaccination.
1.2.5. Overall Benefit/Risk Assessment	Aligned inconsistency in review of blinded data in sentinel group.
9.3. Safety Evaluations	Removed redundant reference to Section 12.1.1.
9.4.1. HIV Testing, 9.4.3. VISP and 12.3.3. HIV Infection	Changed Study Procedures Manual to Laboratory Manual.
17.5. Case Report Form Completion	Removed statement that all data should be recorded in CRF.

SYNOPSIS

A randomized, parallel-group, placebo-controlled, double-blind Phase 1/2a study in healthy HIV-uninfected adults to assess safety/tolerability and immunogenicity of 2 different prime/boost regimens: priming with tetravalent Ad26.Mos4.HIV and boosting with tetravalent Ad26.Mos4.HIV and either Clade C gp140 plus adjuvant OR a combination of Mosaic and Clade C gp140 plus adjuvant

The goal of this study is to evaluate if the addition of Mosaic glycoprotein 140 (gp140) to Clade C gp140 improves the breadth of humoral immune responses (defined as immune recognition of diverse strains/clades of human immunodeficiency virus [HIV]), which will ultimately assist in the selection of the best regimen(s) for evaluation in future efficacy studies.

Subjects enrolled in the LTE phase will be offered participation in an extension of the LTE phase. Eligible subjects who consent to participation will be randomized (3:1 ratio) in a blinded fashion to receive a late boost vaccination with Ad26.Mos4.HIV together with a co-formulation of aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140 (gp140 HIV bivalent vaccine, further referred to as bivalent gp140) or placebo at Week 192 (-4 weeks/+4 months [Visit 22a], ie, approximately 3 years after the 4th vaccination of the primary vaccination series). The goal is to evaluate the impact of a late boost vaccination on the quantity (including magnitude and breadth) and quality of the immune response (humoral and cellular) as well as the safety of such late boost vaccination.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives	Endpoints
Primary	
• To assess safety/tolerability of the different vaccine regimens	• Solicited local and systemic adverse events (AEs) for 7 days after each vaccination. • AEs for 28 days after each vaccination. • Discontinuations from vaccination/from study due to AEs. • Serious adverse events (SAEs) and AEs of special interest (AESIs) of confirmed HIV infection during the course of the study, including the LTE phase.
• To assess Envelope (Env)-binding antibody (Ab) responses of the 2 different vaccine regimens.	• Env-specific binding Abs (titers and breadth).
• To assess safety/tolerability of a late boost vaccination.	• Solicited local and systemic AEs for 7 days after the late boost vaccination. • AEs for 28 days after the late boost vaccination. • SAEs and AESIs of confirmed HIV infection until the end of the study. • AESIs of thrombosis with thrombocytopenia syndrome (TTS) for 6 months after the late boost vaccination.
Secondary (applicable to main study, LTE and late boost vaccination)	
• To assess neutralizing Ab (nAb) responses, Ab functionality (as assessed by phagocytosis), and Ab isotyping.	• Env-specific nAbs (titers and breadth) • Env-specific functional Abs (phagocytosis score and breadth). • Env-specific binding Ab isotypes (immunoglobulin (Ig)A, IgG1-4) (titers and breadth).

Objectives	Endpoints
• To assess T-cell responses.	• Interferon gamma (IFNγ) peripheral blood mononuclear cell (PBMC) responders to mosaic and potential T-cell epitopes (PTE) peptide pools of Env/group-specific antigen (Gag)/polymerase (Pol). • Cluster of differentiation (CD)4+ and CD8+ T-cell functionality (% cells producing ia, IFNγ, interleukin 2 (IL-2), IL-4, tumor necrosis factor α [TNFα]). • T-cell development with emphasis on follicular helper T-cells and memory differentiation.[a]
Exploratory (applicable to main study, LTE and late boost vaccination)	
• To explore whether the adenovirus serotype 26 (Ad26) vector is shed after vaccination.	• Polymerase chain reaction (PCR) positive for Ad26 sequences (urine and mid-turbinate swab).
• To explore Ab functionality (other than phagocytosis).	• Ab functionality evaluation (such as Ab-dependent cellular cytotoxicity [ADCC], Ab-dependent complement deposition [ADCD]; excluding phagocytosis (ie, Ab-dependent cellular phagocytosis [ADCP]).
• To explore Ab Fc characterization.	• Ab Fc (sub)typing.
• To explore T-cell and Ab epitope mapping.	• Epitope mapping of Ab to Env and T-cell responses to Gag/Pol/Env (PTE and vaccine peptide pools).
• To explore gene expression patterns using PBMCs.	• Regulation of genes (or clusters) that predict specific immune responses and human leukocyte antigen (HLA) typing.
• To explore B-cell responses.	• Ab-producing B-cells and characterization of B-cell memory development.
• To explore immune responses against the viral vector.	• Ad26 nAbs (titer).
• To explore the social impact of participation in an HIV-vaccine study for subjects via a social impact questionnaire.	• Social impact.
• To explore durability of the immune responses to the vaccine regimens in the groups selected for the Long-term Extension (LTE) phase.	• Available samples from time points during the LTE phase will be used for determination of long-term durability of the immune responses.

In addition, the following exploratory objectives are applicable to the late boost vaccination only:

Objectives	Endpoints
• To assess Env-binding Ab responses following late boost vaccination approximately 3 years after receiving the 4th vaccination of the primary vaccination series.	• Env-specific binding Abs [ELISA] at 3, 7 or 14 days[b] and 28 days post late boost vaccination (titers and breadth).

[a] The follicular helper T-cells and memory differentiation was included as secondary objective for the main study. Due to difficulty qualifying the assay for these specific markers, these T-cell responses will be considered as an exploratory objective for the late boost vaccination.

[b] Subjects will be divided into three groups: the first 20 enrolled subjects will have the Visit 22b 7 days post late boost, the next 20 enrolled subjects 3 days post late boost and the remainder of the subjects 14 days post late boost.

Objectives	Endpoints
• To explore the role of Ad26 neutralizing antibodies on the immune response to a late boost vaccination.	• Ad26 neutralizing antibodies at the time of vaccination relative to the immune response as evaluated by ELISA.
• To compare the immune response to late boost vaccination with a vaccine matched to the primary vaccination series (Group 2) vs a closely related vaccine (Group 1).	• Relative ELISA magnitudes between groups randomized to Group 1 vs Group 2 in the main study.
• To evaluate whether humoral responses induced by a late boost vaccination are able to mediate protection in non-clinical passive transfer studies.	• Analysis of protection against HIV-related challenge viruses, such as simian human immunodeficiency virus (SHIV), in a suitable animal model, and/or in vitro.

Hypothesis

No formal statistical hypothesis will be tested. The proposed clinical study in healthy HIV uninfected subjects will evaluate the safety/tolerability and the immunogenicity of 2 different prime/boost regimens: priming with Ad26.Mos4.HIV and boosting with Ad26.Mos4.HIV and either Clade C gp140 plus adjuvant or a combination of Clade C and Mosaic gp140 plus adjuvant.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 1/2a study in healthy HIV-uninfected adult men and women between the ages 18 to 50 years, inclusive. A target of 150 subjects will participate in this study with 25 subjects in Group 1, 100 subjects in Group 2, and 25 subjects in Group 3 (see table below). Group 1 represents the "base-case" regimen which allows bridging of data from this study to study VAC89220HPX2004. Randomization will be stratified by region. Subjects will receive intramuscular (IM) doses of study vaccine or placebo at 4 time points: Ad26.Mos4.HIV or placebo will be given at Weeks 0 and 12; Ad26.Mos4.HIV together with either Clade C gp140 plus adjuvant or a combination of Mosaic and Clade C gp140 plus adjuvant, or placebo will be given at Weeks 24 and 48.

The main study will be conducted in 3 phases: a 6-week screening period; a 48-week vaccination period during which subjects will be vaccinated at baseline (Week 0) and at Weeks 12, 24, and 48; and a follow-up period to the final main study visit at Week 72.

An LTE phase (approximately 3 years after Week 72) will be performed for subjects randomized to Group 1 or Group 2, who have received all 4 vaccinations and are negative for HIV infection at Week 72. The vaccination regimens of Group 1 and Group 2 (including Ad26.Mos4.HIV and either Clade C gp140 alone or combined with Mosaic gp140) form the basis for the regimens that will likely be evaluated in future studies. Subjects enrolled in the LTE phase will be offered participation in an extension to the LTE phase to investigate the safety and immunogenicity of a late boost vaccination approximately 3 years after the last vaccination in the main study (depending on availability of IRB and HA approvals per country/site regulations). Assessment of participants' eligibility for the late boost vaccination and vaccination itself will occur within 4 weeks prior to Week 192 until 4 months after Week 192 (Visit 22a, which can be split over several visits). Eligible, consenting subjects will be randomly assigned (3:1 ratio, see Table below) in a blinded fashion to active vaccination with Ad26.Mos4.HIV and bivalent gp140 (Group 1b) or placebo (0.9% saline) (Group 2b). The aim is to have at least 48 participants enrolled in the late boost extension. Randomization will be stratified by region (USA, East Africa: assuming sufficient numbers from Rwanda in the LTE phase agree to participate) and by group randomized to in the main study (Group 1/Group 2). Upon receipt of the late boost vaccination, participants will be followed up for immunogenicity and safety for a further 12 months or, if they consent to longer follow-up, 24 months. Unblinded interim data analysis (sponsor unblinding only) will be performed approximately 4 weeks after the last subject received the late

boost vaccination. LTE subjects declining participation or not eligible to participate in the late boost extension will complete the study at Visit 23 of the LTE phase.

The duration of the subject's participation will be approximately 78 weeks (6-week screening + 72 weeks main study) for subjects not participating in the LTE phase, approximately 222 weeks for subjects participating in the LTE phase but not receiving a late boost vaccination and approximately 246 (12-month follow-up) or 294 (24-month follow-up) weeks for subjects receiving a late boost vaccination.

After vaccination, subjects will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events. In addition, subjects will record solicited events in a diary for 7 days post-vaccination. Further safety evaluations will include monitoring of AEs, physical examinations, vital sign measurements, clinical laboratory tests, and pregnancy testing. Blood samples will be taken at specific clinic visits to assess immune responses. Subjects will complete a social impact questionnaire at specific clinic visits. Optional urine samples and mid-turbinate swabs will be collected from consenting subjects to assess vector shedding. A Protocol Safety Review Team (PSRT) and Data Review Committee (DRC) will be commissioned for this study.

Table: Schematic Overview of the Main Study

Group	N	Week 0	Week 12	Week 24	Week 48
1[b]	25	Ad26.Mos4.HIV	Ad26.Mos4.HIV	Ad26.Mos4.HIV + Clade C gp140 (250 mcg + adjuvant)[a]	Ad26.Mos4.HIV + Clade C gp140 (250 mcg + adjuvant)[a]
2[b]	100	Ad26.Mos4.HIV	Ad26.Mos4.HIV	Ad26.Mos4.HIV + Clade C + Mosaic gp140 (250 mcg + adjuvant)[a]	Ad26.Mos4.HIV + Clade C + Mosaic gp140 (250 mcg + adjuvant)[a]
3	25	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo

[a]250 mcg refers to total protein content (Clade C gp140 [250 mcg] alone or a combination of Mosaic gp140 [125 mcg] and Clade C gp140 [125 mcg]). Sterile aluminum phosphate suspension will be used as adjuvant. Aluminum content will be 0.425 mg/0.5 mL dose.
[b]An LTE phase (approximately 3 years after Week 72) will be performed for subjects randomized to Group 1 or Group 2, who have received all 4 vaccinations and are negative for HIV infection at Week 72.

Table: Schematic Overview of the Late Boost Vaccination		
Group	**N**	**Week 192 (-4 weeks/+4months)**
1b	3*N/4[1]	Ad26.Mos4.HIV + gp140 HIV bivalent vaccine
2b	1*N/4[1]	Placebo + Placebo

Total dose of Ad26.Mos4.HIV is $5x10^{10}$ viral particles (vp)/0.5 mL injection.
gp140 HIV bivalent vaccine: adjuvanted protein co-formulation with a dosage strength of 80 mcg Clade C protein, 75 mcg Mosaic protein and 425 mcg aluminum (as aluminum phosphate adjuvant). Note: the dose of Clade C gp140 and/or Mosaic gp140 as separate entities is 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.
[1] Subjects will be randomly assigned in a 3:1 ratio to active vaccine or placebo. The aim is to have at least 48 subjects enrolled in the late boost extension.

PSRT

A PSRT will review blinded safety data reports on a regular basis (at least 2 times per month) starting from one week after first vaccination until the last subject has completed the Week 52 visit, and thereafter as needed.

Since the study is the first-in-human (FIH) administration of Mosaic gp140, after a sentinel group of 6 subjects receives the third injection, further third injections will be paused until a 1-day safety evaluation is performed. This evaluation will be performed by the PSRT and the PI(s) of the subjects involved and will be based on the information received from the investigator(s) by email/telephone.

If a dose of vaccine is considered, by PSRT review, to raise significant safety concerns, all enrollment and vaccinations will be suspended until recommendations are issued. In specific cases, a DRC meeting will be triggered.

The PSRT will include, but will not be limited to medical and safety representatives from the sponsor, a limited number of sites, the Division of Acquired Immune Deficiency Syndrome (DAIDS), Beth Israel Deaconess Medical Center (BIDMC), HIV Vaccine Trials Network (HVTN), International Acquired Immune Deficiency Syndrome (AIDS) Vaccine Initiative (IAVI), and Military HIV Research Program (MHRP). The PSRT responsibilities, authorities, and procedures will be documented in its charter.

DRC

A DRC will be established for this study, which will monitor data to ensure the safety and well-being of the subjects enrolled. The DRC will review data as indicated below. The conclusions of the DRC will be communicated to the investigators, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and the national regulatory authorities, as appropriate.

The DRC will specifically review safety data (solicited and unsolicited AEs, SAEs, and available laboratory assessments) at 2 time points following injections of Mosaic gp140:

- Review blinded safety data (2 weeks of follow-up) after approximately 25 (15%) of subjects have received their third injection.
- Review blinded safety data (2 weeks of follow-up) after approximately 50 (30%) of subjects have received their third injection.

In addition, ad hoc review may be performed further to the occurrence of any AE/SAE leading to a study holding situation or at request of the PSRT.

The DRC will include medical experts in vaccines and at least one statistician. The DRC can include members from both inside and outside Janssen, but will not include any study team personnel or people otherwise directly involved in the study conduct, data management, or statistical analysis for the study. The DRC responsibilities, authorities, and procedures will be documented in its charter.

SUBJECT POPULATION

Screening for eligible subjects will be performed within 6 weeks before the first administration of study vaccine or placebo at Week 0.

Study subjects must be healthy (on the basis of medical history, physical examination, vital signs measurement, and laboratory assessments), HIV-uninfected adult men and women, aged ≥18 to ≤50 years, and assessed by the clinic staff as being at low risk for HIV infection.

For entering the LTE phase, subjects must have been randomized to Group 1 or Group 2 during the main study, must have received all 4 vaccinations and must be negative for HIV infection at the end of the main study.

For the late boost extension, eligible subjects must be enrolled in the LTE phase, healthy and HIV-uninfected.

DOSAGE AND ADMINISTRATION

During the main study, each subject will receive doses of study vaccine or placebo at 4 time points according to randomization, on Day 1 and Weeks 12, 24, and 48, administered by IM injection into the deltoid. Subjects eligible and consenting to the late boost vaccination will receive an additional dose of Ad26.Mos4.HIV in combination with bivalent gp140 or placebo at Week 192 -4 weeks/+ 4 months (ie, approximately 3 years after the 4th vaccination of the primary vaccination series), administered by IM injection into the deltoid. For visits with only one injection (ie, at Week 0 and 12), preferably the deltoid of the non-dominant upper arm is used. When 2 injections are to be given at one visit (ie, at Week 24 and 48 and at Week 192 [if applicable]), 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 Interventions

Test articles	Ad26.Mos4.HIV	Clade C gp140 with aluminum phosphate	Clade C gp140 + Mosaic gp140 with aluminum phosphate*	gp140 HIV bivalent vaccine*	Placebo
Description	See Section Vaccine Information.				
Dose/delivery (0.5 mL injection)	$5x10^{10}$ viral particle (vp)	250 mcg Clade C gp140, mixed with aluminum phosphate adjuvant (0.425 mg aluminum)	125 mcg Clade C gp140 + 125 mcg Mosaic gp140, mixed with aluminum phosphate adjuvant (0.425 mg aluminum)	80 mcg Clade C gp140/75 mcg Mosaic gp140/ aluminum phosphate adjuvant (425 mcg aluminum)	0.9% saline
Frequency	Week 0, 12, 24, 48, and Week 192** (if applicable)	Week 24 and 48	Week 24 and 48	Week 192** (if applicable)	Week 0, 12, 24, 48, and Week 192** (if applicable)
Delivery method	IM in deltoid	IM in deltoid	IM in deltoid	IM in deltoid	IM in deltoid
Delivery instructions	Refer to the Study Procedures Manual for details.				

* The dosage of DP in the gp140 HIV bivalent vaccine (late boost vaccination) is identical to the dosage of DP in the co-administered separate gp140 formulations (main study) . However, there has been a change of unit for the reported gp140 concentration from mg/mL glycoprotein to mg/mL protein. This will not impact the dose strength of gp140 in the vial or administered to the participants in the late boost extension, compared to the main study, but the gp140 concentration will be expressed in protein instead of glycoprotein in the specification. Consequently, 125 mcg Clade C gp140 and 125 mcg Mosaic gp140 of glycoprotein correspond with 80 mcg Clade C gp140 and 75 mcg Mosaic gp140 of protein, respectively.

** The late boost vaccination is to be administered at Week 192 -4 weeks/+4 months, ie, approximately 3 years after the 4th vaccination of the primary vaccination series.

IMMUNOGENICITY EVALUATIONS

Humoral immune response assays will include, but are not limited to Env-Ab-binding assays (ELISA), virus neutralization assay, and assays for Ab functionality. Additional assays may include binding antibody assays to evaluate the breadth and isotypes of Ig induced and passive transfer assays.

Cellular immune response assays will include, but are not limited to INFγ enzyme-linked immunospot (ELISPOT) assay, intracellular cytokine staining (ICS), and multiparameter flow cytometry.

SAFETY EVALUATIONS

All AEs and situations requiring special notification will be reported from the time the signed and dated study-specific informed consent form (ICF) is obtained until 28 days after first dose of study vaccine, and thereafter, pre-dose on the day of injection and for 28 days after each subsequent dose of study vaccine or placebo. From the time of local regulatory approval of protocol amendment 5 onwards, thrombosis with thrombocytopenia syndrome (TTS) is considered to be an AESI. Thrombotic events and/or thrombocytopenia are considered to be potential AESIs. Thrombocytopenia is defined as platelet count below the lower limit of normal (LLN) range for the testing lab. All AESIs of TTS, including potential AESIs, will be reported to the sponsor from the moment of the late boost vaccination until 6 months after the late boost vaccination. Each potential AESI will be reviewed to identify a TTS case. All SAEs and AEs leading to discontinuation from the study vaccination (regardless of the causal relationship) and AESIs of confirmed HIV infection are to be reported from signing of study-specific ICF onwards for the duration of the study.

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

In addition, symptoms of the following solicited AEs 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.

- Solicited local AEs: erythema, swelling/induration (measured using the ruler supplied) and pain/tenderness.
- Solicited systemic AEs: fever (temperature measurement), fatigue, headache, nausea, myalgia, and chills.
- Temperature should be measured at approximately the same time each day using the thermometer supplied.

STATISTICAL METHODS

The sample size in this study is regarded to be appropriate to assess the safety and tolerability of the different vaccine regimens. Placebo recipients are included for blinding and safety purposes and will provide control specimens for immunogenicity assays. With 25 individuals in a vaccine regimen, the observation of 0 such reactions would be associated with a 90% confidence that the true rate is less than 10%. For Group 2 with Mosaic and Clade C gp140 (n=100), there would be 90% confidence that the true rate is less than 2.5% when 0 events are observed.

The primary population for the safety analyses will consist of all subjects who received at least 1 dose (Ad26.Mos4.HIV or placebo).

Anticipating a dropout rate of approximately 10%, the sample sizes will allow detection of approximately 1.85-fold differences in Env-binding Ab titers, generally accepted to be biologically relevant, between the groups with Mosaic and Clade C gp140 (approximately 90 evaluable subjects) and their corresponding group with Clade C gp140 only (approximately 22 evaluable subjects); with 80% probability, assuming a 2-sided 5% Type I error and an SD of 0.4 on the $\log_{10}$ scale.

Immunogenicity Analyses

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (actual values and changes from reference with 95% confidence interval) will be calculated for continuous parameters. Frequency tabulations will be calculated for discrete parameters. Graphical representations of changes in immunologic parameters will be made as applicable.

Magnitude and breadth of (neutralizing)Ab responses will be explored graphically through the generation of individual magnitude-breadth (M-B) curves. The area-under-the M-B curve (AUC) will be compared between groups.

Safety Analyses

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

TIME AND EVENTS SCHEDULE

Time and Events Schedule for Treatment Phase and Follow-up Phase until Week 72

Phase	*Scr*	*Vac*	*Post-vac FU*			*Vac*	*Post-vac FU*			*Vac*	*Post-vac FU*					*Vac*	*Post-vac FU*			*Second Year FU*[6]		
Visit #	1[1]	2	2a[3]	3	4	5	5a[3]	6[11]	7[11]	8	8a[3,16]	9[11]	10[11]	11[11]	12	13	13a[3]	14[11]	15[11]	16	17[6]	Exit[7]
Visit Week	-6 to 0	0		2	4	12		14	16	24		25	26	28	36	48		50	52	60	72	
Visit Day and window	-42 to 0	1	2 to 4	15 ± 5	29 ± 5	85 -1/+3 wks	86 to 88	99 ± 5	113 ± 5	169 -1/+3 wks	170 to 172	176 ± 1	183 ± 5	197 ± 5	253 ± 5	337 -1/+3 wks	338 to 340	351 ± 5	365 ± 5	421 ± 3 wks	505 ± 3 wks	
Visit Type	Scr	VAC 1	S	S + I	S + I	VAC 2	S	S + I	S + I	VAC 3	S	S	S + I	S + I	S	VAC 4	S	S + I	S + I	S + I	S + I	Early exit
Informed consent[14]	●																				●[6]	
Test of understanding[18]	●																					
Medical history	●																					
Physical exam[2] (incl height[13])	●	❶		●	●	❶		●	●	❶		●	●	●	●	❶		●	●	●	●	●
Vital signs	●	❸		●	●	❸		●	●	❸		●	●	●	●	❸		●	●	●	●	●
HIV-risk assessment	●	●		●	●	●		●	●	●		●	●	●	●	●		●	●	●	●	●
Counseling on HIV	●	●		●	●	●		●	●	●		●	●	●	●	●		●	●	●	●	●
Concomitant meds	●	❶	●	●	●	❶	●	●	●	❶	●	●	●	●	●	❶	●	●	●	●	●	●
Review of inclusion/ exclusion criteria[15]	●	❶																				
Randomization		❶																				
Vaccination		●				●				●						●						
Post-vac observation (30 min)[10]		●				●				●						●						
AE recording[17]	●	❸	●	●	●	❸	●	●	●	❸	●	●	●	●		❸	●	●	●			●
SAE, AE leading to treatment discontinuation, AESI of confirmed HIV infection recording[17]	●	❸	●	●	●	❸	●	●	●	❸	●	●	●	●	●	❸	●	●	●	●	●	●
Diary distribution		●				●				●						●						
Diary review by site staff				●				●				●[19]	●[19]					●				
24h-72 h contact[3]			●				●				●[16]						●					

Phase	*Scr*	*Vac*	*Post-vac FU*			*Vac*	*Post-vac FU*			*Vac*	*Post-vac FU*					*Vac*	*Post-vac FU*			*Second Year FU*[6]		
Visit #	1[1]	2	2a[3]	3	4	5	5a[3]	6[11]	7[11]	8	8a[3,16]	9[11]	10[11]	11[11]	12	13	13a[3]	14[11]	15[11]	16	17[6]	Exit[7]
Visit Week	-6 to 0	0		2	4	12		14	16	24		25	26	28	36	48		50	52	60	72	
Visit Day and window	-42 to 0	1	2 to 4	15 ± 5	29 ± 5	85 -1/+3 wks	86 to 88	99 ± 5	113 ± 5	169 -1/+3 wks	170 to 172	176 ± 1	183 ± 5	197 ± 5	253 ± 5	337 -1/+3 wks	338 to 340	351 ± 5	365 ± 5	421 ± 3 wks	505 ± 3 wks	
Visit Type	Scr	VAC 1	S	S + I	S + I	VAC 2	S	S + I	S + I	VAC 3	S	S	S + I	S + I	S	VAC 4	S	S + I	S + I	S + I	S + I	Early exit
Social impact questionnaire						●										●					●	●
Vector shedding	See TIME AND EVENTS SCHEDULE FOR OPTIONAL VECTOR SHEDDING ASSESSMENT																					
Urinalysis[4]	●	❶				❶				❶						❶					●	●
Serum pregnancy test[9]	●																					
Urine pregnancy test[9]		❶				❶				❶						❶					●	●
Contraceptive counseling[8]	●	●				●				●						●						●
CBC with differential and platelets[5]	●	❶		●		❶		●		❶			●		●	❶		●		●	●	●
Serum chemistry[5]	●	❶		●		❶		●		❶			●		●	❶		●		●	●	●
Hepatitis B/C serologies	❷																					
Syphilis serology	❷																					
Urine chlamydia/ gonorrhea	●																					
Trichomonas[9,12]	●																					
Local HIV testing	●	❶																				
Central HIV testing						❷				❷						❷					❷	❷
HLA test		❷																				
Humoral immuno Assays		❶		●	●	❶		●	●	❶			●	●		❶		●	●	●	●	●
Cellular immuno Assays		❶			●			●	●				●	●				●	●	●	●	●

AE = adverse event; AESI = AE of special interest; CBC = complete blood count; FU = follow-up; HIV = human immunodeficiency virus; h = hour; HLA = human leukocyte antigen; immuno = immunogenicity; incl = including; meds=medication; min = minutes; S = safety; S + I = safety + immunogenicity; SAE = serious adverse event; scr = screening; vac = vaccination; wks = weeks

❶ pre-dose; ❷ no extra blood required; ❸ pre- and post-dose

[1]Screening visit may be split into multiple days/visits. The maximum screening period is 6 weeks.

[2]Complete physical exam will be performed at screening and final main study visit. At all other visits, an abbreviated, symptom-directed exam will be performed as indicated by the investigator. Weight will be measured at every visit.
[3]Within 24-72 hours post-vaccination a member of the site staff will have a (remote) safety follow-up communication with the subject (by e-mail, telephone, or visit; according to the subject's preference). A (remote) safety follow-up communication 24-72 hours post-vaccination is not required if the vaccination was missed.
[4]Microscopic reflex testing in the event of abnormal urinalysis, except when the investigator considers the abnormal urinalysis result to be from menstrual origin.
[5] If medical status and/or physical examination on Day 1 suggest significant changes may have occurred since screening, the clinically relevant screening assessments will be repeated and the Day 1 visit rescheduled, provided that the rescheduled visit is within 42 days of the initial screening assessment. In case a Grade 3 or 4 laboratory abnormality, or any laboratory abnormality accompanied by clinically relevant signs or symptoms, occurs (from the baseline visit onwards), all attempts will be made to perform a confirmatory test within 48 hours after the results have become available. After that, laboratory tests will be repeated weekly until values are resolved or stable.
[6]All subjects will be followed up until Week 72 to assess durability of immune response. Subjects who have been prematurely withdrawn from study vaccine administration will be encouraged to complete the post-vaccination follow-up visits of the last vaccination received and a 12 and 24 weeks follow-up visit after the last vaccination received, specified as Week 60 and Week 72. Upon sponsor unblinding at the Week 28 analysis, subjects randomized to Group 1 or Group 2 who have received all 4 vaccinations, will be asked to participate in the LTE phase and sign the ICF appendix for the LTE phase at Week 72. During the first visit of the LTE phase, the remaining eligibility criteria for the LTE phase will be verified. Subjects who attend their Week 72 visit prior to the sponsor's unblinding at the Week 28 analysis, will be enrolled in the LTE phase if they consent and sign the ICF appendix for the LTE phase and meet the eligibility criteria for the LTE phase. When the Week 28 sponsor unblinding subsequently occurs, subjects that started the LTE phase but turn out to have received placebo in the main study will be withdrawn from the LTE phase. If signing the ICF appendix is not possible at Week 72, signing should be performed at an extra visit (Visit 17bis) as soon as possible after Week 72 and at the latest before any assessment is done on the first visit of the LTE phase. See TIME AND EVENTS SCHEDULE FOR THE LONG-TERM EXTENSION PHASE (FROM WEEK 72 ONWARDS, GROUP 1 AND GROUP 2)
[7]For those subjects who are unable to continue participation in the study, an exit visit will be conducted as soon as possible.
[8]For both male and female subjects.
[9]For female subjects only. (pregnancy test only for female subjects of childbearing potential)
[10]Observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events.
[11]Timings of visits at 1, 2 and 4 weeks post-vaccination will be determined relative to the actual day of vaccination.
[12]Urine or vaginal swab may be used.
[13]Only at screening.
[14] Must be signed before first study-related activity.
[15]Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.5. Check clinical status again before first dose of study vaccine.
[16]For the sentinel group of 6 subjects, this will need to be an actual visit, 1 day post vaccination.
[17]Solicited local and systemic events will be recorded for 7 days after each vaccination; AEs will be recorded from signing of the study-specific ICF onwards until 28 days after first vaccination, and thereafter, pre-dose on the day of injection and for 28 days after each subsequent vaccination; SAEs, AEs leading to treatment discontinuation, and AESIs of confirmed HIV infection will be recorded from signing of the study-specific ICF onwards throughout the study.
[18]The test of understanding (TOU) must be completed by all subjects, as the first assessment after signing of the ICF.
[19]If on Visit 9, the 7-day diary observation period is not complete, the diary will be returned at Visit 10. If the diary card review is missed, the diary card will be reviewed in the following visit. If a participant misses a vaccination, the diary covering the period after the missed vaccination does not have to be filled in.

TIME AND EVENTS SCHEDULE FOR OPTIONAL VECTOR SHEDDING ASSESSMENT

Phase	*Vac*	*Post-vac FU*					
Visit #	2	2b	2c	2d	3	3a	4
Visit Day	1 ± 1	2 ± 1	4 ± 1	8 ± 1	15 ± 1	22 ± 1	29 ± 1
Vector shedding[1]	❶	●	●	●	●	●	●

Grey columns represent visits that are already present in the general TIME AND EVENTS SCHEDULE
vac = vaccination; ❶ = pre-dose
[1]Presence of Ad26 vector in urine and mid-turbinate swab samples will be tested by PCR. Vector shedding procedures are optional, and will only be performed at selected sites on subjects who provide consent.)

TIME AND EVENTS SCHEDULE FOR THE LONG-TERM EXTENSION PHASE (FROM WEEK 72 ONWARDS, GROUP 1 AND GROUP 2)

Phase		Long-term Extension					
Visit #	**17 bis[1]**	**18[1]**	**19**	**20**	**21**	**22[3]**	**23/Final Visit**
Visit Week		**96[1]**	**120**	**144**	**168**	**192[3]**	**216**
Visit Day[4]		**673 ± 4 wks**	**841 ± 4 wks**	**1009 ± 4 wks**	**1177 ± 4 wks**	**1345 - 4wks/+4months**	**1513 ± 4 wks**
Informed consent	●						
Review of inclusion/ exclusion criteria		●					
HIV-risk assessment		●	●	●	●	●	●
Counseling on HIV		●	●	●	●	●	●
Concomitant meds[2]		●	●	●	●	●	●
SAE and AESI of confirmed HIV infection recording		●	●	●	●	●	●
Social impact questionnaire		●	●	●	●	●	●
Central HIV testing		●	●	●	●	●	●
Humoral immuno. assays		●	●	●	●	●	●
Cellular immuno. assays		●	●	●	●	●	●

AESI = adverse event of special interest; HIV = human immunodeficiency virus; SAE = serious adverse event; wks = weeks.
The COVID-19 Appendix in Section 18 provides guidance to investigators for managing study-related procedures during the COVID-19 pandemic.
[1]This visit only needs to occur if the informed consent form (ICF) appendix for the LTE phase is not signed at Week 72. Visit 17bis should occur as soon as possible after the Week 72 visit. The ICF appendix for the LTE phase needs to be signed at the latest before any assessment is done on the first visit of the LTE phase.
[2]Restricted to concomitant therapies given in conjunction with an SAE, any chronic or recurrent use of immunomodulators/suppressors, oral or parenteral corticosteroids, any allowed vaccination and/or any HIV prevention medication. Subjects will also be asked during all visits whether they are participating in another clinical study.
[3] Subjects will be asked to participate in an extension to the LTE phase in which they will be randomized to receive a late boost vaccination with Ad26.Mos4.HIV in combination with bivalent gp140 or placebo. Subjects willing to participate should follow the TIME AND EVENTS SCHEDULE FOR THE LATE BOOST EXTENSION. Subjects not willing to participate in the late boost extension should continue to follow the above visit schedule.
[4] If a visit can't be scheduled within the allowed window, it will be assessed on a case-by-case basis upon discussion between the investigator and the sponsor whether this visit can still be performed. Note that 1 month should be interpreted as 30 days and 1 week as 7 days; hence, the visit window for visit 22 ought to be interpreted as -28 days/+120 days.

TIME AND EVENTS SCHEDULE FOR THE LATE BOOST EXTENSION

Visit # (period interval)	22a[1]		22b[2] (3,7 or 14 days[3] post late boost)	22c[2] (1 month post late boost)	22d[2] (3 months post late boost)	23a[2] (6 months post late boost)	24[2] (12 months post late boost)/Final visit[15]	25[2,14] (24 months post late boost)/Final visit[15]	Exit[16]
Visit Week	**192**		**193**	**196**	**204**	**216**	**240**	**288**	
Visit Day (visit window)[17]	**1345 (-4wks/+4 months)**		**1352 (1348 [-1/+2 days], 1352 [±3 days] or 1359 [±3 days])**	**1373 or (±2wks)**	**1429 (±4wks)**	**1513 (±4wks)**	**1681 (±4wks)**	**2017 (±4wks)**	
	Screening Assessments	Assessments Vaccination Day							
Informed consent	●[4]								
Review of inclusion/ exclusion criteria	●[5]	❶[6]							
Physical examination[7]	●	❶[8]							●
Vital signs	●	❸[8]							●
HIV-risk assessment	●	●[8]				●	●	●	●
Serum pregnancy test[9]	●								
Urine pregnancy test[9]		❶							
Hepatitis B/C serologies	❷								
Contraceptive counselling	●	●[8]							
Counselling on HIV	●	●[8]				●	●	●	●
Concomitant medications[10]	●	●[8]	●	●	●	●	●	●	●
SAE, AESI of confirmed HIV infection recording[11]	●	❸[8]	●	●	●	●	●	●	●
AESI of TTS recording[11]		❸	●	●	●	●			●
AE recording[11]	●	❸[8]	●	●					●
Central HIV testing	●	●				●	●	●	●
Randomization		❶							
Boost Vaccination		●							
Post-vac observation (30 min)[12]		●							

Visit # (period interval)	22a[1]		22b[2] (3,7 or 14 days[3] post late boost)	22c[2] (1 month post late boost)	22d[2] (3 months post late boost)	23a[2] (6 months post late boost)	24[2] (12 months post late boost)/Final visit[15]	25[2,14] (24 months post late boost)/Final visit[15]	Exit[16]
Visit Week	**192**		**193**	**196**	**204**	**216**	**240**	**288**	
Visit Day (visit window)[17]	**1345 (-4wks/+4 months)**		**1352 (1348 [-1/+2 days], 1352 [±3 days] or 1359 [±3 days])**	**1373 or (±2wks)**	**1429 (±4wks)**	**1513 (±4wks)**	**1681 (±4wks)**	**2017 (±4wks)**	
	Screening Assessments	Assessments Vaccination Day							
Distribution of subject diary[11]		●							
Review of diary by site staff			●	●[13]					
Humoral immuno assays		❶	●	●	●	●	●	●	●
Cellular immuno assays		❶	●	●	●	●	●	●	●
Social impact questionnaire		●				●			●

❶ = pre-dose, ❷ no extra blood required; ❸ pre- and post-dose

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

[1] Visit 22a can be split over several visits within the specified time window (Week 192 -4 weeks/+4 months). Vaccination should occur within 4 to 6 weeks after screening; the maximum screening period is 6 weeks.

[2] Timings of Visits 22b (Week 193), 22c (Week 196), 22d (Week 204), 23a (Week 216), 24 (week 240), and 25 (Week 288) will be determined relative to the actual day of vaccination.

[3] Subjects will be divided into three groups: the first 20 enrolled subjects will have the Visit 22b 7 days post late boost, the next 20 enrolled subjects 3 days post late boost and the remainder of the subjects 14 days post late boost.

[4] For subjects willing to participate, informed consent for the late boost vaccination and the optional 2-year post late boost follow-up visit (Visit 25) should be collected. The ICF appendix needs to be signed at the latest before any assessment is done.

[5] Subjects not eligible for boost vaccination should continue to follow the TIME AND EVENTS SCHEDULE FOR THE LONG-TERM EXTENSION PHASE (FROM WEEK 72 ONWARDS, GROUP 1 AND GROUP 2)).

[6] Check clinical status again before boost vaccination.

[7] An abbreviated, symptom-directed exam will be performed as indicated by the investigator. Weight will be measured.

[8] If the vaccination occurs on the same day as the screening, the pre dose vital signs assessment and physical examination do not need to be repeated and HIV risk assessment, contraceptive counselling, and counselling on HIV will be performed once. AE recording will occur once prior to vaccination. Post-dose assessment of vital signs and post-dose recording of AEs must still be performed.

[9] Only for female subjects of childbearing potential.

[10] All concomitant medication should be recorded from day of vaccination until 28 days post-vaccination. At other time points, recording of concomitant medication is restricted to concomitant therapies given in conjunction with an SAE, an AESI of TTS, any chronic or recurrent use of immunomodulators/suppressors, oral or parenteral corticosteroids, any allowed vaccination and/or any HIV prevention medication, including any COVID-19 vaccination.
[11] Solicited local and systemic signs and symptoms will be recorded by the subject in the diary and solicited local and systemic AEs recorded in the CRF for 7 days after boost vaccination; unsolicited AEs will be recorded from signing of ICF addendum for boost vaccination onwards until 28 days after boost vaccination; SAEs and AESIs of confirmed HIV infection will be recorded from signing of the initial ICF of the main study onwards until the end of the study. Applicable from the time of local regulatory approval of protocol amendment 5 onwards: AESIs of TTS (including potential AESIs) are to be reported to the sponsor until 6 months after the late boost vaccination. 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.
[12] Observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events.
[13] In case the diary was not completed (7 days post-boost) at the time of Visit 22b.
[14] Approximately 6 months post Visit 24, the investigator or study-site personnel will have a (remote) follow-up communication with subjects consenting to the 24-month follow-up (by e-mail, telephone, or visit; according to the subject's preference) to collect information on occurrence of any SAEs.
[15] Visit 25 is an optional visit. Visit 24 and Visit 25 will be the final visit for subjects who, respectively, do not consent and subjects who consent to the 24-month follow-up.
[16] For those subjects who are unable to continue participation in the study, an exit visit will be conducted as soon as possible.
[17] If a visit can't be scheduled within the allowed window, it will be assessed on a case-by-case basis upon discussion between the investigator and the sponsor whether this visit can still be performed. Note that 1 month should be interpreted as 30 days and 1 week as 7 days; hence, the visit window for visit 22a ought to be interpreted as -28 days/+120 days.

ABBREVIATIONS AND DEFINITIONS

Ab	antibody
Ad	adenovirus
Ad5	adenovirus serotype 5
Ad26	adenovirus serotype 26
ADCC	antibody-dependent cellular cytotoxicity
ADCD	antibody-dependent complement deposition
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AUC	area under curve
β-hCG	β-human chorionic gonadotropin
BIDMC	Beth Israel Deaconess Medical Center
BMI	body mass index
CBC	complete blood count
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
CRF	case report form
DAIDS	Division of Acquired Immunodeficiency Syndrome
DRC	Data Review Committee
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DS	drug substance
eDC	electronic data capture
ELISPOT	enzyme-linked immunospot
Env	envelope
ENVA	envelope A
EUA	Emergency Use Authorization
EUL	Emergency Use Listing
FDA	Food and Drug Administration
FIH	first-in-human
Gag	group-specific antigen
GCP	Good Clinical Practice
gp	glycoprotein
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HITT	heparin-induced thrombocytopenia and thrombosis
HLA	human leukocyte antigen
HSV-2	herpes simplex virus type 2
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	intracellular cytokine staining
IFNγ	interferon gamma
Ig	immunoglobulin
IL	interleukin
IRB	Institutional Review Board
IM	intramuscular
IPCAVD	Integrated preclinical/Clinical AIDS Vaccine Development
IWRS	interactive web response system
LLN	lower limit of normal
LTE	Long-term Extension
M-B	magnitude-breadth
Mos1	Mosaic 1

MVA	Modified Vaccinia Ankara
nAb	neutralizing antibody
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
Pol	polymerase
PQC	Product quality complaint
PSRT	Protocol Safety Review Team
PTE	potential T-cell epitopes
RNA	ribonucleic acid
SAE	serious adverse event
SHIV	simian human immunodeficiency virus
SIV	simian immunodeficiency virus
SUSAR	suspected unexpected serious adverse reaction
TNF	tumor necrosis factor
TOU	test of understanding
TTS	thrombosis with thrombocytopenia syndrome
ULN	upper limit of normal
VISP	vaccine-induced seropositivity
vp	viral particle

For the purpose of this protocol following terminology is applied:

Vaccine regimen/primary vaccination series	Vaccination 1 through 4
Prime	Vaccination 1 and 2 (Ad26.Mos4.HIV or placebo at Week 0 and Week 12)
Boost	Vaccination 3 and 4 (Ad26.Mos4.HIV and adjuvanted Clade C gp140 or a combination of adjuvanted Clade C gp140 and Mosaic gp140 or placebo at Week 24 and Week 48, respectively)
Late boost	Vaccination with Ad26.Mos4.HIV and bivalent gp140 at Week 192 (-4 weeks/+4 months, ie, approximately 3 years after the 4th vaccination of the primary vaccination series)

1. INTRODUCTION

A safe and effective HIV vaccine is the presently elusive cornerstone of HIV prevention.[28] Optimally, both a robust $CD4^+$ and $CD8^+$ T-cell responses and a potent humoral response with multiple effectors should be induced by a vaccine. An objective of the HIV-vaccine development program being pursued by the sponsor and its partners is to optimize a vaccine candidate for improved potency, where potency is defined as the quantitative response, frequency, and amplitude of a variety of potent antibody (Ab) and Ab-mediated cellular effector mechanisms, coupled with appropriate cellular responses. A second objective is to increase the breadth of response, defined as immune recognition of diverse strains/clades of HIV to include multiple clades.

A successful global prophylactic HIV vaccine will likely need to protect against the diverse strains and clades of HIV that may be encountered. Improving the magnitude and breadth of epitope coverage is thought to be key to development of a successful Ab and T-cell based preventive HIV vaccine. Strategies to accomplish this include the use of vaccines containing immunogens from a number of prevalent clades and/or using mosaic sequences, ie, proteins assembled from natural sequences of the different clades by in silico recombination, optimized for potential T-cell epitopes.[10]

Vaccines used in this study are Ad26.Mos4.HIV, Clade C gp140, and Mosaic gp140 (for details see Section 14).

For the most comprehensive nonclinical and clinical information regarding Ad26.Mos4.HIV, Clade C gp140, and Mosaic gp140, see the latest version of the Investigator's Brochure and Addenda (if applicable) 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 are also involved in this study, referred to in this protocol as "partners". For this protocol, the organizations are the DAIDS, BIDMC, HIV Vaccine Trials Network (HVTN), International AIDS Vaccine Initiative (IAVI), and Military HIV Research Program (MHRP).

1.1. Background

Nonclinical and clinical information below summarize data available at the time of the initial protocol writing (issued date 29 February 2016) [18,19] unless specified otherwise.

1.1.1. Nonclinical Studies

1.1.1.1. Repetitive gp120/gp140 Vaccinations

In order to mimic the native trimeric structure of the HIV-Env-gp “spike” (gp120/gp41) and induce native Env-reactive antibodies, trimeric gp140 proteins based on human Clade A and Clade C sequences were developed and found to induce significantly higher titers of potent nAb responses for a cross-clade set of tier 1 (Clades A, B, and C) and tier 2 (Clade C) viruses than the corresponding gp120 monomers in guinea pigs.[23] Although tier 1/2 pseudovirus neutralization is

likely not predictive of neutralization capacity against circulating HIV-1 viruses, the results suggest a broader and more avid Ab recognition of native HIV-1 Env.

1.1.1.2. Ad26/gp140 and Ad26/Ad35 Vaccinations

The protective efficacy of boosting with gp140 protein following priming with Ad26 vectors was evaluated in stringent simian immunodeficiency virus (SIV)- and SHIV-challenge models in non-human primates (Part 1).[5] Boosting with adjuvanted SIV_{MAC32H} gp140 protein afforded 50% protection against the complete series of 6 heterologous, intrarectal challenges with SIV_{MAC251} in animals that were primed with the Ad26 vector expressing SIV_{SME543} Env/Gag/Pol antigens, which was significantly higher than in animals that were similarly primed, but boosted with the corresponding Ad35 vector expressing SIV_{SME543} Env/Gag/Pol antigens (17% protection). Binding Ab titers and ADCP responses correlated with protection against acquisition of infection. Cellular immune responses measured by IFNγ ELISPOT assays in response to SIV_{MAC239} and SIV_{SME543} Env/Gag/Pol peptide pools were also detected in all animals after vaccination. By ICS assays, gp140 boosting primarily expanded Env-specific IFNγ $CD4^+$ T-lymphocyte responses in the Ad26/gp140 group.

1.1.1.3. Ad26/Ad5 and Repetitive gp140 Vaccinations

A similar level of protection (40%) was seen after a series of 6 heterologous, intrarectal challenges with SHIV-SF162P3 in a first group of animals primed with Ad26 and $Ad5_{HVR48}$ vectors expressing mosaic, consensus, or natural Clade C HIV-1 Env/Gag/Pol antigens and boosted six times 2 years later with HIV-1 Clade C Env gp140 trimer (Part 2).[5] A second group of animals received only the 6 gp140 immunizations. Although the gp140 vaccine afforded only minimal protection, 40% of Ad/gp140-vaccinated animals were completely protected against this challenge series. As for Section 1.1.1.2, Ad26/gp140 and Ad26/Ad35 Vaccinations, binding Ab titers and ADCP responses correlated with protection against acquisition of infection.

1.1.1.4. Tetravalent Ad26 Vaccinations

In ongoing clinical trials the trivalent Ad26.Mos.HIV viral vector is being used. But subsequent non-clinical data in rabbits have shown that the addition of a vector, expressing Mos2S Env protein, to Ad26.Mos1.Env increases the magnitude of binding Ab titers and neutralizing capacity for tier 1A Clade C HIV virus in the absence of negative effects on Clade B neutralization capacity. Thus, addition of Ad26.Mos2S.Env to Ad26.Mos.HIV has the potential to substantially increase the breadth of humoral immune responses. Therefore, a clinical study (VAC89220HPX2004) is planned to study safety and immunogenicity of the tetravalent Ad26.Mos4.HIV. In study VAC89220HPX2004, a DRC will review blinded interim safety results (4 weeks of follow-up) after 15% of subjects have received their first injection and will allow administration of the first dose of Ad26.Mos4.HIV/placebo (first injection) in this study (VAC89220HPX2003) only if no significant safety concerns are identified.

1.1.1.5. Mosaic gp140 Vaccinations

In an attempt to possibly broaden the nAb response, a trimeric Mosaic gp140 has recently been developed.[25] In guinea pigs, the Mosaic gp140 induced nAb primarily against Clade B virus

whereas Clade C gp140 trimer induced nAb primarily against Clade A and C viruses. A mixture of both proteins elicited nAb responses that were comparable to the better of the 2 individual immunogens in the cocktail, against each virus tested. There was therefore no loss of potency due to dilution or competition in the mixture and the overall immunogenicity was superior to and broader than either immunogen given alone.

1.1.2. Clinical Studies

1.1.2.1. Prototypes and Similar Vaccines

There is considerable clinical experience with vaccines similar to Ad26.Mos.HIV, Ad26.Mos4.HIV, and gp140 that demonstrated their class safety and tolerability.

Ad5 and Ad26 Vaccines

In 2 previous HIV-efficacy studies utilizing Ad5, a trend towards increased HIV-1 infection was observed in vaccine recipients as compared with placebo recipients.[7,13] The HVTN 502/Step (Merck Ad5) study showed no efficacy and a trend towards increased HIV-1 infections in vaccine recipients as compared with placebos in the subgroup of men who were baseline Ad5 seropositive and uncircumcised.[7] The HVTN 503/Phambili (Merck Ad5, MRKAd5) study was terminated and unblinded early, but follow-up of these individuals revealed increased HIV-1 infections in vaccine recipients as compared with placebo, particularly in men, which occurred after approximately 24 months of follow-up during the unblinded period.[13] There was also differential dropout of high-risk placebos during this time period. Additionally, a third study, the HVTN 505 (NIH VRC deoxyribonucleic acid [DNA]/Ad5) study[14], revealed no efficacy at the interim analysis. More HIV-1 infections were observed in vaccine recipients as compared with placebos in this study, including after the DNA prime and prior to the Ad5 boost, but these differences were not statistically meaningful. To clearly understand whether vaccine-associated increase of HIV-1 acquisition has occurred in one or more studies, a meta-analysis was recently conducted using up-to-date participant-level data from the 3 efficacy trials and three Phase 1-2 studies.[15] The meta-analysis provides evidence for increased risk associated with the MRKAd5 vaccine overall and in various subgroups except circumcised and Ad5-negative men. While the meta-analysis does not provide a reliable basis for predicting whether rAd5-vectored vaccines for other pathogens or other rAd-vectored vaccines for HIV-1 would increase susceptibility to infection in HIV-1 at-risk populations, for large efficacy trials of such vaccines it provides a rationale for adding monitoring plans enabling detection of such increased susceptibility.

The mechanism for this possible increase in HIV-1 acquisition risk remains unclear, but a leading hypothesis involves activation of vector-specific $CD4^+$ T-lymphocytes at mucosal surfaces following Ad5 vaccination, potentially resulting in increased targets for HIV-1 infection.[6,14] This hypothesis has never been directly evaluated in humans with Ad5 vectors. Nevertheless, to assess the extent of mucosal $CD4^+$ T-cell activation with Ad26 vectors, a randomized, double-blinded, placebo-controlled clinical study (Integrated Preclinical/Clinical AIDS Vaccine Development, IPCAVD-003) was performed to determine whether vaccination of healthy human subjects with an Ad26 vector expressing HIV-1 Env would result in increased numbers or activation status of total or vector-specific $CD4^+$ T-lymphocytes in the colorectal mucosa. The findings of this study

are reassuring in that this vector did not detectably increase the numbers or activation status of total or vector-specific $CD4^+$ T-cells in colorectal mucosa in humans[3].

The rationale to continue clinical development of Ad26 vector-based vaccines for HIV-1 is based on data showing that: (1) Ad26 is biologically substantially different than Ad5; (2) Ad26-based vaccines afford superior protective efficacy compared with Ad5-based vaccines against SIV_{MAC251} challenges in rhesus monkeys; and (3) Ad26 did not increase the number or activation status of total or vector-specific $CD4^+$ T-lymphocytes at mucosal surfaces in humans following vaccination in a randomized, double-blind, placebo-controlled clinical study (IPCAVD-003).

In 3 Phase 1 studies (IPCAVD-001, IPCAVD-003, and IPCAVD-004[1])[18], Ad26.ENVA.01, at IM doses over the range 10^9 to 10^{11} vp, was found to induce Env-specific humoral and cell-mediated responses when given on up to 3 occasions to more than 200 healthy subjects. Ad26.ENVA.01 was generally well tolerated in these studies. An IM dose of $5x10^{10}$ vp was found to provide the optimal balance of immunogenicity and reactogenicity. Therefore, this is the dose of Ad26.Mos.HIV chosen for further evaluation in this study.

In IPCAVD-003, 24 HIV-1 negative subjects were randomized 3:1 to receive a single vaccination with Ad26.ENVA.01 or placebo. Eight of the subjects were Ad26 seropositive at screening. The T-cell responses by IFNγ ELISPOT assays were slightly lower in the baseline Ad26-seropositive subjects; ICS and enzyme-linked immunosorbent assay responses proved comparable between subjects who were Ad26 seropositive and Ad26 seronegative at baseline, both in peripheral blood and in colorectal mucosa. In addition, systemic and mucosal responses persisted for at least 1 year in the majority of subjects after a single IM vaccine dose. These data suggest that the impact of baseline Ad26 nAbs, at the titers observed in that study, on the immunogenicity of this Ad26 vaccine is modest. Additionally, there were no consistent increases in Ad26-specific $CD4^+$ T-lymphocyte responses at mucosal surfaces following vaccination in either Ad26-seronegative or Ad26-seropositive subjects.

A subset of volunteers in IPCAVD-001 and IPCAVD-004 was evaluated for shedding in urine and respiratory secretions after vaccination and during intercurrent illnesses; all shedding samples were negative for adenovirus.[1,4]

gp120 Vaccines

A monovalent gp120 protein (AIDSVAX B) was tested in 671 healthy subjects at 3 doses, 100, 300, and 600 mcg.[17] The 300-mcg dose was found to be the most effective, inducing a higher Ab response without significant side effects. In the Thai trial RV144[26], the only vaccine study to date to demonstrate efficacy in prevention of acquisition of HIV, a bivalent gp120 protein (AIDSVAX B/E; 300-mcg dose) was used as a booster following priming with a recombinant canarypox vector (ALVAC-HIV) and afforded more than 30% protection from infection in the absence of either $CD8^+$ T-cells or nAb to primary HIV isolates. Therefore, a similar dose (250 mcg) of Clade C gp140 was chosen for evaluation in this study.

For subjects who will receive a combination of Clade C and Mosaic gp140, the total dose will be 250 mcg (125 mcg of each protein). The total dose of aluminum phosphate adjuvant and gp140

protein (Clade C gp140 mixed 1:1 with Mosaic gp140) will not exceed the maximum doses that were tested in previous GLP toxicity studies (TOX10872 and TOX10873), ie, 250 mcg total gp140 protein + 425 mcg aluminum phosphate adjuvant.

1.1.2.2. Current Studies

At the time of initial protocol writing (issued date 29 February 2016), 2 ongoing FIH studies in healthy HIV-uninfected subjects were evaluating safety/tolerability and immunogenicity of the following vaccines:

- Clade C gp140 (HIV-V-A003).
- Ad26.Mos.HIV, Modified Vaccinia Ankara (MVA)-Mosaic, and Clade C gp140 (HIV-V-A004; FIH for Ad26.Mos.HIV).

One additional study was planned in healthy HIV-uninfected subjects to evaluate safety/tolerability and immunogenicity of the following vaccines: Ad26.Mos4.HIV and Clade C gp140 (VAC89220HPX2004; FIH for Ad26.Mos4.HIV).

HIV-V-A003[18,19] is a single-center, randomized, placebo-controlled, double-blind, FIH Phase 1 study to evaluate safety/tolerability, and immunogenicity of 2 dose levels (50 and 250 mcg) of Clade C gp140, with or without aluminum phosphate adjuvant, in healthy HIV-uninfected adult subjects. The blinded evaluation that was performed by the Data Monitoring Committee (DMC) at Week 6 (2 weeks after all of the 50 enrolled subjects had received their second and last vaccination) showed that Clade C gp140, administered as 50 or 250 mcg, with or without aluminum phosphate adjuvant, was well tolerated and no safety concerns were identified. The DMC concurred with proceeding with the clinical development as planned and with administration of Clade C gp140 in HIV-V-A004.

HIV-V-A004[18,19] is a multi-center, randomized, parallel-group, placebo-controlled, double-blind Phase 1/2a study to evaluate safety/tolerability, and immunogenicity of various regimens containing Ad26.Mos.HIV, MVA-Mosaic, and/or Clade C gp140 (with aluminum phosphate adjuvant) components in approximately 400 healthy HIV-uninfected adult subjects. As pre-specified in the protocol, enrollment was paused when approximately 10% of subjects had received their first injection (Ad26.Mos.HIV/placebo) and the Protocol Safety Review Team (PSRT) has reviewed blinded safety data of 2 weeks after this first injection of 39 subjects and on 18 June 2015 all members agreed that the study could resume enrollment. The independent DMC also reviewed the blinded 2 week safety data after 30% of subjects had their first vaccination and unblinded 2 week safety data after 10% of subjects had their third vaccination (Ad26.Mos.HIV/MVA-Mosaic/placebo and Clade C gp140/placebo). In both instances, they recommended continuing the study without modification.

VAC89220HPX2004 is a randomized, parallel-group, placebo-controlled, double-blind Phase 1/2a clinical study to evaluate the safety/tolerability and immunogenicity of a regimen including tetravalent Ad26.Mos4.HIV and a regimen including trivalent Ad26.Mos.HIV in 198 healthy HIV-uninfected adult men and women aged 18 through 50 years. Better Clade C responses

are to be expected with the tetravalent Ad26.Mos4.HIV compared to the trivalent Ad26.Mos.HIV. A Data Review Committee (DRC) will review blinded safety data (4 weeks of follow-up) after 15% of subjects have received their first injection. Administration of the first dose of Ad26.Mos4.HIV (first injection) in this study, VAC89220HPX2003, will be allowed only if no significant safety concerns are identified.

At the time of the writing of the HPX2003 protocol amendment 3, safety and immunogenicity data from study HPX2004 and the current study HPX2003 had become available. A summary of information relevant to the current study HPX2003 is provided below. Detailed information is available in the Investigator's Brochures of Ad26.Mos4.HIV, Clade C gp140, and Mosaic gp140.[36,37]

Study **VAC89220HPX2004/HVTN 117:** In the Week 72 analysis (final analysis of the main study), both vaccine regimens evaluated in this study were found to be safe and well tolerated, with no remarkable differences between the vaccine regimens. The most frequently reported solicited adverse events post any dose were injection site pain/tenderness, fatigue, headache, and myalgia. No deaths, AESIs (HIV infections), or grade 4 AEs were reported. Overall, few SAEs were reported, one of which was considered related to the study vaccination (SUSAR: rheumatoid arthritis; refer to the Investigator Brochures[36,37] for more information). Few Grade 3 related AEs and AEs leading to discontinuation were reported.

Throughout the vaccination series and the follow-up period to Week 72, the tetravalent Ad26.Mos4.HIV was significantly more immunogenic than the trivalent Ad26.Mos.HIV. In general, the tetravalent group had higher and broader immune responses than the trivalent group. These differences were present in both binding and functional humoral responses as well as cellular immune responses after the 3rd vaccination and remained consistent through Week 72.

Furthermore, LTE Week 96 and Week 120 immunogenicity data are available for the ELISA and ELISpot assay (data on file) from participants who received the tetravalent vaccine during the main study. Data indicated that both binding humoral responses as well as cellular immune responses were maintained up to Week 120 in all participants.

Study **VAC89220HPX2003/HVTN 118**: In the Week 72 analysis (final analysis of the main study), 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, SAEs, AESIs (HIV infections) or grade 4 AEs were reported. Few Grade 3 related AEs and AEs leading to discontinuation were reported. Overall, both vaccine regimens were immunogenic and favor the selection of the bivalent regimen (see Section 3.2).

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.[20]

1.1.2.3. 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.[c]

- A total of 104 post-marketing events that met the Brighton TTS Case Definition Criteria Level 1 to 3.[7] 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.[27] 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[1]). 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 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.

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

1.2. Benefit/Risk Section

1.2.1. Known Benefits

The clinical benefits of prime-boost combinations of Ad26.Mos.HIV and Clade C/ Mosaic gp140 have yet to be established.

1.2.2. Potential Benefits

Subjects may benefit from clinical testing and physical examination; others may benefit from the knowledge that they may aid in the development of an HIV vaccine. There is no direct individual benefit from vaccination for the subjects at the current development stage.

1.2.3. Known Risks

This is a first in human study of Mosaic gp140 and therefore the safety profile of this vaccine is unknown. At the time of initial protocol writing (issued date 29 February 2016), there were limited safety data available from 2 ongoing Phase 1 studies in which Clade C gp140 is given alone (HIV-V-A003; N= 50 subjects) or in combination with Ad26.Mos.HIV (HIV-V-A004; N= approximately 400 subjects). Scheduled reviews of safety data in both studies by the DMC have not identified any significant safety concerns that have required a change of study conduct.

Please refer to Section 1.1.2.2 for further details of these studies.Ad26- and Ad35-based vaccines with different gene inserts had also been administered to more than 200 human volunteers in clinical studies. In these studies, local and systemic reactions, typical of injectable vaccines occurred. No serious safety concerns were identified in study participants.

In addition, there was extensive clinical experience (N= >10,000 subjects) with HIV Env proteins such as gp120 or gp140 proteins that are structurally-related to Clade C/ Mosaic gp140. In these studies, local and systemic reactions, typical of injectable vaccines occurred. No serious safety concerns were identified in study participants. Please refer to Section 1.1.2.1 for further details.

At the time of the writing of HPX2003_Protocol_Amend_3, a total of 3,420 healthy adult participants had been enrolled in clinical studies, of which 429 participants for whom the treatment assignment is known (unblinded), received at least 1 vaccination with Ad26.Mos.HIV and 236 participants received at least one vaccination with Ad26.Mos4.HIV.[36] At that time, a total of 3,470 healthy adult participants had been enrolled in clinical studies, of which 563 participants, for whom the treatment assignment is known (unblinded), received gp140. Of these, 362 participants received 250 mcg glycoprotein of Clade C gp140, 108 participants received 50 mcg glycoprotein of Clade C gp140, and 93 participants received 250 mcg glycoprotein Clade C gp140 + Mosaic gp140.[37]

Clinical data on Ad26.Mos.HIV, Ad26.Mos4.HIV, Clade C gp140 and Mosaic gp140 demonstrated that the vaccine regimens have an acceptable safety profile in HIV-uninfected participants with no emerging significant safety concerns to date.[36,37]

1.2.4. Potential Risks

The following potential risks for Ad26.Mos.HIV and Clade C/ Mosaic gp140 will be monitored during the study and are specified in the protocol:

Risks Related to Vaccination

Subjects may exhibit general signs and symptoms associated with administration of a vaccine, or vaccination with placebo, including fever, chills, rash, myalgia, nausea/vomiting, headache, dizziness, arthralgia, general itching, and fatigue. In addition, subjects may experience local (injection site) reactions such as local itching, warmth, pain/tenderness, erythema/redness, induration/swelling, arm discomfort or bruising of the skin at the injection site. 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, subjects should be observed until the symptoms resolve. Fear of injection might lead to fainting and fast breathing.

Subjects may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, urticaria or even anaphylaxis. Severe reactions are rare. Medications must be available in the clinic to treat severe allergic reactions. Subjects with a known allergy, or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine excipients will be excluded from the study.

The risks related to vaccine-induced seropositivity (VISP) are discussed in Section 9.4.3.

Based on data with other replication-incompetent adenovirus vector vaccines, the risk of shedding of the Ad26 vector is considered negligible, if any.[4]

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 have been used safely in vaccines for more than 70 years. A few studies have 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%.[29,30,31,32] Two studies examining infant exposure to aluminum from both diet and vaccines concluded that aluminum adjuvants at the levels included in vaccines are well below the calculated safe body burden.[33,34] A 2017 review found that current data do not support a causal relationship between aluminum-containing vaccines and a variety of autoimmune disorders.[35]

Pregnancy and Birth Control

The effect of the study vaccines on a fetus or nursing baby is unknown, as well as the effect on semen, so women of childbearing potential, and men having sexual intercourse with women, are required to agree to practice adequate birth control measures for sexual intercourse from at least 28 days before the first vaccination (or immediately prior to first vaccination for men) until at least 3 months after the last vaccination (see Section 4.1) of the main study and from at least 28 days

before the late boost vaccination until 3 months after the late boost vaccination (see Section 4.5). Women who are pregnant or breast-feeding, or are planning to become pregnant while enrolled in the main study until 3 months after the last vaccination, will be excluded from enrollment into the main study. In addition, women who are pregnant, breast-feeding or planning to become pregnant from screening for the late boost vaccination until 3 months after the vaccination will not be eligible to receive the late boost vaccination.

Risks from Blood Draws

Blood drawing may cause pain/tenderness, bruising, bleeding, becoming lightheaded, dizziness, vaso-vagal response, and, rarely, infection at the site where the blood is taken.

Risks from Human Leukocyte Antigen (HLA) Testing

Tests results can be used to provide information about how susceptible subjects are to certain diseases. Used inappropriately, this information could be discriminatory (for example, by insurance companies). HLA typing can also be used to determine paternity. However, the blood samples donated will not be used for this purpose; they will be used only to provide study investigators information about the immune system. The results will be coded to protect subject identity.

Unknown Risks

There may be other serious risks that are not known.

Subjects may believe that this vaccine provides protection against acquiring HIV infection, and therefore practice riskier behavior. They will receive extensive counseling throughout the study to address this potential problem. It is not known if the study vaccines increase or decrease the chance of becoming HIV infected when exposed, or if upon becoming HIV infected, the person's disease course progresses faster or slower to AIDS.

In previous HIV-efficacy studies utilizing Ad5, a trend towards increased HIV-1 infection was observed in vaccine recipients as compared with placebo recipients. Ad26 is biologically substantially different than Ad5 and Ad26-based vaccines afford superior protective efficacy compared with Ad5-based vaccines against SIV_{MAC251} challenges in rhesus monkeys. Further, Ad26 did not increase the number or activation status of total or vector-specific $CD4^+$ T-lymphocytes at mucosal surfaces in humans following vaccination in a randomized, double-blind, placebo-controlled clinical study.

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:

Preliminary safety data from the ongoing clinical studies and safety data generated with the related vaccines containing different inserts revealed no significant safety issues (see Section 1.1.2.1).

- Only subjects 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 subjects in the study.
- Safety will be closely monitored throughout the study:
  - After each vaccination, subjects will remain in the clinic and be closely observed by study staff for at least total 30 minutes post-vaccination, or longer if deemed necessary by the investigator, to monitor the development of any acute reactions. Any unsolicited, solicited local or systemic adverse events will be documented during this period. Subjects will use a diary to document solicited local and systemic AEs in the evening after each vaccination and then daily for the next 7 days at approximately the same time each day.
  - Subjects will undergo safety follow-up by study staff 24-72h after each vaccination in the main study, by telephone, email or clinic visit.
  - The investigator or the designee will document unsolicited AEs, SAEs and (potential) adverse events for special interest (AESIs) as indicated in section 12.3.1.
  - Safety evaluations, including physical examinations, vital sign measurements, clinical safety laboratory testing (performed at screening, pre-dose, 2 weeks after each dose and at Weeks 36, 60 and 72 of the main study) and pregnancy testing (prior to each vaccination), will be performed at scheduled visits during the study. In addition, a symptom-directed physical examination, vital sign measurements and pregnancy testing will be performed at screening for the late boost vaccination.
  - 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 (see Section 12.3.2).
- Several safety measures are included in this protocol to minimize the potential risk to subjects, including the following:
  - Since this is a first in human study of Mosaic gp140, enrolment will be paused after the first 6 subjects have received their third vaccination (first vaccination with Mosaic gp140, depending on assignment), the Protocol Safety Review Committee (PSRT) and Principal Investigators have reviewed blinded safety data collected 1 day after vaccination and established that there are no concerns.
  - For all subjects, there are pre-specified rules that would result in pausing of further vaccinations if predefined conditions occur, preventing exposure of new subjects to study vaccine until the PSRT and/or DRC reviews all safety data (see Section 11.9).
  - Subjects will discontinue study vaccine for the reasons included in Section 10.2.
  - Confirmed HIV infection will be monitored as an AESI.
  - From the time of local regulatory approval of protocol amendment 5 onwards, TTS will be monitored as an AESI. Thrombotic events and/or thrombocytopenia are considered to be potential AESIs.

- 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, the subject may be vaccinated within the window allowed for the scheduled vaccination.
- Contraindications to vaccination are included in Section 10.3.

1.3. Overall Rationale for the Study

The proposed clinical study in healthy HIV-uninfected subjects will evaluate the safety/tolerability and the immunogenicity of 2 different prime/boost regimens: priming with Ad26.Mos4.HIV and boosting with Ad26.Mos4.HIV and either Clade C gp140 plus adjuvant or a combination of Clade C and Mosaic gp140 plus adjuvant. The goal of this study is to evaluate if the addition of Mosaic gp140 to Clade C gp140 improves the breadth of humoral immune responses (defined as immune recognition of diverse strains/clades of HIV), which will ultimately assist in the selection of the best regimen(s) for evaluation in future efficacy studies.

To assess the durability of the immune responses, a Long-term Extension (LTE) phase of approximately 3 years was introduced for subjects randomized to Group 1 or Group 2, who have received all 4 vaccinations and are negative for HIV infection at the end of the main study. The vaccination regimens of Group 1 and Group 2 (including Ad26.Mos4.HIV and either Clade C gp140 alone or combined with Mosaic gp140) form the basis for the regimens that will likely be evaluated in future studies.

In addition, subjects enrolled in the LTE phase will be offered participation in an extension of the LTE phase. Eligible subjects who consent to participation will be randomized (3:1 ratio) to receive a boost vaccination with Ad26.Mos4.HIV together with bivalent gp140 or placebo at Week 192 (-4 weeks/+4 months [Visit 22a], ie, approximately 3 years after the 4th vaccination of the primary vaccination series). The goal is to evaluate the impact of a late boost vaccination on the quantity (including magnitude and breadth) and quality of the immune response (humoral and cellular) as well as the safety of such late boost vaccination.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess safety/tolerability of the different vaccine regimens	• Solicited local and systemic adverse events (AEs) for 7 days after each vaccination. • AEs for 28 days after each vaccination. • Discontinuations from vaccination/from study due to AEs. • Serious adverse events (SAEs) and AEs of special interest (AESIs) of confirmed HIV infection during the course of the study, including the LTE phase.

Objectives	Endpoints
• To assess Envelope (Env)-binding antibody (Ab) responses of the 2 different vaccine regimens.	• Env-specific binding Abs (titers and breadth).
• To assess safety/tolerability of a late boost vaccination.	• Solicited local and systemic AEs for 7 days after the late boost vaccination. • AEs for 28 days after each the late boost vaccination. • SAEs and AESIs of confirmed HIV infection until the end of the study. • AESIs of TTS for 6 months after the late boost vaccination
Secondary (applicable to main study, LTE and late boost vaccination)	
• To assess neutralizing Ab (nAb) responses, Ab functionality (as assessed by phagocytosis), and Ab isotyping.	• Env-specific nAbs (titers and breadth) • Env-specific functional Abs (phagocytosis score and breadth). • Env-specific binding Ab isotypes (immunoglobulin (Ig)A, IgG1-4) (titers and breadth).
• To assess T-cell responses.	• Interferon gamma (IFNγ) peripheral blood mononuclear cell (PBMC) responders to mosaic and potential T-cell epitopes (PTE) peptide pools of Env/group-specific antigen (Gag)/polymerase (Pol). • Cluster of differentiation (CD)4+ and CD8+ T-cell functionality (% cells producing ia, IFNγ, interleukin 2 (IL-2), IL-4, tumor necrosis factor α [TNFα]). • T-cell development with emphasis on follicular helper T-cells and memory differentiation.[d]
Exploratory (applicable to main study, LTE and late boost vaccination)	
• To explore whether the adenovirus serotype 26 (Ad26) vector is shed after vaccination.	• Polymerase chain reaction (PCR) positive for Ad26 sequences (urine and mid-turbinate swab).
• To explore Ab functionality (other than phagocytosis).	• Ab functionality evaluation (such as Ab-dependent cellular cytotoxicity [ADCC], Ab-dependent complement deposition [ADCD]; excluding phagocytosis (ie, Ab-dependent cellular phagocytosis [ADCP]).
• To explore Ab Fc characterization.	• Ab Fc (sub)typing.
• To explore T-cell and Ab epitope mapping.	• Epitope mapping of Ab to Env and T-cell responses to Gag/Pol/Env (PTE and vaccine peptide pools).
• To explore gene expression patterns using PBMCs.	• Regulation of genes (or clusters) that predict specific immune responses and human leukocyte antigen (HLA) typing.
• To explore B-cell responses.	• Ab-producing B-cells and characterization of B-cell memory development.
• To explore immune responses against the viral vector.	• Ad26 nAbs (titer).

[d] The follicular helper T-cells and memory differentiation was included as secondary objective for the main study. Due to difficulty qualifying the assay for these specific markers, these T-cell responses will be considered as an exploratory objective for the late boost vaccination.

Objectives	Endpoints
• To explore the social impact of participation in an HIV-vaccine study for subjects via a social impact questionnaire.	• Social impact.
• To explore durability of the immune responses to the vaccine regimens in the groups selected for the Long-term Extension (LTE) phase.	• Available samples from time points during the LTE phase will be used for determination of long-term durability of the immune responses.

In addition, following exploratory objectives are applicable to the late boost vaccination only:

Objectives	Endpoints
• To assess Env-binding antibody Ab responses following late boost vaccination approximately 3 years after receiving the 4th vaccination of the primary vaccination series.	• Env-specific binding Abs [ELISA] at 3, 7 or 14[e] days and 28 days post late boost vaccination (titers and breadth).
• To explore the role of Ad26 neutralizing antibodies on the immune response to a late boost vaccination.	• Ad26 neutralizing antibodies at the time of vaccination relative to the immune response as evaluated by ELISA.
• To compare the immune response to late boost vaccination with a vaccine matched to the primary vaccination series (Group 2) vs a closely related vaccine (Group 1).	• Relative ELISA magnitudes between groups randomized to Group 1 vs Group 2 in the main study.
• To evaluate whether humoral responses induced by a late boost vaccination are able to mediate protection in non-clinical passive transfer studies.	• Analysis of protection against HIV-related challenge viruses, such as simian human immunodeficiency virus (SHIV), in a suitable animal model, and/or in vitro.

See Section 9 for evaluations related to endpoints.

2.2. Hypothesis

No formal statistical hypothesis will be tested. The proposed clinical study in healthy HIV-uninfected subjects will evaluate the safety/tolerability and the immunogenicity of 2 different prime/boost regimens: priming with Ad26.Mos4.HIV and boosting with Ad26.Mos4.HIV and either Clade C gp140 plus adjuvant or a combination of Clade C and Mosaic gp140 plus adjuvant. In addition, the study will evaluate the immunogenicity (humoral and cellular responses) and safety of a late boost vaccination with Ad26.Mos4.HIV together with bivalent gp140.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 1/2a study in healthy HIV-uninfected adult men and women between the ages 18 to 50 years, inclusive. A target of 150 subjects will participate in this study with 25 subjects in Group 1, 100 subjects in

[e] Subjects will be divided into three groups: the first 20 enrolled subjects will have the Visit 22b 7 days post late boost, the next 20 enrolled subjects 3 days post late boost and the remainder of the subjects 14 days post late boost.

Group 2, and 25 subjects in Group 3. Group 1 represents the "base-case" regimen which allows bridging of data from this study to study VAC89220HPX2004. A diagram of the study design is provided in Table 1. Randomization will be stratified by region. Subjects will receive IM doses of study vaccine or placebo at 4 time points: Ad26.Mos4.HIV or placebo will be given at Weeks 0 and 12; Ad26.Mos4.HIV together with either Clade C gp140 plus adjuvant or a combination of Mosaic and Clade C gp140 plus adjuvant, or placebo will be given at Weeks 24 and 48.

The main study will be conducted in 3 phases: a 6-week screening period; a 48-week vaccination period during which subjects will be vaccinated at baseline (Week 0) and at Weeks 12, 24, and 48; and a follow-up period to the final main study visit at Week 72. An LTE phase (approximately 3 years after Week 72) will be performed for subjects randomized to Group 1 or Group 2, who have received all 4 vaccinations and are negative for HIV infection at Week 72. The vaccination regimens of Group 1 and Group 2 (including Ad26.Mos4.HIV and either Clade C gp140 alone or combined with Mosaic gp140) form the basis for the regimens that will likely be evaluated in future studies.

Subjects enrolled in the LTE phase will be offered participation in an extension to the LTE phase to investigate the safety and immunogenicity of a late boost vaccination approximately 3 years after the last vaccination in the main study (depending on availability of IRB and HA approvals per country/site regulations). Assessment of participants' eligibility for the late boost vaccination and vaccination itself will occur within 4 weeks prior to Week 192 until 4 months after Week 192 (Visit 22a, which can be split over several visits). Eligible, consenting subjects will be randomly assigned (3:1 ratio, see Table 2 below) in a blinded fashion to active vaccination with Ad26.Mos4.HIV and bivalent gp140 (Group 1b) or placebo (0.9% saline) (Group 2b). The aim is to have at least 48 participants enrolled in the late boost extension. Randomization will be stratified by region (USA, East Africa: assuming sufficient numbers from Rwanda in the LTE phase) and by group randomized to in the main study (Group 1/Group 2). Upon receipt of the late boost vaccination, participants will be followed up for immunogenicity and safety for a further 12 months or, if they consent to longer follow-up, 24 months. Unblinded interim data analysis (sponsor unblinding only) will be performed approximately 4 weeks after the last subject received the late boost vaccination. LTE subjects declining participation or not eligible for participation in the late boost extension will complete the study at Visit 23 of the LTE phase.

The duration of the subject's participation will be approximately 78 weeks (6-week screening + 72 weeks main study) for subjects not participating in the LTE phase and approximately 222 weeks for subjects participating in the LTE phase but not receiving a late boost vaccination and approximately 246 (12-month follow-up) or 294 (24-month follow-up) weeks for subjects receiving a late boost vaccination.

After vaccination, subjects will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events. In addition, subjects will record solicited events in a diary for 7 days post-vaccination as described in Section 9.1.1. See Section 12.1.3 for grading of severity of solicited AEs. From the time of local regulatory approval of protocol amendment 5 onwards, TTS is considered to be an AESI. Thrombotic events and/or

thrombocytopenia are considered to be potential AESIs. Thrombocytopenia is defined as platelet count below the lower limit of normal (LLN) range for the testing lab. All AESIs of TTS (including potential AESIs) will be reported to the sponsor from the moment of the late boost vaccination until 6 months after the late boost vaccination. Each potential AESI will be reviewed to identify a TTS case. Further safety evaluations will include monitoring of AEs, physical examinations, vital sign measurements, clinical laboratory tests, and pregnancy testing. Blood samples will be taken at specific clinic visits to assess immune responses. Subjects will complete a social impact questionnaire at specific clinic visits. Optional urine samples and mid-turbinate swabs will be collected from consenting subjects to assess vector shedding. For details see TIME AND EVENTS SCHEDULE. A PSRT and DRC will be commissioned for this study. See Sections 11.7 and 11.8 for details.

A DRC will review blinded interim safety results (4 weeks of follow-up) after 15% of subjects have received their first injection in the VAC89220HPX2004 study (FIH for Ad26.Mos4.HIV) and will allow administration of the first dose of Ad26.Mos4.HIV/placebo (first injection) in this study (VAC89220HPX2003) only if no significant safety concerns are identified.

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

Table 1: Schematic Overview of the Main Study

Group	N	Week 0	Week 12	Week 24	Week 48
1[b]	25	Ad26.Mos4.HIV	Ad26.Mos4.HIV	Ad26.Mos4.HIV + Clade C gp140 (250 mcg + adjuvant)[a]	Ad26.Mos4.HIV + Clade C gp140 (250 mcg + adjuvant)[a]
2[b]	100	Ad26.Mos4.HIV	Ad26.Mos4.HIV	Ad26.Mos4.HIV + Clade C + Mosaic gp140 (250 mcg + adjuvant)[a]	Ad26.Mos4.HIV + Clade C + Mosaic gp140 (250 mcg + adjuvant)[a]
3	25	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo

[a]250 mcg refers to total protein content (Clade C gp140 [250 mcg] alone or a combination of Mosaic gp140 [125 mcg] and Clade C gp140 [125 mcg]). Sterile aluminum phosphate suspension will be used as adjuvant. Aluminum content will be 0.425 mg/0.5 mL dose.
[b]An LTE phase (approximately 3 years after Week 72) will be performed for subjects randomized to Group 1 or Group 2, who have received all 4 vaccinations and are negative for HIV infection at Week 72.

Table 2:	Schematic Overview of the Late Boost Vaccination	
Group	**N**	**Week 192 (-4 weeks/+4months)**
1b	3*N/4[1]	Ad26.Mos4.HIV + gp140 HIV bivalent vaccine
2b	1*N/4[1]	Placebo + Placebo

Total dose of Ad26.Mos4.HIV is $5x10^{10}$ viral particles (vp)/0.5 mL injection.
gp140 HIV bivalent vaccine: adjuvanted protein co-formulation with a dosage strength of 80 mcg Clade C protein, 75 mcg Mosaic protein and 425 mcg aluminum (as aluminum phosphate adjuvant). Note: the dose of Clade C gp140 and/or Mosaic gp140 as separate entities is 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. [37]
[1] Subjects will be randomly assigned in a 3:1 ratio to active vaccine or placebo. The aim is to have at least 48 subjects enrolled in the late boost extension.

3.2. Study Design Rationale

Vaccines and Dose Selection Rationale

The rationale behind selection of study vaccines and doses is described in Section 1.

Blinding, Control, Study Phase/Periods, Treatment Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Late Boost Vaccination

A late boost vaccination with Ad26.Mos4.HIV in combination with bivalent gp140 or placebo, approximately 3 years after the fourth vaccination of the primary vaccination series will allow evaluation of the effect on quantity (including magnitude and breadth) and quality of the resultant immune responses (humoral and cellular). Results could inform current and future clinical development programs with this regimen.

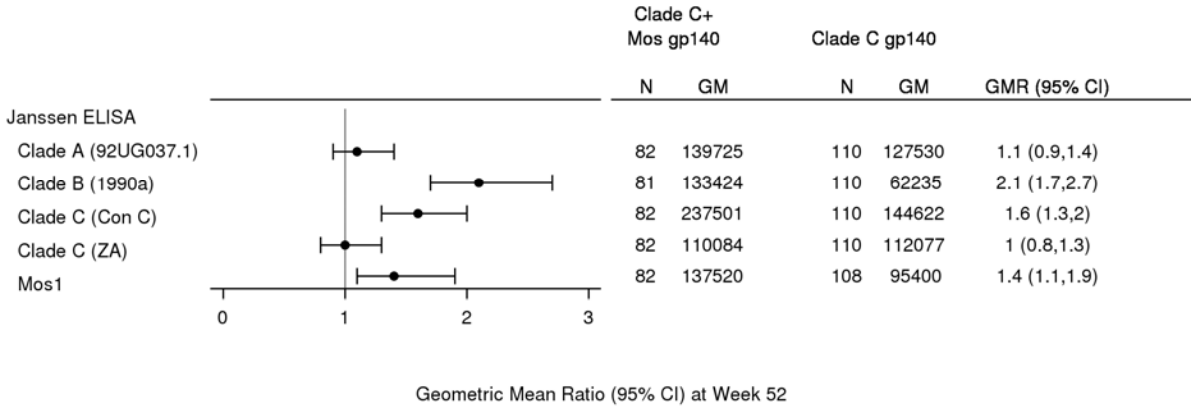
Since there is currently no direct or indirect evidence from preclinical or clinical studies that a late boost vaccination would be needed to confer protection against HIV infection, the timing of the late boost vaccination, approximately 3 years after the 4^{th} vaccination of the primary vaccination series, was selected because of the planned duration of the ongoing LTE phase at the time of the writing of amendment 3.

Based on the data described below, Ad26.Mos4.HIV in combination with bivalent gp140 was chosen as late boost vaccination in the current study.

Based on the primary analysis of HPX2003 and HPX2004, 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 for use in Phase 3. 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 improved immunological 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 at Month 7, 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 the regimen containing the bivalent protein formulation is globally relevant. 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.

The Month 13 (Week 52; 4 weeks post 4th vaccination) analysis results of HPX2003 strengthened the original choice of the combination of aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140 over the Clade C gp140 alone. After completion of the vaccination series, the Clade C responses were still comparable between regimens while the combination of Clade C gp140 and Mosaic gp140 improved responses beyond Clade C. The geometric mean ratio (GMR) and 95% CI of binding antibody levels induced by the bivalent relative to the Clade C alone regimen for Clade B and Mos1 (2.1 [1.7 - 2.7] and 1.4 [1.1 - 1.9], respectively) after completion of the vaccination series (Figure 1) significantly improved from the Clade C alone regimen.

Figure 1: GMR (95% CI) of the Clade C+ Mos gp140 /Clade C gp140 Groups (Pooling VAC89220HPX2003-VAC89220HPX2004)



[GIMHUMCEL99A.RTF]
[/SAS/Z HIVVACCINEPX/Z ADHOC/FILES/RE/POOLED HPX2003 HPX2004 W52/PROGRAMS/GIMHUMCEL99A.SAS]
18JAN2019, 08:14

Although not covered by the available GLP toxicology studies[36,37], administration of this late boost vaccination does not trigger a safety concern, considering the long interval (more than 2 years) between the 4th vaccination of the primary vaccination series and the late boost administration. A similar late boost dose administration will be tested in a nonclinical immunogenicity study in NHPs that completed the primary 4-dose vaccination series more than 2 years ago. In this study, clinical observations, body weight, body temperature and injection site effects will be monitored. Initial results from this study will be available prior to administering a late boost dose to study participants and will provide supportive nonclinical safety data. In addition, for another Ad26-based vaccine (Ad26.RSV.preF) a GLP toxicology study has been conducted in NZW rabbits in which the animals received up to 5 vaccinations (at $1x10^{11}$ vp per dose) with a 2-week interval between the injections (TOX11592). In this study no vaccine-related adverse effects were noted, indicating that a regimen of 5 respective vaccinations with an Ad26-based vaccine is unlikely to cause a significant safety signal in human subjects.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 6 weeks before the first administration of study vaccine or placebo at Week 0.

The inclusion and exclusion criteria for enrolling subjects 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 sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection see Section 11.3.

4.1. Inclusion Criteria for the Main Study

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

1. Each subject must sign an ICF indicating that he or she understands the purpose of and procedures required for the study and is voluntarily willing to participate in the study.

2. Subjects are ≥18 to ≤50 years old on the day of signing the ICF.

3. Subject must be healthy on the basis of medical history, physical examination, and vital signs measurement performed at screening.

4. Subjects must meet following laboratory criteria prior to randomization*:

   a) Hemoglobin: Women ≥10.5 g/dL; Men ≥11.0 g/dL

   b) White cell count: 2,500 to 11,000 cells/mm^3, inclusive

   c) Absolute neutrophil count: >1,000 cells/mm^3

   d) Platelets: 125,000 to 450,000 per mm^3, inclusive

   e) Urinalysis: protein <1+, blood <1+ (men) and <2+ (women), and glucose negative

   f) Alanine aminotransferase (ALT)/aspartate aminotransferase (AST): <1.25x upper limit of normal (ULN)

   g) Creatinine: <1.1x ULN

   *If laboratory screening tests are out of range, repeat of screening tests is permitted once.

5. Subjects are negative for HIV infection at screening[f].

6. All female subjects of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) at the screening visit, and a negative urine pregnancy test pre-dose on Day 1[g].

7. Contraceptive requirements for heterosexually active female subjects (from 28 days prior first vaccination up until 3 months after last vaccination)[h]:

   a) If not of childbearing potential: postmenopausal (>45 years of age with amenorrhea for at least 2 years, or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone [FSH] level >40 IU/L) or surgically sterile: no additional contraception required.

[f] If possible, the site should select an assay that is US FDA-approved

[g] Note: negative urine pregnancy also required prior to the second, third, and fourth vaccinations

[h] Verbal assurance should be given that adequate birth control measures have been followed for 28 days prior to first vaccination

b) If of child-bearing potential, but has a vasectomized partner (after vasectomy: sperm count below the limit of detection if procedure occurred <1 year ago[i]): no additional contraception required.

c) If of child-bearing potential, but has a non-vasectomized partner, or partner had a positive sperm count after a vasectomy procedure of <1 year ago[i], should be practicing an acceptable effective method of contraception. Acceptable methods for this study include:

- Hormonal contraception,
- Intrauterine device (IUD),
- Intrauterine hormone-releasing system (IUS),
- Male or female condom with or without spermicide,
- Cap, diaphragm or sponge with vaginal spermicide, or
- Sexual abstinence *

Sexual abstinence is considered an effective method **only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study vaccine. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*

Women who are not heterosexually active at screening, but become sexually active during the study must agree to utilize an effective method of birth control as mentioned above.

8. Contraceptive requirements for heterosexually active male subjects (from day of first vaccination until 3 months after last vaccination):

   a) If male subject had a vasectomy (after vasectomy: sperm count below the limit of detection if procedure occurred <1 year ago[i]): no additional contraception required.

   b) If male subject did not have a vasectomy or had a positive sperm count after a vasectomy procedure of <1 year ago[i]: contraceptive methods will depend on child-bearing potential of female partner: same criteria to be followed as for female subjects in inclusion criterion 7.

9. A woman must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction after the first dose until 3 months after receiving the last dose of study vaccine or placebo. A man must agree not to donate sperm after the first dose until 3 months after receiving the last dose of study vaccine or placebo.

10. Subjects are willing/able to adhere to the prohibitions and restrictions specified in the protocol and study procedures.

11. Subjects are amenable to HIV-risk reduction counseling and committed to maintaining behavior consistent with low risk of HIV exposure through the last required protocol clinic visit.

[i] Based on verbal confirmation

12. Subjects are assessed by the clinic staff as being at low risk for HIV infection (for guidelines see Attachment 2).
13. Passed the test of understanding (TOU, see Attachment 3). The TOU must be completed by all subjects, as the first assessment after signing of the ICF.

4.2. Exclusion Criteria for the Main Study

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

1. Subject has chronic hepatitis B (measured by hepatitis B surface antigen test) or active hepatitis C (measured by hepatitis C virus [HCV] Ab test; if positive, HCV ribonucleic acid (RNA) PCR test will be used to confirm active versus past HCV infection), active syphilis infection, chlamydia, gonorrhea, or trichomonas[j]. Active syphilis documented by serology unless positive serology is due to past treated infection.
2. In the 12 months prior to randomization, subject has a history of newly acquired herpes simplex virus type 2 (HSV-2), syphilis, gonorrhea, non-gonococcal urethritis, chlamydia, pelvic inflammatory disease, trichomonas, mucopurulent cervicitis, epididymitis, proctitis, lymphogranulomavenereum, chancroid, or hepatitis B.
3. Subject has any condition, including any clinically significant acute or chronic medical condition, for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. In case of questions, the investigator is encouraged to contact the study responsible physician.
4. Subject has had major surgery (eg, requiring general anesthesia) within the 4 weeks before screening, or will not have fully recovered from surgery, or has surgery planned through the course of the study.

   Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.
5. Subject has had a thyroidectomy or active thyroid disease requiring medication during the last 12 months (not excluded: a stable thyroid supplementation).
6. Subject has had major psychiatric illness and/or substance abuse problems during the past 12 months (including hospitalization or periods of work disability) that in the opinion of the investigator would preclude participation.
7. Current or past drug/alcohol use that investigator assesses poses any more than a remotely increased risk of the ability of the subject to comply with the protocol requirements.
8. Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study, or within 3 months after the last dose of vaccine or placebo.

[j] Trichomonas testing will only be performed for female subjects

9. Subject is a man who plans to father a child while enrolled in this study, or within 3 months after the last dose of vaccine or placebo.
10. Subject has been in receipt of any licensed vaccine within 14 days prior to the first dose of study vaccine or placebo, plans to receive within 14 days after the first study vaccination, or plans to receive within 14 days before or after the second, third or fourth vaccination.
11. Subject has used experimental therapeutic drugs within 30 days of randomization. For experimental vaccines see exclusion criterion 12.
12. Subject is a recipient of a prophylactic or therapeutic HIV vaccine candidate at any time, or a recipient of other experimental vaccine(s) within the last 12 months prior to the Day 1 visit (Vaccination 1). For subjects who received an experimental vaccine (except HIV vaccine) more than 12 months prior to the Day 1 visit (Vaccination 1), documentation of the identity of the experimental vaccine must be provided to the sponsor, who will determine eligibility on a case-by-case basis.

    Exceptions: Subjects can be included if the vaccine received was subsequently licensed (see exclusion criterion 10). Subjects with proof of having received only a placebo vaccine can also be included.
13. Subject 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 sponsor.
14. Subject has been in receipt of blood or immunoglobulin products in the past 3 months.
15. Subject has known allergies, hypersensitivity, or intolerance to vaccines or its excipients.[18,19]
16. Subject has a history of chronic urticaria (recurrent hives) or a history of chronic or recurrent eczema and/or atopic dermatitis that requires oral/parenteral immunomodulators/immunosuppressors.
17. Subject has chronic or recurrent use of immunomodulators/suppressors, eg, cancer chemotherapeutic agents, and oral or parenteral corticosteroids. Inhaled, ocular, and topical steroids are allowed.
18. Subject who cannot communicate reliably with the investigator.
19. Subject 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, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject'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 subject should be excluded from participation in the study. Section 9.1.3 describes options for retesting. Section 17.5 describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects 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. Agree to follow the contraceptive requirements as noted in Section 4.1 during the main study.

2. Criterion modified per Amendment 3:

   Following vaccination, subjects may be excluded from donating blood products due to induced vaccine seropositivity (see Section 9.4.3) for as long as VISP persists .

3. Male subjects must agree not to donate sperm from the first administration of study vaccine or placebo until 3 months after the last dose of study vaccine or placebo.

4. Female subjects must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction until 3 months after the last dose of study vaccine or placebo.

5. See Section 8 for details regarding prohibited and restricted medication during the study.

6. Current drug/alcohol use that investigator assesses poses any more than a remotely increased risk of the ability of the subject to comply with the protocol requirements.

7. Concurrent participation in another interventional study is disallowed during the main study. Concurrent participation in an observational study without sponsor approval is disallowed during the main study. Subjects who enter the LTE phase are allowed to participate in another clinical study, except for studies with investigational HIV vaccines or other investigational HIV prevention which could be determined to interfere with HIV vaccine response in this study (ie, CD4-Ig depleting Env-specific Abs), which are disallowed and studies with experimental immunomodulators/suppressors which need prior sponsor approval.

8. Subjects should be amenable to HIV-risk reduction counseling and committed to maintaining behavior consistent with low risk of HIV exposure through the last required protocol clinic visit.

4.4. Inclusion and Exclusion Criteria for the Long-term Extension Phase

Each potential subject must satisfy all of the following inclusion criteria to be enrolled in the LTE phase of the study upon completion of the final main study visit at Week 72.

1. Each subject must sign an ICF appendix for the LTE phase indicating that he or she understands the purpose of and procedures required for the LTE phase and is voluntarily willing to participate in the LTE phase of the study.
2. Subject must be randomized to Group 1 or Group 2 of the main study.

   Note: Upon sponsor unblinding at the Week 28 analysis, subjects randomized to Group 1 or Group 2 who have received all 4 vaccinations, will be asked to participate in the LTE phase and sign the ICF appendix for the LTE phase at Week 72. Subjects who attend their Week 72 visit prior to the sponsor's unblinding at the Week 28 analysis, will be enrolled in the LTE phase if they consent and sign the ICF appendix for the LTE phase and meet the eligibility criteria for the LTE phase. When the Week 28 sponsor unblinding subsequently occurs, subjects that started the LTE phase but turn out to have received placebo in the main study will be withdrawn from the LTE phase.
3. Subject must have received all 4 vaccinations of the main study.
4. Subject must be negative for HIV infection at the final main study visit at Week 72.
5. Subject must be willing/able to adhere to the prohibitions and restrictions for the LTE phase, as specified in the protocol and study procedures.

Any potential subject who meets any of the following exclusion criteria at the end of the main study will be excluded from participating in the LTE phase of the study.

1. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
2. Subject is planning to participate in an interventional study during the LTE phase, concerning studies with investigational HIV vaccines or other investigational HIV prevention which could be determined to interfere with HIV vaccine response in this study (ie, CD4-Ig depleting Env-specific Abs), which are disallowed.
3. Subject is planning to participate in an interventional study during the LTE phase, concerning an experimental immunomodulator/suppressor that is not allowed per the sponsor. Documentation of the identity of the experimental immunomodulator/suppressor must be provided to the sponsor, who will determine eligibility on a case-by-case basis.

4.5. Inclusion Criteria, Exclusion Criteria and Prohibitions and Restrictions for the Late Boost Vaccination

Assessment of participants' eligibility will be performed within 4-6 weeks before the administration of the late boost vaccination. Each potential participant must satisfy all of the following inclusion criteria to be eligible to receive the late boost vaccination.

1. Each subject must sign an ICF appendix indicating that he or she understands the purpose of and procedures required for the late boost vaccination and is voluntarily willing to receive this vaccination.
2. Subject must be enrolled in the LTE phase.
3. All female subjects of childbearing potential must have a negative serum (β-hCG) at the screening visit, and a negative urine pregnancy test pre-late boost vaccination.
4. Contraceptive requirements for heterosexually active female subjects (from 28 days prior to the late boost vaccination up until 3 months after the late boost vaccination)[k]:

    a) If not of childbearing potential: postmenopausal (>45 years of age with amenorrhea for at least 2 years, or any age with amenorrhea for at least 6 months and a serum follicle stimulating hormone [FSH] level >40 IU/L) or surgically sterile: no additional contraception required.

    b) If of child-bearing potential, but has a vasectomized partner (after vasectomy: sperm count below the limit of detection if procedure occurred <1 year ago[l]): no additional contraception required.

    c) If of child-bearing potential, but has a non-vasectomized partner, or partner had a positive sperm count after a vasectomy procedure of <1 year ago[l], should be practicing an acceptable effective method of contraception. Acceptable methods for this study include:

        - Hormonal contraception,
        - IUD,
        - IUS,
        - Male or female condom with or without spermicide,
        - Cap, diaphragm or sponge with vaginal spermicide, or
        - Sexual abstinence *

Sexual abstinence is considered an effective method **only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study vaccine. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*

[k] Verbal assurance should be given that adequate birth control measures have been followed for 28 days prior to the boost vaccination

[l] Based on verbal confirmation

Women who are not heterosexually active at screening, but become sexually active during the time window indicated above must agree to utilize an effective method of birth control as mentioned above.

5. Subject must be negative for HIV infection.
6. Subject must be willing/able to adhere to the prohibitions and restrictions for late boost vaccination, as specified in the protocol and study procedures.

Any potential participant who meets any of the following exclusion criteria will be excluded from receiving the late boost vaccination.

1. Subject has chronic hepatitis B (measured by hepatitis B surface antigen test) or active hepatitis C (measured by hepatitis C virus [HCV] Ab test; if positive, HCV ribonucleic acid (RNA) PCR test will be used to confirm active versus past HCV infection.
2. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
3. Subject is planning to participate in an interventional study from signing of the ICF addendum until the end of the study, concerning studies with investigational HIV vaccines or other investigational HIV prevention which could be determined to interfere with HIV vaccine response in this study (ie, CD4-Ig depleting Env-specific Abs), which are disallowed.
4. Subject is planning to participate in an interventional study from signing of the ICF appendix until the end of the study, concerning an experimental immunomodulator/suppressor that is not allowed per the sponsor. Documentation of the identity of the experimental immunomodulator/suppressor must be provided to the sponsor, who will determine eligibility on a case-by-case basis.
5. Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant within 3 months after the late boost vaccination.
6. 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.
7. Potential participant has a history of TTS or heparin-induced thrombocytopenia and thrombosis (HITT)

8 Potential participant received or plans to receive:

   a. 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 late boost study vaccination.

b. 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 late boost study vaccination.

9 Participant is planning to participate in an interventional study with COVID-19 vaccines, from signing of the ICF appendix until the end of the study.

Potential participants must be willing and able to adhere to the following prohibitions and restrictions to be eligible to receive the late boost extension:

1. Agree to follow the contraceptive requirements as noted in the inclusion criterion 4.

2. Following vaccination, subjects may be excluded from donating blood products due to induced vaccine seropositivity (see Section 9.4.3) for as long as VISP persists

3. Male subjects must agree not to donate sperm from the administration of the late boost until 3 months after the boost vaccination.

4. Female subjects must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction from the administration of the late boost until 3 months after the boost vaccination.

5. See Section 8 for details regarding prohibited and restricted medication during the study.

6. Subjects should be amenable to HIV-risk reduction counseling and committed to maintaining behavior consistent with low risk of HIV exposure through the last required protocol clinic visit.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization

Central randomization will be implemented in this study. In the main study, subjects will be randomly assigned to 1 of 3 treatment groups 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 randomly permuted blocks and stratified by region. Similarly, subjects eligible for the late boost vaccination will be randomly (3:1 ratio) assigned to active vaccine or placebo. The randomization will be balanced by using randomly permuted blocks and stratified by region (USA, East Africa: assuming sufficient numbers from Rwanda in the LTE phase) and by group randomized to in the main study (Group 1/Group 2).

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

Blinding

The subjects, study-site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and investigator will be blinded to study vaccine allocation of the main study until Week 72, with the exception of the partial unblinding for the start of the LTE phase (see below). The sponsor will be blinded to study vaccine allocation until the primary (Week 28) analysis (see Section 11.6).

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 subjects can be performed by a qualified healthcare provider from the study site (including the pharmacist who prepared the study vaccine) who will have, on the day of administration, no other study function related to safety, study data evaluation or recording of AEs for those subjects that he/she vaccinated on that day.

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

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.

Under normal circumstances, the blind to study vaccine allocation of the main study should not be broken by the investigator until the end of the main study and the Week 72 electronic data capture (eDC) database is finalized for the subjects, study-site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and investigator. However, for the purpose of the LTE phase, the investigator, the study-site personnel, and the subject will be informed if the subject qualifies for the LTE phase (ie, subject is randomized to Group 1 or Group 2: qualifies, subject is randomized to Group 3: does not qualify) when the subject reaches the Week 72 visit, or as soon as possible following Week 72 upon sponsor unblinding at the Week 28 analysis. This will result in the partial unblinding of the investigator, the study-site personnel, and the subjects, as they will be informed if the subject qualifies for the LTE phase but will not be informed which qualifying group the subject was randomized to.

The subjects, study-site personnel (except for those with primary responsibility for study vaccine preparation and dispensing), and investigator will be blinded to study vaccine allocation of the late boost vaccination until the subject's last visit. The sponsor will be blinded until the interim data analysis approximately 4 weeks after the last subject received the late boost vaccination.

The investigator may in an emergency 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 contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor 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 subject's source documents in a secure manner.

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

6. DOSAGE AND ADMINISTRATION

During the main study, each subject will receive doses of study vaccine or placebo at 4 time points according to randomization, on Weeks 0, 12, 24, and 48, administered by IM injection into the deltoid. Subjects eligible and consenting for the late boost vaccination will receive an additional dose of Ad26.Mos4.HIV in combination with bivalent gp140 or placebo at Week 192 -4 weeks/+ 4 months (ie, approximately 3 years after the 4th vaccination of the primary vaccination series).

For visits with only one injection (ie, at Week 0 and 12), preferably the deltoid of the non-dominant upper arm is used. When 2 injections are to be given at one visit (ie, at Week 24, 48 and late boost vaccination), 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. If a subject cannot be vaccinated within the allowed window, then that vaccination should not be administered. However, if the window is missed due to a study pause (see Section 11.9), vaccination will be assessed on a case-by-case basis, upon discussion between sponsor and investigator. If a subject misses more than one study vaccination, he/she will be withdrawn from further study vaccination (see Section 10.2).

Table 3: Description of Interventions

Test articles	Ad26.Mos4.HIV	Clade C gp140 with aluminum phosphate	Clade C gp140 + Mosaic gp140 with aluminum phosphate*	gp140 HIV bivalent vaccine*	Placebo
Description	See Section Vaccine Information.				
Dose/delivery (0.5 mL injection)	$5x10^{10}$ viral particle (vp)	250 mcg Clade C gp140, mixed with aluminum phosphate adjuvant (0.425 mg aluminum)	125 mcg Clade C gp140 + 125 mcg Mosaic gp140, mixed with aluminum phosphate adjuvant (0.425 mg aluminum)	80 mcg Clade C gp140/75 mcg Mosaic gp140/ aluminum phosphate adjuvant (425 mcg aluminum)	0.9% saline
Frequency	Week 0, 12, 24, 48, and Week 192** (if applicable)	Week 24 and 48	Week 24 and 48	Week 192** (if applicable)	Week 0, 12, 24, 48, and Week 192** (if applicable)
Delivery method	IM in deltoid	IM in deltoid	IM in deltoid	IM in deltoid	IM in deltoid
Delivery instructions	Refer to the Study Procedures Manual for details.				

* The dosage of DP in the gp140 HIV bivalent vaccine (late boost vaccination) is identical to the dosage of DP in the co-administered separate gp140 formulations (main study) . However, there has been a change of unit for the reported gp140 concentration from mg/mL glycoprotein to mg/mL protein. This will not impact the dose strength of gp140 in the vial or administered to the participants in the late boost extension, compared to the main study, but the gp140 concentration will be expressed in protein instead of glycoprotein in the specification. Consequently, 125 mcg Clade C gp140 and 125 mcg Mosaic gp140 of glycoprotein correspond with 80 mcg Clade C gp140 and 75 mcg Mosaic gp140 of protein, respectively.

** The late boost vaccination is to be administered at Week 192 -4 weeks/+4 months, ie, approximately 3 years after the 4th vaccination of the primary vaccination series.

7. TREATMENT COMPLIANCE

Subjects will receive doses of study vaccine or placebo at 4 or 5 time points administered by IM injection by qualified study-site personnel at the study sites.

The date and time of each study vaccine administration will be recorded in the CRF.

8. PRESTUDY AND CONCOMITANT MEDICATION

Prestudy medication administered up to 30 days before the screening visit will be recorded in the CRF at screening. In case a subject received an experimental vaccine more than 12 months prior to the Day 1 visit (Vaccination 1) and is determined to be eligible, administration of this experimental vaccine will be recorded in the CRF. For participants that consent to receive the late boost study vaccination, any COVID-19 vaccination must also be recorded at screening, regardless of how long before screening the vaccination took place.

Concomitant medication must be recorded in the CRF throughout the study from the signing of the ICF to the final main study visit at Week 72 and from the day of late boost vaccination until 28 days thereafter, if applicable. Beyond these time windows, only concomitant therapies given in conjunction with an SAE or in conjunction with AESIs of TTS will be collected. In addition, any chronic or recurrent use of immunomodulators/suppressors, oral or parenteral corticosteroids (see

below), any allowed vaccination and/or any HIV prevention medication and any COVID-19 vaccination should be recorded in the CRF.

Use of any experimental medication (including experimental vaccines other than the study vaccine) during the main study is disallowed. Vaccination with any licensed vaccine within the 14 days prior to or after any dose of study vaccine or placebo is prohibited. However, if a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine. Subjects who enter the LTE phase are allowed to use any experimental medication during the LTE phase, irrespective of them receiving the late boost vaccination, except for:

- studies with investigational HIV vaccines or other investigational HIV prevention which could be determined to interfere with HIV vaccine response in this study (ie, CD4-Ig depleting Env-specific Abs), which are disallowed and studies with experimental immunomodulators/suppressors which are disallowed from signing of the ICF appendix for the late boost vaccination until the end of the study or would need prior sponsor approval if the subject will not receive the late boost vaccination.

- 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 late boost 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.

- For participants planning to receive the late boost study vaccination, concomitant participation in an interventional study with COVID-19 vaccines is not allowed.

Study subjects can receive medications, such as acetaminophen, non-steroidal anti-inflammatory drugs, or antihistamines as needed, although their use must be documented and use of these medications as routine prophylaxis prior to study vaccination is discouraged.

Chronic or recurrent use of:

- Immunomodulators/suppressors, eg, cancer chemotherapeutic agents
- Oral or parenteral corticosteroids, eg, glucocorticoids

is an exclusion criterion for the main study (Section 4.2), and these medications are prohibited during the main study. During the LTE phase, use of these medications is discouraged, except when required by the medical condition of the subject, and each use should be reported during clinical visits. In case a subject uses or is planning to use these medications at the time of the late boost vaccination, it should be discussed with the sponsor on a case-by-case basis if this subject is allowed to receive the late boost vaccination. Ocular and topical steroids are allowed, as well as inhaled steroids for the treatment of pulmonary conditions.

The sponsor 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 immunogenicity and safety measurements applicable to the study.

Evaluation of the safety/tolerability and immunogenicity of the vaccine regimens will include laboratory assessments, physical examinations by clinical staff, and subject reports on 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.

Subjects will be provided with a thermometer, ruler, and subject diary to measure and record body temperature and solicited local (at injection site) and systemic events.

The diary includes instructions how to capture the data and grading scales to assess severity of the symptoms. The study staff is responsible for providing appropriate training to the subject to avoid missing or incorrect data. The diary card will be reviewed by the study personnel at visits indicated on the TIME AND EVENTS SCHEDULE. If the diary card review is missed, the diary card will be reviewed in the following visit. If a participant misses a vaccination, the diary covering the period after the missed vaccination does not have to be filled in.

From screening to the final main study visit at Week 72, the total blood volume to be collected from each subject will be approximately 1,200 mL. The total blood volume to be collected during the LTE phase (Group 1 and Group 2) in case the subject does not receive the boost vaccination will be approximately 470 mL over a 3-year period. In case subjects receive the boost vaccination, the total blood volume collected from the start of the LTE phase until 12 months post late boost will be approximately 1,201 mL. For subjects followed-up to 24 months post late boost, an additional 145,5 mL of blood will be collected. The total blood volume to be collected is considered to be within the US Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP), and US Food and Drug Administration (FDA) guidelines of 550 mL in any 8-week period. Volumes for humoral immunogenicity testing will be approximately 20 to 30 mL/visit and for cellular immunogenicity testing approximately 50-102 mL/visit except for the Visit 22c (subjects who received the late boost vaccination), during which 200 mL of blood will be collected.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Visit Windows

The maximum screening period is 6 weeks.

For the study visits, following windows will be allowed as indicated:

- Visit 3: Day 15 ± 5 days
- Visit 4: Day 29 ± 5 days
- Visit 5: Day 85 -1 week, +3 weeks (second vaccination)
- Visit 6*: Visit 5 + 14 days (Day 99) ± 5 days
- Visit 7*: Visit 5 + 28 days (Day 113) ± 5 days
- Visit 8: Day 169 -1 week, +3 weeks (third vaccination)
- Visit 9*: Visit 8 + 7 days (Day 176) ± 1 day
- Visit 10*: Visit 8 + 14 days (Day 183) ± 5 days
- Visit 11*: Visit 8 + 28 days (Day 197) ± 5 days
- Visit 12: Day 253 ± 5 days
- Visit 13: Day 337 -1 week, +3 weeks (fourth vaccination)
- Visit 14*: Visit 13 + 14 days (Day 351) ± 5 days
- Visit 15*: Visit 13 + 28 days (Day 365) ± 5 days
- Visit 16: Day 421 ± 3 weeks
- Visit 17: Day 505 ± 3 weeks
- Visit 18 to 21 inclusive and Visit 23/Visit 23a*: Days 673 (Week 96), 841 (Week 120), 1009 (Week 144), 1177 (Week 168), and 1513 (Week 216) ± 4 weeks
- Visit 22/Visit 22a: Day 1345 (Week 192) -4 weeks/+4 months
- Visit 22b*: Visit 22a + 3, 7 or 14 days** (Day 1348 [-1/+2 days], 1352 [± 3 days] or 1359 [± 3 days]; Week 193)
- Visit 22c*: Day 1373 ± 2 weeks (Week 196)
- Visit 22d*, 24*, and 25* (optional visit): Days 1429 (Week 204), 1513 (Week 216), 1681 (Week 240) and 2017 (Week 288)

The visit window for the optional vector shedding assessments will be ± 1 day for every visit. For those vector shedding visits that are also included in the general study schedule (Visit 3 and 4), the ± 1 day window will apply instead of the general ± 5 day window listed above.

*If a subject is not vaccinated on the given day of vaccination, the timings of the visits 1, 2 and 4 weeks post-vaccination of the main study and the Visits 22b, 22c, 22d, 23a, 24, and 25 following late boost vaccination (see TIME AND EVENTS SCHEDULE) will be determined relative to the actual day of vaccination.

** Subjects will be divided into three groups: the first 20 enrolled subjects will have the Visit 22b 7 days post late boost, the next 20 enrolled subjects 3 days post late boost and the remainder of the subjects 14 days post late boost.

If a subject cannot be vaccinated within the allowed window, then that vaccination should not be administered. However, if the window is missed due to a study pause (see Section 11.9) or a special situation such as a pandemic (see e.g. Section 18, COVID-19 APPENDIX: GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC), vaccination will be assessed on a case-by-case basis upon discussion between investigator and sponsor. If a subject misses more than 1 study vaccination, he/she will be withdrawn from further study vaccination (see Section 10.2).

For the LTE and late boost extension phases (from Week 72 onwards): If a visit can't be scheduled within the allowed window, it will be assessed on a case-by-case basis upon discussion between investigator and sponsor whether this visit can still be performed.

9.1.3. Screening Phase (Week -6 to 0)

Only healthy subjects negative for HIV infection (if possible, an assay that is FDA-approved should be selected) and complying with the inclusion and exclusion criteria specified in Section 4, Subject Population, will be included into the study. The investigator or designee will provide detailed information on the study to the subjects and will obtain written informed consent prior to each subject's participation in the study. All the procedures described in the TIME AND EVENTS SCHEDULE and TIME AND EVENTS SCHEDULE FOR OPTIONAL VECTOR SHEDDING ASSESSMENT will only take place after written informed consent has been obtained.

Screening may be conducted in part via a sponsor- and IRB/IEC-pre-approved non-study specific screening consent process, but only if the relevant pre-screening tests are identical to the per protocol screening tests and are within 6 weeks prior to first vaccination. However, no study specific procedures, other than screening assessments, will be performed until the subject has signed the study-specific ICF. The study-specific ICF date and time will be entered into the CRF. The non-study specific ICF will be considered source data.

During screening, subjects must pass the TOU, a questionnaire provided to the subject to document his/her understanding of the study (see Section 16.1 and Attachment 3). The TOU must be completed by all subjects, as the first assessment after signing of the ICF. Adaptations to the TOU are allowed for local purposes, after IRB/IEC and sponsor approval.

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

- Medical history
- Complete physical examination, including weight and height
- Vital signs measurement
- Review of pre-study medications
- HIV-risk assessment (see Attachment 2) and counseling on avoidance of HIV infection, for both male and female subjects
- Review of inclusion/exclusion criteria
- Blood sampling for complete blood count (CBC) with differential and platelets, blood chemistry, hepatitis B/C serology, and HIV testing (including pre- and post-HIV-test counseling)
- Sexually-transmitted infection (STI) testing (syphilis, chlamydia, gonorrhea, trichomonas [trichomonas for female subjects only; urine or vaginal swab may be used])
- Contraceptive counseling for both male and female subjects
- Female subjects of childbearing potential: serum β-hCG pregnancy testing
- Urinalysis

General eligibility for this clinical study will be dependent on results of laboratory tests and the medical assessment. Study subjects who qualify for inclusion based on the medical history, physical examination, and laboratory results will be contacted and scheduled for vaccination (Visit 2) within 6 weeks from signing ICF.

Subjects with laboratory values or 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.

After medical history, physical examination, and laboratory data have been reviewed for completeness and adherence to inclusion/exclusion criteria, the subject can be deemed to be eligible for the study.

All AEs will be recorded on the CRF, from signing of the study-specific ICF onwards, together with information about any concomitant medications.

If a subject is a screen failure, but at some point in the future is expected to meet the subject eligibility criteria, the subject may be rescreened on one occasion only. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.

Subjects who consent to the optional vector shedding assessment (see Section 9.1.8) may have baseline samples taken during screening instead of pre-vaccination on Day 1.

9.1.4. Vaccination

Visit 2/Randomization/Vaccination 1

After re-check of inclusion/exclusion criteria (including concomitant medication), abbreviated, symptom-directed physical examination (including weight measurement), measurement of vital signs, and a urine pregnancy test (for women of childbearing potential), eligible subjects 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 will be repeated and the Day 1 visit rescheduled, provided that the rescheduled visit is within 42 days of the initial screening assessment.

Pre-dose samples for hematology, biochemistry, HIV testing, urinalysis, and immunogenicity will be collected. HLA will be tested using the baseline blood sample.

Pre- and post-dose AEs (including SAEs, AEs leading to treatment discontinuation, and AESIs of confirmed HIV infection) will also be collected, together with information about any concomitant medications.

Study vaccine will be prepared by the 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 subject can be performed by a qualified healthcare provider from the study site (including the pharmacist who prepared the study vaccine) who will have, on the day of administration, no other study function related to safety, study data evaluation or recording of AEs for those subjects that he/she vaccinated on that day.

After each vaccination, subjects will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events (see Section 9.3), and vital signs measurement will be repeated.

Subjects will be provided with a thermometer, ruler, and subject diary to measure and record solicited events for 7 days post-vaccination (day of vaccination and the subsequent 7 days).

In addition to an HIV-risk assessment (see Attachment 2), counseling related to avoidance of HIV infection, pre- and post-HIV-test counseling, and contraceptive counseling will be provided to all subjects (men and women).

Optional urine samples and mid-turbinate swabs will be collected for vector shedding assessments from consenting subjects.

Visit 5/Vaccination 2

An abbreviated, symptom-directed physical examination (including weight measurement) and measurement of vital signs will be performed for all subjects pre-vaccination. A urine pregnancy test must be performed before vaccination for women of childbearing potential, and results must be available and negative prior to vaccination. Pre-dose samples for hematology, biochemistry, HIV testing, and urinalysis will be collected. A pre-dose blood sample for the humoral immunogenicity assays will be drawn.

Pre- and post-dose AEs (including SAEs, AEs leading to treatment discontinuation, and AESIs of confirmed HIV infection) will also be collected, together with information about any concomitant medications.

Study vaccine will be prepared by the 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 subject can be performed by a qualified healthcare provider from the study site (including the pharmacist who prepared the study vaccine) who will have, on the day of administration, no other study function related to safety, study data evaluation or recording of AEs for those subjects that he/she vaccinated on that day.

After each vaccination, subjects will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events (see Section 9.3), and vital signs measurement will be repeated.

Subjects will be provided with a thermometer, ruler, and subject diary to measure and record solicited events for 7 days post-vaccination (day of vaccination and the subsequent 7 days).

In addition to an HIV-risk assessment (see Attachment 2), counseling related to avoidance of HIV infection, pre- and post-HIV-test counseling, and contraceptive counseling will be provided to all subjects (men and women).

Subjects will complete a social impact questionnaire (Attachment 4).

Visit 8/Vaccination 3

The procedures for Visit 8 will be the same as at Visit 5 as detailed above. No social impact questionnaire will be completed.

Visit 13/Vaccination 4

The procedures for Visit 13 will be the same as at Visit 5 as detailed above.

9.1.5. Post-vaccination Follow-up Phase

Visits 2a, 3, and 4

At Visit 2a (24-72 hours post-vaccination), a member of the site staff will have a (remote) safety follow-up communication with the subject (by e-mail, telephone, or visit, according to the subject's preference). The subject will be brought in for a clinic visit based on this assessment, if

deemed necessary by the investigator/sub-investigator or upon request of the subject. A (remote) safety follow-up communication 24-72 hours post-vaccination is not required if the vaccination was missed.

Visit 3 is a clinic visit that will include an abbreviated, symptom-directed physical examination (including weight measurement), vital signs measurement, recording of concomitant medications and any AEs (including SAEs, AEs leading to treatment discontinuation, and AESIs of confirmed HIV infection), and review of the diary for 7 days post-vaccination (day of vaccination and the subsequent 7 days). Samples will be collected for safety laboratory testing (CBC and serum chemistry) and the humoral immunogenicity assays. In addition to an HIV-risk assessment (see Attachment 2), counseling related to avoidance of HIV infection will be provided to all subjects. Optional urine samples and mid-turbinate swabs will be collected for vector shedding assessments from consenting subjects.

Visit 4 is a clinic visit that will include an abbreviated, symptom-directed physical examination (including weight measurement), vital signs measurement, recording of concomitant medications and any AEs (including SAEs, AEs leading to treatment discontinuation, and AESIs of confirmed HIV infection), and collection of samples for humoral and cellular immunogenicity assays. In addition to an HIV-risk assessment (see Attachment 2), counseling related to avoidance of HIV infection will be provided to all subjects.

Visits 5a, 6, and 7

The procedures for Visits 5a, 6, and 7 will be the same as for Visits 2a, 3, and 4, respectively. Exception: for Visit 6, both cellular and humoral immunogenicity assays will be done.

Visits 8a, 9, 10, and 11

The procedures for Visits 8a, 10, and 11 will be the same as for Visits 2a, 3, and 4, respectively. Exception: for the sentinel group of 6 subjects, Visit 8a will need to be an actual visit 1 day post-vaccination (only valid for Visit 8a, not required for Visit 2a, 5a, or 13a). And for Visit 10, both cellular and humoral immunogenicity assays will be done.

Visit 9 is a clinic visit for safety follow-up only, and will include an abbreviated, symptom-directed physical examination (including weight measurement), vital signs measurement, and recording of concomitant medications, AEs (including SAEs, AEs leading to treatment discontinuation, and AESIs of confirmed HIV infection) and review of the diary for 7 days post-vaccination (day of vaccination and the subsequent 7 days). In addition to an HIV-risk assessment (see Attachment 2), counseling related to avoidance of HIV infection will be provided to all subjects. Note: If on Visit 9, the 7-day diary observation period is not complete, the diary will be returned at the subsequent visit.

Visit 12

Visit 12 is a clinic visit for safety follow-up only, and will include an abbreviated, symptom-directed physical examination (including weight measurement), vital signs measurement, recording of concomitant medication, recording of SAEs, AEs leading to treatment

discontinuation, and AESIs of confirmed HIV infection, and collection of samples for safety laboratory testing (CBC and serum chemistry). In addition to an HIV-risk assessment (see Attachment 2), counseling related to avoidance of HIV infection will be provided to all subjects.

Visits 13a, 14, and 15

The procedures for Visits 13a, 14, and 15 will be the same as at Visits 2a, 3, and 4, respectively. Exception: no special requirements for the sentinel group for Visit 13a. And for Visit 14, both cellular and humoral immunogenicity assays will be done.

9.1.6. Second Year Follow-up Phase

Follow-up visits will be performed at the clinic at Week 60 and 72 (Visits 16 and 17). Each visit includes a physical examination (abbreviated at Week 60, full at Week 72, both including weight measurement), vital signs measurement, recording of concomitant medications, recording of SAEs, AEs leading to treatment discontinuation, and AESIs of confirmed HIV infection, and collection of samples for immunogenicity and safety laboratory testing (CBC and serum chemistry). In addition to an HIV-risk assessment (see Attachment 2), counseling related to avoidance of HIV infection will be provided to all subjects. Optional urine samples and mid-turbinate swabs will be collected for vector shedding assessments from consenting subjects.

At the final main study visit (Week 72), samples for HIV testing and urinalysis will be collected. Pre- and post-HIV-test counseling will be provided to all subjects. Subjects will also complete a social impact questionnaire (Attachment 4).

9.1.7. Early Withdrawal/Exit Visit

In the event of early withdrawal from the main study (ie, before Week 72), an exit visit will be conducted as soon as possible. The following procedures will be performed: an abbreviated, symptom-directed physical examination (including weight measurement), vital signs measurement, recording of concomitant medications and any AEs (including SAEs, AEs leading to treatment discontinuation, and AESIs of confirmed HIV infection), and collection of samples for safety laboratory testing (CBC and serum chemistry), the immunogenicity assays, urinalysis, and HIV testing. In addition to an HIV-risk assessment (see Attachment 2), counseling related to avoidance of HIV infection, pre- and post-HIV-test counseling, and contraceptive counseling will be provided to all subjects (men and women). A urine pregnancy test will be carried out for women of childbearing potential. Additionally, subjects will complete a social impact questionnaire (Attachment 4).

9.1.8. Vector Shedding Evaluations

Vector shedding sampling is optional. The target is to include approximately 30 subjects. Urine samples (approximately 5-10 mL) and mid-turbinate swabs (culture swab in universal transport medium) for vector shedding assessments will be collected at selected sites according to the TIME AND EVENTS SCHEDULE FOR OPTIONAL VECTOR SHEDDING ASSESSMENT from consenting subjects. Ad26 vector shedding will be analyzed by PCR.

9.1.9. Long-term Extension Phase

An LTE phase (approximately 3 years after Week 72) will be performed for subjects randomized to Group 1 or Group 2, who have received all 4 vaccinations and are negative for HIV infection at Week 72.

The sponsor will be unblinded to study treatment at the Week 28 analysis and will notify the investigator and study-site personnel of subjects randomized to Group 1 or Group 2. At Week 72, subjects randomized to Group 1 or Group 2 who have received all 4 vaccinations, will be asked to participate in the LTE phase and sign the ICF appendix for the LTE phase. During the first visit of the LTE phase, the remaining eligibility criteria for the LTE phase will be verified. Subjects who attend their Week 72 visit prior to the sponsor's unblinding at the Week 28 analysis, will be enrolled in the LTE phase if they consent and sign the ICF appendix for the LTE phase and meet the eligibility criteria for the LTE phase. When the Week 28 sponsor unblinding subsequently occurs, subjects that started the LTE phase but turn out to have received placebo in the main study will be withdrawn from the LTE phase.

If signing the ICF appendix is not possible at Week 72, signing should be performed at an extra visit (Visit 17bis) as soon as possible after Week 72 and at the latest before any assessment is done on the first visit of the LTE phase.

Subjects will attend follow-up visits at the clinic from Week 96 until the final visit at Week 216. Each visit includes recording of any SAEs, AESIs of HIV infection, and concomitant medications (any medication given in conjunction with an SAE, as well as any recurrent or chronic use of immunomodulators/suppressors and corticosteroids), and collection of samples for cellular and humoral immunogenicity assays.

Samples for HIV testing will be collected. In addition to an HIV-risk assessment, counseling related to avoidance of HIV infection, pre- and post-HIV test counseling will be provided to all subjects.

Also, at each visit, subjects will complete a social impact questionnaire (Attachment 4).

Approximately at the time of the Visit 22 of the LTE phase, subjects will be informed on the option to participate in an extension to the LTE phase, including an additional boost vaccination. See Section 9.1.10 for more information. Subjects not willing to participate will continue the LTE phase as outlined in the TIME AND EVENTS SCHEDULE FOR THE LONG-TERM EXTENSION PHASE (FROM WEEK 72 ONWARDS, GROUP 1 AND GROUP 2).

9.1.10. Late Boost Vaccination

Assessments are summarized in the TIME AND EVENTS SCHEDULE FOR THE LATE BOOST EXTENSION. Only subjects enrolled in the LTE phase who are complying with the inclusion and exclusion criteria specified in Section 4.5 will be eligible to receive a late boost vaccination. The investigator or designee will obtain written informed consent prior to any assessment of the late boost extension.

Screening of subjects and vaccination will be performed at Week 192 -4 weeks/+4 months (ie, approximately 3 years after the 4th vaccination of the primary vaccination series), ie, Visit 22a, which may be split into several visits within the specified time window. Screening should occur within 4-6 weeks before the administration of the late boost vaccination.

No study procedures specific to the late boost vaccination will be performed until the subject has signed the appendix to the ICF. The ICF date and time will be entered into the CRF.

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

- Abbreviated symptom-directed physical examination, including weight
- Vital signs measurement
- Review of pre-boost medications
- HIV-risk assessment (see Attachment 2) and counseling on avoidance of HIV infection, for both male and female subjects
- Review of inclusion/exclusion criteria
- Blood sampling for hepatitis B/C serology, and HIV testing (including pre- and post-HIV-test counseling)
- Contraceptive counseling for both male and female subjects
- Female subjects of childbearing potential: serum β-hCG pregnancy testing

General eligibility for boost vaccination will be dependent on results of the medical assessment. Study subjects who qualify to receive the late boost vaccination based on this assessment will receive the vaccination within the -4 week/+ 4 month time window to Visit 22a.

Subjects vital signs not meeting eligibility criteria on the screening visit may have one repeat testing during the screening period.

Screen failures should continue the LTE phase as outlined in Section 9.1.9.

After re-check of inclusion/exclusion criteria, abbreviated, symptom-directed physical examination (including weight measurement), measurement of vital signs, and a urine pregnancy test (for women of childbearing potential), eligible subjects will be randomized as described in Section 5. If the vaccination occurs on the same day as the screening, the pre dose vital signs assessment and physical examination do not need to be repeated.

If medical status and/or physical examination suggest(s) significant changes have occurred since screening, the clinically relevant screening assessments will be repeated and the vaccination visit rescheduled, provided that the rescheduled visit is within 42 days of the initial screening assessment and all screening assessments and vaccination are still possible within the -4 week/+4 month time window around Visit 22a (Week 192).

Pre-dose samples for immunogenicity will be collected.

Pre- and post-dose AEs (including SAEs, AEs leading to treatment discontinuation, and AESIs [confirmed HIV infection and TTS]) will also be collected, together with information about any concomitant medications. If the vaccination occurs on the same day as the screening pre-dose AEs will only be collected once.

Study vaccine will be prepared by the 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 subject can be performed by a qualified healthcare provider from the study site (including the pharmacist who prepared the study vaccine) who will have, on the day of administration, no other study function related to safety, study data evaluation or recording of AEs for those subjects that he/she vaccinated on that day.

After the late boost vaccination, subjects will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events (see Section 9.3), and vital signs measurement will be repeated.

Subjects will be provided with a thermometer, ruler, and subject diary to measure and record solicited events for 7 days post-vaccination (day of vaccination and the subsequent 7 days).

In addition to an HIV-risk assessment (see Attachment 2), counseling related to avoidance of HIV infection, pre- and post-HIV-test counseling, and contraceptive counseling will be provided to all subjects (men and women). If the vaccination occurs on the same day as the screening HIV risk assessment, contraceptive counselling, and pre-dose counselling on HIV will only be performed once.

Subjects will complete a social impact questionnaire (Attachment 4).

Subjects will have a follow-up clinic visits approximately 3, 7 or 14 days post boost (Visit 22b [Week 193]; first 20 subjects 7 days post late boost, next 20 subjects 3 days post late boost and the remainder of the subjects 14 days post late boost). This visit will include the recording of all concomitant medications and AEs (including SAEs, AEs leading to treatment discontinuation, and AESIs [confirmed HIV infection and TTS]) and review of the diary for 7 days post-vaccination (day of vaccination and the subsequent 7 days). Samples will be collected for humoral and cellular immunogenicity assays.

Subsequent follow-up visits will occur 1 (Visit 22c [Week 196]), 3 (Visit 22d [Week 204]), 6 (Visit 23a), 12 (Visit 24), and, optionally (separate consent to be provided), 24 months post late boost (Visit 25), calculated from the actual day of vaccination. Assessments during these visits include the recording of concomitant medications: all concomitant medications until 28 days post vaccination and from then onwards, concomitant medication given in conjunction with an SAE or AESI of TTS, any chronic or recurrent use of immunomodulators/suppressors, oral or parenteral corticosteroids, any allowed vaccination and/or any HIV prevention medication, including any COVID-19 vaccination. Solicited AEs will be recorded until 7 days post vaccination and unsolicited AEs until 28 days post vaccination. SAEs and AESIs of confirmed HIV infection will be recorded until the end of the study. AESIs of TTS will be recorded up to Visit 23a (6 months

after the late boost vaccination). Each visit will include collection of humoral and cellular immunogenicity assays. In addition, at Visit 23a, 24 and 25 (if applicable), HIV testing will be performed, an HIV-risk assessment (see Attachment 2) will be performed and counseling related to avoidance of HIV infection will be provided to all subjects. At Visit 23 subjects will complete a social impact questionnaire (Attachment 4).

In the event of early withdrawal from study following the late boost vaccination (ie, before Week 240), an exit visit will be conducted as soon as possible. The following procedures will be performed: an abbreviated, symptom-directed physical examination (including weight measurement), vital signs measurement, recording of concomitant medications and any AEs (including SAEs, AEs leading to treatment discontinuation, and AESIs [confirmed HIV infection and TTS, if applicable]), the immunogenicity assays, and HIV testing. In addition to an HIV-risk assessment (see Attachment 2), counseling related to avoidance of HIV infection, and pre- and post-HIV-test counseling will be provided to all subjects (men and women). Additionally, subjects will complete a social impact questionnaire (Attachment 4).

9.2. Immunogenicity Evaluations

Humoral immune response assays will include, but are not limited to Env-Ab-binding assays (ELISA), virus neutralization assay, and assays for Ab functionality. Additional assays may include binding antibody assays to evaluate the breadth and isotypes of Ig induced and passive transfer assays.

Cellular immune response assays will include, but are not limited to IFNγ ELISPOT assay, ICS, and multiparameter flow cytometry.

9.3. Safety Evaluations

Details regarding the PSRT and DRC are provided in Section 11.7 and 11.8, respectively.

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 endpoint is reached (see Section 12.3.2).

The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE.

AEs

All AEs will be reported from the time the signed and dated study-specific ICF is obtained until 28 days after first dose of study vaccine, and thereafter, pre-dose on the day of injection and for 28 days after each subsequent dose of study vaccine. Unsolicited AEs 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 on the CRF AE page. All SAEs and AEs leading to discontinuation from the study vaccination and AESIs of confirmed HIV infection are to be reported from signing of study-specific ICF onwards for the duration of the study (see Section 12.3.1 for details). Adverse events will be followed by the investigator as specified in

Section 12.1.3. From the time of local regulatory approval of protocol amendment 5 onwards, TTS is considered to be an AESI. Thrombotic events and/or thrombocytopenia are considered to be potential AESIs. Thrombocytopenia is defined as platelet count below the LLN range for the testing lab. All AESIs of TTS, including potential AESIs, will be reported to the sponsor from the moment of the late boost vaccination until 6 months after the late boost vaccination. Each potential AESI will be reviewed to identify a TTS case.

For solicited AEs, the following applies.

Solicited AEs

After vaccination, subjects will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events. In addition, subjects will record solicited events in a diary for 7 days post-vaccination. All subjects will be provided with a diary and instructions on how to complete the diary (Section 9.1.1). Diary information will be transcribed by the study personnel in the appropriate CRF pages. Once a solicited symptom from a diary is considered to be of severity Grade 1 or above, it will be referred to as a solicited adverse event. For AE severity criteria, see Section 12.1.3.

Injection Site (Local) AEs

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

- **Injection Site Pain/Tenderness**

  Injection site pain (eg, stinging, burning) is an unpleasant sensory and emotional experience associated with actual or potential tissue damage and occurring at the immunization site (with or without involvement of surrounding tissue). Injection site tenderness is a painful sensation localized at the injection site upon palpation and/or movement of the limb. Due to subjective nature of the reaction, the severity assessment of pain/tenderness is self-reported.[12]

- **Injection Site Erythema**

  Injection site erythema is a redness of the skin caused by dilatation and congestion of the capillaries localized at the injection site. It can best be described by observation and measuring.

- **Injection Site Swelling/Induration**

  Injection site swelling is a visible enlargement of an injected limb. It may be either soft (typically) or firm (less typical). Injection site induration is a palpable thickening, firmness, or hardening of soft tissue, usually has well-demarcated palpable borders, can be visible (raised or sunken compared to surrounding skin), is often 'woody' to touch and has a flat shape. As differentiation between swelling and induration may be difficult without health care professional's assessment, both symptoms have been combined to allow self-assessment by the subjects. Both swelling and induration can best be described by observation and measuring.[21,22]

  Note: any other injection site events not meeting the above case definitions should be reported separately as unsolicited AEs.

Systemic AEs

Subjects will be instructed on how to record daily temperature using a thermometer provided for home use. Subjects 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.[24]

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

The severity of these solicited systemic AEs will be graded according to the criteria presented in Section 12.1.3.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected (fasting not required). The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

In case a Grade 3 or Grade 4 laboratory abnormality, or any laboratory abnormality accompanied by clinically relevant signs or symptoms occurs (from the baseline visit onwards), all attempts will be made to perform a confirmatory test within 48 hours after the results have become available. After that, laboratory tests will be repeated weekly until values are resolved or stable.

The following tests will be performed by the local laboratory (*parameters only measured at screening):

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell (RBC) count
  -white blood cell (WBC) count with differential
  -platelet count

A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count and/or RBC parameters and/or RBC morphology, which will then be reported by the laboratory.

In addition, any other abnormal cells in a blood smear will also be reported.

- Serum Chemistry Panel

  -creatinine
  -glucose*
  -AST
  -ALT
  -creatine phosphokinase (CPK)*
  -bilirubin*
  -FSH (post-menopausal women only)*

- Urinalysis

  Dipstick
  -specific gravity
  -pH
  -glucose
  -protein
  -blood
  -ketones

  Microscopic reflex testing will be carried out in the event of abnormal urinalysis tests, except when the investigator considers the abnormal urinalysis result to be from menstrual origin.

In the microscopic examination, observations other than the presence of WBC, RBC, and casts may also be reported by the laboratory.

Laboratory values will be graded according to a modified version of the Division of Acquired Immunodeficiency Syndrome (DAIDS) grading table, Version 2.0 (Attachment 1), and, if clinically significant, reported as AEs. Laboratory reference ranges will be applied according to the subject's sex at birth.

Additional clinical laboratory assessments to be performed are as follows:

- Serum (at screening of the main study and screening for the late boost vaccination) and Urine (pre-dose at vaccinations, Week 72, and the early Exit visit of the main study) Pregnancy Testing for women of childbearing potential only.

- Serology (hepatitis B surface antigen [HBsAg], hepatitis C virus Ab; at screening of the main study and screening for the late boost vaccination)
- HIV testing (at screening of the main study and screening for the late boost vaccination, vaccinations, Week 72, the early Exit visit, and at each visit of the LTE phase and each post-late boost vaccination follow-up visit) (see Section 9.4.1)
- Syphilis, chlamydia, gonorrhea, trichomonas (trichomonoas for female subjects only; urine or vaginal swab may be used) at screening of the main study
- In case of a potential AESI of TTS (see Section 12.3.3.2), 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).

If any clinically significant changes in vital signs are noted, they will be reported as AEs and followed to resolution, or until reaching a clinically stable endpoint.

Physical Examination

Full physical examination will be carried out at screening of the main study and at the final main study visit (Week 72). At all other main study visits and at screening of the late boost vaccination, an abbreviated, 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 of the main study. Weight will be measured at every study visit including a physical examination.

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. Any clinically relevant post-baseline abnormality or any clinically relevant worsening versus baseline conditions should be documented in the AE pages of the CRF.

9.4. Human Immunodeficiency Virus Testing and Vaccine Induced Seropositivity

9.4.1. HIV Testing

HIV testing will be performed as indicated in the TIME AND EVENTS SCHEDULE.

At screening of the main study and baseline, subjects will be tested for HIV infection, and must be negative to be entered into the study. If possible, an assay that is US FDA-approved should be selected.

At all other main study visits that include HIV-testing, a study-specific HIV-testing algorithm (detailed in the Laboratory Manual) will be followed. Information provided to the clinical staff of the study site will not include the results of specific tests, but will state only the final interpretation as "HIV infected" or "HIV uninfected". This system allows timely HIV testing without compromising the double-blind nature of the study. The algorithm used for HIV testing throughout the main study aims to differentiate VISP from true HIV infection (see Section 9.4.3).

During the LTE phase, the study-specific HIV-testing algorithm described above will be followed as long as treatment assignment is blinded. Upon study unblinding (after the week 72 database lock), unblinded HIV and VISP results will be reported.

At screening for the late boost vaccination and all subsequent visits of the TIME AND EVENTS SCHEDULE FOR THE LATE BOOST EXTENSIONTIME AND EVENTS SCHEDULE FOR THE LATE BOOST , the study-specific HIV-testing algorithm as described above for the main study will be followed. .Information provided to the clinical staff of the study site will not include the results of specific tests, but will state only the final interpretation as "HIV infected" or "HIV uninfected".

9.4.2. Management of Subjects who Become HIV-infected During the Study

Test results performed to confirm the diagnosis will be forwarded to the study staff. Subjects who become HIV infected during the study, including the LTE phase, will be (see Section 12.3.3.1):

- Excluded from further vaccinations.
- Provided counseling and referred for medical treatment.
- Informed about observational studies monitoring subjects with HIV infection.
- Excluded from initiation of the LTE phase.

9.4.3. VISP

In general, HIV-uninfected subjects who participate in preventative HIV-vaccine studies may develop HIV-specific antibodies as a result of an immune response to the candidate HIV vaccine, referred to as VISP. 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.

Should an HIV-Ab test give a positive result for a particular subject 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 Laboratory Manual.

To avoid possible unblinding as a result of positive HIV testing due to VISP, subjects should not donate blood during the study. Blood donation options for those subjects 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 subject requires an HIV test outside the study (eg, to obtain a travel visa or insurance, or for medical reasons), he/she should contact the research center. The center can issue a written statement giving details on VISP and on the testing algorithm to be followed. If requested by a subject, repeat HIV testing will be available at most every 3 months to confirm their HIV status. It is highly preferable that this repeat HIV testing will be performed through the research center. More frequent testing is only allowed after sponsor approval. Testing for a particular subject will be available as long as VISP is present for this subject.

Depending on the local availability of a follow-up protocol, subjects could join into such a study that specifically follows the course of VISP. Such a study may not be available at all sites. However, if such a study is not available, HIV testing will be provided on request as described in the previous paragraph.

In addition to providing testing, subjects will always receive pre- and post-test HIV counseling.

9.4.4. Social Impact

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

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

For these reasons, subjects will complete a social impact questionnaire (Attachment 4; at the time points specified in the TIME AND EVENTS SCHEDULE) to evaluate any potential consequences of the subject's participation. For more information, please refer to the Study Procedures Manual.

9.5. Sample Collection and Handling

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

See 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 Procedures Manual 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 Laboratory Manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject who is not participating in the LTE phase will be considered to have completed the study if he or she has completed the assessments at Week 72.

A subject who is participating in the LTE phase will be considered to have completed the main study if he or she has completed the assessments at Week 72 and will be considered to have completed the LTE phase if he or she has completed the assessments at the last visit of the LTE phase (Week 216).

Subjects receiving the late boost vaccination will have completed the study if he or she has completed the assessments at Week 240, if opting for 12 months of follow-up post-boost, or Week 288, if opting for 24 months of follow-up post- late boost.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

Subjects will be withdrawn from study vaccine administration during the main study for the reasons listed below. These subjects must not receive any additional dose of study vaccine but should enter the follow-up phase with assessments of safety and immunogenicity. The subject will be encouraged to complete the post-vaccination follow-up visits of the last vaccination received and a 12 and 24 weeks follow-up visit after the last vaccination received, specified as Week 60 and Week 72 in the TIME AND EVENTS SCHEDULE. Additional unscheduled visits may be performed for safety/tolerability reasons, if needed. In case the subject withdraws before receiving the first vaccination, the subject is not required to attend follow-up visits. In case of questions, the investigator is encouraged to contact the study responsible physician. Subjects who have been prematurely withdrawn from study vaccine administration are not eligible for the LTE phase.

- Unblinding
- Anaphylactic reaction following vaccination
- Pregnancy
- Any related SAE
- Any related AE, worsening of health status or intercurrent illnesses that, in the opinion of the investigator, requires discontinuation from study vaccine
- Confirmed HIV infection
- Chronic or recurrent use of immunosuppressants (after discussion with the sponsor)

- Missing more than 1 study vaccination

Withdrawal From the Study

Each subject 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 subjects who did not return for scheduled visits or follow-up. Although the subject 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 subject's rights.

A subject 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 subject is lost to follow-up, every reasonable effort (at least 2 documented attempts to contact the subject by telephone and at least one documented written attempt) must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject 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 subject may not be assigned to another subject. Subjects who are vaccinated and who withdraw will not be replaced. If a subject withdraws early from the study, assessments for early withdrawal should be obtained (see Section 9.1.7).

Subjects 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. The exit visit is only applicable to the main study until Week 72 and for subjects who received the late boost vaccination.

A subject who withdraws from the study will have the following options regarding the use of optional research samples which were collected:

- The collected samples will be retained and used in accordance with the subject's original informed consent appendix for optional research samples.

- The subject may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent

for the optional research samples and to request sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

10.3. Contraindications to Vaccination

The following events constitute a contraindication to vaccination at that point in time. 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 (oral temperature ≥38.0°C) at the planned time of vaccination.

10.4. Withdrawal From the Use of Samples in Future Research

The subject 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 or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the safety and immunogenicity data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Subject Information

For all subjects, demographic characteristics (eg, age, height, weight, body mass index [BMI], race, and gender), and other baseline characteristics (eg, medical history, concomitant diseases) will be tabulated and summarized with descriptive statistics.

11.2. Analysis Populations

The safety population will consist of all subjects who received at least one dose of study vaccine, and for whom any post-dose data is available.

The immunogenicity population will consist of all subjects who received at least one dose of study vaccine, and who have immunogenicity data from at least one evaluable post-dose blood sample.

The per protocol immunogenicity population will consist of all randomized and vaccinated subjects for whom immunogenicity data are available, excluding subject samples with major protocol deviations expecting to impact the immunogenicity outcomes (for example missed vaccinations, natural infections, etc).

11.3. Sample Size Determination

The sample size in this study is regarded to be appropriate to assess the safety and tolerability of the different vaccine regimens. Placebo recipients are included for blinding and safety purposes and will provide control specimens for immunogenicity assays. With 25 individuals in a vaccine regimen, the observation of 0 such reactions would be associated with a 95% confidence that the true rate is less than 12%. For Group 2 with Mosaic and Clade C gp140 (n=100), there would be 95% confidence that the true rate is less than 3% when 0 events are observed. The following table shows the probabilities of observing at least one AE given true AE rates.

	Probability of Observing at Least One AE in n Subjects	
True AE Rate	n = 25	n = 100
0.1%	2%	9.5%
0.5%	12%	39%
1.0%	22%	63%
2.5%	47%	92%
5.0%	72%	99%
10.0%	93%	100%

The primary population for the safety analyses will consist of all subjects who received at least 1 dose (Ad26.Mos4.HIV or placebo).

Anticipating a dropout rate of approximately 10%, the sample sizes will allow detection of approximately 1.85-fold differences in Env-binding Ab titers, generally accepted to be biologically relevant, between the groups with Mosaic and Clade C gp140 (approximately 90 evaluable subjects) and their corresponding group with Clade C gp140 only (approximately 22 evaluable subjects); with 80% probability, assuming a 2-sided 5% Type I error and an SD of 0.4 on the $\log_{10}$ scale.

11.4. Immunogenicity Analyses

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

No formal hypothesis on immunogenicity will be tested. The analysis of immunogenicity will be done on the (per protocol) immunogenicity population as defined in Section 11.2.

Breadth of the binding Ab response will be summarized as the number of HIV clades to which a subject shows an Ab response. Magnitude and breadth of (n)Ab responses will be explored graphically through the generation of individual magnitude-breadth (M-B) curves. The area under the M-B curve (AUC) provides an overall summary of the M-B profile. The AUCs will be compared between groups using the Wilcoxon-Mann-Whitney test.

Differences between groups at a specific time point will be tested for exploratory purposes by a 2-sample t-test if the data appear to be normally distributed. If not, the non-parametric Wilcoxon rank sum test will be used. If portions of the measurements are censored below the assay

quantification limit, the Gehan-Wilcoxon test will be employed. All statistical tests will be 2-sided and will be considered statistically significant if $p<0.05$.

Frequency tabulations will be calculated for discrete (qualitative) immunologic parameters. Significant differences between groups will be determined by a 2-sided Fisher's exact test.

11.5. Safety Analyses

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

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

AEs

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs and events-related diary information (solicited local at injection site and systemic, and unsolicited) with onset within 28 days after vaccination (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by vaccine group.

Treatment-emergent AEs are AEs with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

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

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

Solicited local (at injection site) and systemic AEs will be summarized descriptively. The overall frequencies per vaccine group as well as frequencies according to severity and duration will be calculated for solicited AEs. In addition, the number and percentages of subjects with at least one solicited local (at injection site) or systemic AE will be presented. Frequencies of solicited and unsolicited AEs, separately for all and vaccination-related only, will be presented by System Organ Class and preferred term.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Laboratory abnormalities will be determined according to a modified version of the DAIDS grading table, Version 2.0 (Attachment 1), and in accordance with the normal ranges of the clinical laboratory. Laboratory abnormalities will be tabulated per vaccine group and/or treatment group.

Vital Signs

The percentage of subjects with values beyond pre-specified limits (see Attachment 1) will be summarized.

Physical Examination

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

Social Impact Questionnaire

Data from the Social Impact Questionnaire will be summarized using descriptive statistics.

Vector Shedding Analyses

Vector shedding data will be analyzed descriptively.

11.6. Analysis Time Points

The primary analysis (unblinded, see Section 5) will be performed once all subjects have completed the Week 28 visit (ie, 4 weeks after the third injection) or discontinued earlier. An additional analysis will be performed once all subjects have completed the Week 52 visit (ie, 4 weeks after the fourth injection) or discontinued earlier. The final analysis of the main study will be performed once all subjects have completed their final main study visit at Week 72 or discontinued earlier. The final analysis of the study will be performed once all included subjects have completed the last visit of the LTE phase (Week 216) or last post late boost follow-up visit (Week 240 or Week 288), or discontinued earlier. Additional analyses of the immune responses during the LTE phase may be performed. An interim analysis of the data from the late boost vaccination will be performed approximately 4 weeks after the last subject received the late boost vaccination.

11.7. Protocol Safety Review Team

A PSRT will review blinded safety data reports on a regular basis (at least 2 times per month) starting from one week after first vaccination until the last subject has completed the Week 52 visit, and thereafter as needed.

Since this study is the FIH administration of Mosaic gp140, after a sentinel group of 6 subjects receives the third injection, further third injections will be paused until a 1-day safety evaluation is performed. This evaluation will be performed by the PSRT and the PI(s) of the subjects involved and will be based on the information received from the investigator(s) by email/telephone.

If a dose of vaccine is considered, by PSRT review, to raise significant safety concerns, all enrollment and vaccinations will be suspended until recommendations are issued (see Section 11.9). In specific cases, a DRC meeting will be triggered.

The PSRT will include, but will not be limited to medical and safety representatives from the sponsor, a limited number of sites, DAIDS, BIDMC, HVTN, IAVI, and MHRP. The PSRT responsibilities, authorities, and procedures will be documented in its charter.

11.8. Data Review Committee

A DRC will be established for this study, which will monitor data to ensure the safety and well-being of the subjects enrolled. The DRC will review data as indicated below. The conclusions of the DRC will be communicated to the investigators, the IRB/IEC, and the national regulatory authorities, as appropriate.

The DRC will specifically review safety data (solicited and unsolicited AEs, SAEs, and available laboratory assessments) at 2 time points following injections of Mosaic gp140:

- Review blinded safety data (2 weeks of follow-up) after approximately 25 (15%) of subjects have received their third injection.
- Review blinded safety data (2 weeks of follow-up) after approximately 50 (30%) of subjects have received their third injection.

In addition, ad hoc review may be performed further to the occurrence of any AE/SAE leading to a study holding situation as outlined in Section 11.9, or at request of the PSRT.

The DRC will review blinded data first, but is entitled to and has the right to require submission of unblinded data if deemed necessary.

The DRC will include medical experts in vaccines and at least one statistician. The DRC can include members from both inside and outside Janssen, but will not include any study team personnel or people otherwise directly involved in the study conduct, data management, or statistical analysis for the study. The DRC responsibilities, authorities, and procedures will be documented in its charter.

11.9. Study Holding Rules

If an administration of vaccine is considered, by the PSRT, to raise significant safety concerns, all screening and vaccinations will be suspended until recommendations are issued. The AEs that may lead to a safety pause or prompt PSRT AE review are summarized below in Table 4. These study holding rules apply to related AEs that occur up to 4 weeks after vaccination and to SAEs occurring up to 4 weeks after the last vaccination.

Table 4: AE Notification and Safety Pause/AE Review Rules[1]

(S)AE and Relationship[2]	Severity	Site Principal Investigator Action	PSRT/DRC Action[3]
SAE, related	Any grade	Notify Study Responsible Physician or designee AND fax or email SAE form to Global Medical Safety Office, immediately and no later than 24 h after becoming aware of the event	Immediate pause for PSRT review of safety data
SAE, not related	Grade 5	Notify Study Responsible Physician or designee AND fax or email SAE form to Global Medical Safety Office, immediately and no later than 24 h after becoming aware of the event	PSRT review and consideration of pause
AE[4], related	Grade 3 or Grade 4	Notify Study Responsible Physician immediately and no later than 24 h after becoming aware of the event	PSRT review and consideration of pause
Three subjects with a similar related AE[5]	Grade 3 or Grade 4	Not applicable	Immediate pause for DRC review of safety data

The contact details of the medical team are in the Contact Information page(s). The Study Responsible Physician (or designee) is responsible for the immediate notification of PSRT/DRC members and coordination of a PSRT/DRC meeting.

1 Applicable for AEs/SAEs occurring up to 4 weeks after the last vaccination. For a Grade 3/4 laboratory related AE, the test must be repeated at least once, within 48 hours of the site becoming aware of the abnormal value. PSRT evaluation for consideration of a pause will proceed without waiting for repeat testing. Start of DRC review will require a confirmation of the laboratory test within 48 hours.

2 Related: suspicion of relationship between the study vaccine and the AE. Not related: no suspicion of relationship between the study vaccine and the AE. (Relationship as assessed by investigator)

3 All sites will be notified immediately in case of a safety pause.

4 For Grade 3 solicited related AEs, immediate PSRT review is mandatory only if the event persists as Grade 3 for longer than 3 consecutive days. PSRT evaluation for consideration of a pause will proceed for all other cases not specified in footnote 4.

5 Applicable for the following related AEs:
- All Grade 4 AEs (regardless of duration)
- Grade 3 unsolicited AEs (regardless of duration)
- Grade 3 solicited AEs (only if persisting for longer than 3 consecutive days)

After each DRC review of a similar AE, the DRC will indicate the conditions under which they require further notification and/or review of the subsequent similar AEs.

Vaccinations for an individual subject may be suspended for safety concerns other than those described in the table, at the discretion of the investigator if he/she feels the subject's safety may be threatened. The investigator may ask for a PSRT meeting to be held for any single event or combination of multiple events which, in his/her professional opinion, jeopardize the safety of the subjects or the reliability of the data.

Vaccinations for the study may be suspended for safety concerns other than those described in the table, or before pause rules are met, if, in the judgment of the DRC, subject safety may be threatened.

For events in the table above, the investigator notifies the sponsor's study responsible physician (or designee) immediately, and in all cases within 24 hours at the latest after the site observes, or

is notified of, the AE, and the study responsible physician (or contacted sponsor's representative) then notifies the PSRT immediately. If the case(s) is (are) deemed to fulfill the potential holding rules, the PSRT will convene within one business day to review these AEs. The PSRT will review and determine disposition, including whether the DRC needs to review the event(s).

If a study pause is triggered by the PSRT, all screening and vaccinations will be held until review by the PSRT or DRC is complete. Resumption of screening and study treatment may be determined by the PSRT or DRC (in consultation with the FDA, if required) following a cumulative review of the available safety data as outlined in the charter. The clinical sites will be allowed to resume activities upon receipt of a written notification from the sponsor. As needed, the appropriate regulatory authorities will be informed in writing of the decision by the PSRT and/or DRC to resume or discontinue study activities. The site is responsible for notifying their IRB/IEC according to local standards and regulations. The sponsor is responsible for notifying the FDA.

12. AE REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, 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 AEs, AESIs, and SAEs

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

Solicited AEs

Solicited AEs are predefined local and systemic events for which the subject is specifically questioned and symptoms of which are noted by subjects in their diary (see Section 9.1.1).

Unsolicited AEs

Unsolicited AEs are all AEs for which the subject is specifically not questioned in the subject diary.

AESIs

For details, see section 12.3.3.

12.1. Definitions

12.1.1. AE Definitions and Classifications

AE

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE 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: The sponsor collects AEs starting with the signing of the study-specific ICF (see Section 12.3.1 for time of last adverse event recording).

SAE

An SAE 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 subject 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 subject 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 vaccine and the event (eg, death from anaphylaxis), the event must

be reported as a serious and unexpected suspected adverse reaction by the sponsor to the Health Authorities and by the investigator to the IRB/IEC according to regulatory and local requirements.

Unlisted (Unexpected) AE/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 Investigator's Brochure.

AE Associated With the Use of the Vaccine

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

AESI

Confirmed HIV infection in a subject during the study is considered an AESI. All AESIs, irrespective if considered serious or not by the investigator, shall be reported to the sponsor immediately and aggregate analyses performed either at the end of study and possible at interim time points during the study. For details of the AESI of TTS, see Section 12.3.3.2.

12.1.2. Attribution Definitions

Every effort should be made by the investigator to explain any AE and assess its potential causal relationship, ie, to administration of the study vaccine or to alternative causes (eg, natural history of the underlying diseases, concomitant medication). This applies to all AEs, whether serious or non-serious.

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

Related: there is a reasonable possibility that the study vaccine contributed to the AE.

Unrelated: there is no suspicion that there is a relationship between the study vaccine and the AE; there are other more likely causes and administration of the study vaccine is not suspected to have contributed to the AE.

By definition, all solicited AEs at the injection site (local) will be considered related to the study vaccine administration.

12.1.3. Severity Criteria

All AEs, laboratory data, and fever will be coded for severity using a modified version of the DAIDS grading table, Version 2.0 (Attachment 1).

The severity of solicited AEs will be graded in the diary by the subject based on the severity assessment provided in the diary and then verified by the investigator using the DAIDS grading table.

For AEs not identified in the grading table (eg, diagnosis of HIV infection), the following guidelines will be applied:

Mild	Grade 1	Symptoms causing no or minimal interference with usual social and functional activities
Moderate	Grade 2	Symptoms causing greater than minimal interference with usual social and functional activities
Severe	Grade 3	Symptoms causing inability to perform usual social and functional activities
Potentially life-threatening	Grade 4	Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability
Fatal	Grade 5	For any AE where the outcome is death, the severity of the AE is classified as Grade 5

12.2. Situations Requiring Special Notification

Safety events of interest on a sponsor study vaccine that require expedited notification to the sponsor 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 subject exposure to the sponsor study vaccine, eg, name confusion)
- Exposure to a sponsor study vaccine from breastfeeding
- AESI of confirmed HIV infection[m]
- AESIs of TTS (including potential AESIs), to be reported to the sponsor within 24 hours of awareness.

Subject-specific situations requiring special notification should be recorded in the CRF. Any situation requiring special notification that meets the criteria of an SAE should be recorded on the SAE form. Additional reporting from the sites to IEC/IRB and HA should be performed according to local regulations.

[m] New HIV infection has to be notified to the sponsor within 24 hours of awareness, followed by the completed questionnaire to collect additional information/data.

12.3. Procedures

12.3.1. All AEs

All AEs and situations requiring special notification (see Section 12.2) will be reported from the time the signed and dated study-specific ICF is obtained until 28 days (including relevant visit window, if applicable) after first dose of study vaccine, and thereafter, pre-dose on the day of injection and for 28 days (including relevant visit window, if applicable) after each subsequent dose of study vaccine. Unsolicited AEs 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 on the CRF AE page.

All SAEs and AEs leading to discontinuation from the study vaccination (regardless of the causal relationship) and AESIs of confirmed HIV infection are to be reported for the duration 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.

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

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

The investigator will monitor and analyze study data including all AE and laboratory data as they become available and will make determinations regarding the severity of the adverse experiences and their relation to study vaccine. AEs will be deemed either related to study vaccine or not related to study vaccine, according to Section 12.1.2. To ensure that all AEs are captured in a timely manner, CRFs will be entered in real-time, and subjected to review to identify AEs which may invoke study pausing rules.

The investigator or designee must review both collected solicited events and other AE CRFs to insure prompt and complete identification of all events that require expedited reporting as SAEs, invoke study pausing rules or are other serious and unexpected events.

All AEs, regardless of seriousness, severity, or presumed relationship to vaccine, 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 AE to the study vaccine. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs 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 subject 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 subject 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
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. SAEs

All SAEs 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 SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours of their knowledge of the event. The initial and follow-up reports of an SAE should be made by facsimile (fax) or email.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation 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 vaccine or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject 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 an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (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 SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a subject in a study during the entire study period, whether or not the event is expected or associated with the vaccine, is considered an SAE.

12.3.3. 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.

12.3.3.1. HIV Infection

HIV testing will be carried out at times indicated in the TIME AND EVENTS SCHEDULE. Subjects will be tested for HIV infection at screening of the main study and baseline, and must be negative to be entered into the study. If possible, an assay that is US FDA-approved should be selected. At all other main study visits that include HIV testing, a study-specific HIV testing algorithm (detailed in the Laboratory Manual) will be followed. During the LTE phase, the study-specific HIV-testing algorithm described above will be followed as long as treatment assignment is blinded. Upon study unblinding (after the week 72 database lock), unblinded HIV and VISP results will be reported. In addition, subjects will need to be HIV negative to be eligible to receive the late boost vaccination and all post late boost visits include HIV testing. The study-specific HIV-testing algorithm described above for the main study will be followed as long as treatment assignment is blinded. Any subject with confirmed HIV infection must be discontinued from any further study vaccine administration, but should remain in the study and be followed up for safety and immunogenicity until the end of the study.

Confirmed HIV infection in a subject during the study is considered an AESI. All AESIs, irrespective if considered serious or not by the investigator, shall be reported to the sponsor immediately (see Section 12.2). An aggregate analysis will be performed either at the end of study and possible at interim time points during the study.

Test results performed to confirm the diagnosis will be forwarded to the study staff. Subjects who become HIV infected during the study, including the LTE phase, will be (see Section 9.4.2):

- Excluded from further vaccinations.
- Provided counseling and referred for medical treatment.
- Informed about observational studies monitoring subjects with HIV infection.
- Excluded from initiation of the LTE phase.

12.3.3.2. Thrombosis with Thrombocytopenia Syndrome

As described in Section 1.1.2.3, TTS has been observed following vaccination with the Janssen COVID-19 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.[1,7]

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 5,

  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[1]; British Society of Haematology 2021[8]; CDC 2021[10]). The use of heparin may be harmful and alternative treatments may be needed. Consultation with a hematologist is strongly recommended.

12.3.4. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects 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 SAEs and must be reported using the SAE Form. Any subject who becomes pregnant during the study must promptly discontinue further vaccinations but should continue participation in the study for follow-up (see Section 10.2).

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

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 subjects, 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 an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2). 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. VACCINE INFORMATION

14.1. Physical Description of Vaccines

The Ad26.Mos4.HIV, Clade C gp140, and Mosaic gp140 supplied for this study are formulated as:

Ad26.Mos4.HIV

Ad26.Mos4.HIV is a tetravalent vaccine containing the following 4 active pharmaceutical ingredients (APIs) pre-mixed in a 1:1:1:1 vp ratio:

- Ad26.Mos1.Gag-Pol = recombinant, replication-incompetent Ad26 encoding for Mosaic 1 (Mos1) HIV-1 Gag and Pol proteins, manufactured in PER.C6® cells (JNJ-55471494-AAA).
- Ad26.Mos2.Gag-Pol = recombinant, replication-incompetent Ad26 encoding Mosaic 2 (Mos2) HIV-1 Gag and Pol proteins, manufactured in PER.C6® cells (JNJ-55471520-AAA).
- Ad26.Mos1.Env = recombinant, replication-incompetent Ad26 encoding Mos1 HIV-1 Env protein, manufactured in PER.C6® cells (JNJ-55471468-AAA).
- Ad26.Mos2S.Env = recombinant, replication-incompetent Ad26 encoding modified (substitute, S) Mos2 HIV-1 Env protein, manufactured in PER.C6® cells (JNJ-64219324-AAA).

The Ad26.Mos4.HIV vaccine is formulated as a tetravalent vaccine, as a colorless to slightly yellowish/brownish solution for IM injection and will be provided in individual dosage vials at a concentration of $1x10^{11}$ vp/mL. Refer to the Investigator's Brochure for a list of excipients.[18]

Clade C gp140

Clade C gp140 is a monovalent vaccine containing the following API:

- Clade C gp140 Drug Substance (DS) is a trimeric, recombinant HIV-1 Env gp140 of Clade C, produced on a PER.C6® cell line. Aluminum phosphate suspension is used as adjuvant (JNJ-55471585-AAA: Clade C gp140 + aluminum phosphate adjuvant).

Clade C gp140 is formulated as a colorless to slightly yellowish/brownish solution for IM injection. Clade C gp140 will be supplied as a frozen liquid in a vial to be thawed prior to use, and will be practically free from particles. Clade C gp140 will be supplied at a nominal strength of either 1 mg/mL or 0.2 mg/mL. Refer to the Investigator's Brochure for a list of excipients.[19] The aluminum phosphate adjuvant will be supplied as a formulated refrigerated liquid suspension in a vial with a nominal aluminum content of 1.7 mg/mL. It will be mixed with Clade C gp140 at the site pharmacy prior to administration.

Mosaic gp140

Mosaic gp140 is a monovalent vaccine containing the following API:

- Mosaic gp140 DS is a trimeric, recombinant HIV-1 Env gp140 engineered to contain motifs of multiple HIV-1 variants, produced on a PER.C6® cell line. Aluminum phosphate suspension is used as adjuvant (JNJ-64219311-AAA: Mosaic gp140 + aluminum phosphate adjuvant).

Mosaic gp140 is formulated as a colorless to slightly yellowish/brownish solution for IM injection. Mosaic gp140 will be supplied as a frozen liquid in a vial to be thawed prior to use, and will be essentially free from particles. Mosaic gp140 will be supplied at a nominal strength of 1 mg/mL. Refer to the Investigator's Brochure for a list of excipients.[19] Mosaic gp140 will be mixed with Clade C gp140 at a 1:1 (volume/volume) ratio. The adjuvant will then be mixed in a 1:1 volume/volume ratio with the protein mixture prior to injection.

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 (GMP). All study vaccines will be packaged and labeled 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 Site Investigational Product Procedures Manual.

14.3. Preparation, Handling, and Storage

See the Site Investigational Product Procedures Manual for guidance on study vaccine preparation, handling, and storage. Study vaccine storage conditions are also mentioned on the clinical label.

Study vaccine must be stored in a secured location at controlled temperature with no access for unauthorized personnel. The study freezer and refrigerator must be equipped with a continuous temperature monitor and alarm. Study freezers should be equipped with back-up power systems. 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 subjects can be performed by a qualified healthcare provider from the study site (including the pharmacist who prepared the study vaccine) who will have, on the day of administration, no other study function related to safety, study data evaluation or recording of AEs for those subjects that he/she vaccinated on that day.

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 subject must be documented on the vaccine accountability form. All study vaccine will be stored and disposed of according to the sponsor's instructions.

Study vaccine 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 vaccine return form. When the study site is an authorized destruction unit and study vaccine supplies are destroyed on-site, this must also be documented on the vaccine return 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 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 subjects participating in the study. Study vaccine may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study vaccine 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 Brochure for Ad26.Mos.HIV and Clade C gp140
- Laboratory Manual, Study Procedures Manual
- IWRS Manual
- eDC Manual/electronic CRF completion guidelines and randomization instructions
- Sample ICF
- Subject diary
- TOU
- Social Impact Questionnaire
- Ruler (to measure diameter of any erythema and induration/swelling), thermometer
- Subject wallet cards
- Recruitment tools, as applicable

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects 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 subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

From screening to the final main study visit at Week 72, the total blood volume to be collected from each subject will be approximately 1,200 mL. The total blood volume to be collected during

the LTE phase (Group 1 and Group 2) in case the subject does not receive the late boost vaccination will be approximately 470 mL over a 3-year period. In case subjects receive the late boost vaccination, the total blood volume collected from the start of the LTE phase until 12 months post late boost will be approximately 1,201 mL. For subjects followed-up to 24 months post late boost, an additional 145,5 mL of blood will be collected. The total blood volume to be collected is considered to be within the US Department of HHS OHRP, and US FDA guidelines of 550 mL in any 8-week period. Volumes for humoral immunogenicity testing will be approximately 20 to 30 mL/visit and for cellular immunogenicity testing approximately 50-102 mL/visit except for the Visit 22c (subjects who received the late boost vaccination), during which 200 mL of blood will be collected.

See Section 1.2 for benefit-risk assessment.

Test of Understanding

The TOU is a short assessment of the subject's understanding of key aspects of the study. The test will help the study staff to determine how well subjects understand the study and their requirements for participation.

The TOU must be completed by all subjects, as the first assessment after signing of the ICF. The TOU is reviewed one-on-one with the subjects and a member of the study team. Subjects are allowed to retake the test as many times as necessary to achieve the passing score (≥90%) required for participation in the study. If a subject fails to achieve the passing score, further information and counseling will be provided by the study team member.

Any subject 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 participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects 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 subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects 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 subjects
- 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 subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has 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 subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects 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 AEs that are serious, unlisted/unexpected, and associated with the vaccine
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects 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 subjects, 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 subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF must be signed before performance of any study-related activity. The ICF that is used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and 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 subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects 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 subject will receive. Finally, they will be told that the investigator will maintain a subject 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 personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, which includes permission to obtain information about his or her survival status if applicable. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations and subsequent disease-related treatment, if needed.

The subject 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 subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Subjects will be asked for consent to provide optional samples for research (where local regulations permit). Refusal to participate in the optional research will not result in ineligibility for the study.

If the subject 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 subject is obtained.

For participation in the LTE phase of the study, an ICF appendix will be available. Upon sponsor unblinding at the Week 28 analysis, subjects randomized to Group 1 or Group 2 who have received all 4 vaccinations, will be asked to participate in the LTE phase and sign the ICF appendix for the LTE phase at Week 72. Subjects who attend their Week 72 visit prior to the sponsor's unblinding at the Week 28 analysis, will be enrolled in the LTE phase if they consent and sign the ICF appendix for the LTE phase and meet the eligibility criteria for the LTE phase. When the Week 28 sponsor unblinding subsequently occurs, subjects that started the LTE phase but turn out to have received placebo in the main study will be withdrawn from the LTE phase. If signing the ICF appendix is not possible at Week 72, signing should be performed at an extra visit (Visit 17bis) as soon as possible after Week 72 and at the latest before any assessment is done on the first visit of the LTE phase.

For participation who are willing to participate in the late boost vaccination extension to the LTE phase, an ICF appendix will be available. Subjects will be asked to sign the ICF appendix for the late boost vaccination and for the additional, optional, follow-up visit 24 months post late boost at the Visit 22a.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects 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 personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject 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 subject 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 DNA, immunogenicity, and social impact questionnaire research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects 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

Each study subject will be asked to consent voluntarily for their blood samples to be stored for other research studies that may be done after this study is completed. Future testing may involve deoxyribonucleic acid/ribonucleic acid (DNA/RNA) tests. For subjects unwilling to have their blood samples stored for future use, they can consent to participate in this study only, without having their blood samples stored for future testing (see Section 10.4). In this case, their blood samples will be destroyed after all the tests specified for this study have been concluded.

All samples, for which consent has been obtained and for which additional material is available after study-specified testing is complete, will be stored for future testing. All applicable approvals will be sought before any such samples are used for analysis not specified in the protocol or a protocol amendment approved by the IRB.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (see Section 10.4).

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 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 subjects, 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 IRB/IEC (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 sponsor 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 sponsor 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 vaccine 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, subject 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 subject:

- 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. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used.

The investigator must also complete a subject screening log, which reports on all subjects 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: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; vaccine receipt/dispensing/return records; vaccine administration information; and date of study completion and reason for early discontinuation of vaccine 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. 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 may not be limited to that found in the CRF. Data in this system may be considered source documentation.

The subject's diary used to collect information regarding solicited events after vaccination will be considered source data.

17.6. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject 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.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject 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, and 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 CRFs 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 subject, 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 may 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 the 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 subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject 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 subjects by the investigator
- Discontinuation of further vaccine 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. Subject 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

All information, including but not limited to information regarding Ad26.Mos4.HIV, Clade C gp140, and Mosaic gp140 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 generated as a result of this study, are considered confidential and remain the sole property of the sponsor and/or its partners. 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 Ad26.Mos4.HIV, Clade C gp140, and Mosaic gp140, 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 any 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 subject 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 with its partners shall have the right to publish such primary (multicenter) 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 for review at least 60 days before submission for publication or presentation. 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 multicenter 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 multicenter 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 multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE 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 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.

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.[n] 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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[n] An on-site visit is defined as a visit during which the participant and the qualified 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 site staff (telephone or video call).

A home visit is defined as a visit during which the participant and the qualified 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.

Vaccination Visits

- For the late boost vaccination, vaccination outside of the window can be assessed on a case-by-case basis and will ultimately be approved by the sponsor. The out of window vaccination will be documented as 'COVID-19-related'.

Other Study Visits and Assessments

- Participants may have remote visits for reactogenicity and safety assessments until such time that on-site visits can be resumed. The actual visit date should be captured in the eCRF according to the eCRF completion guidelines.

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.

Informed Consent:

- Consenting and re-consenting of participants for the measures taken (including also remote consenting by phone or video consultation) will be performed as applicable and according to local guidance for informed consent applicable during the COVID-19 pandemic. The process is to be documented in the source documents.

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: Division of Aids Table for Grading the Severity of Adult and Pediatric AEs – Including Modifications

The Division of AIDS Table for Grading the Severity of Adult and Pediatric AEs (Version 2.0, November 2014), or 'DAIDS grading table', is a descriptive terminology to be utilized for AE reporting in this study. A grading (severity) scale is provided for each AE term. Modifications made by the sponsor are footnoted.

General Instructions

Estimating Severity Grade for Parameters Not Identified in the Grading Table

If the need arises to grade a clinical AE that is not identified in the DAIDS grading table, use the category 'Estimating Severity Grade' located at the top of the table on the following page. In addition, all deaths related to an AE are to be classified as Grade 5.

Grading Adult and Pediatric AEs

The DAIDS grading table includes parameters for grading both adult and pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both adult and pediatric populations, separate sets of parameters for adult and/or pediatric populations (with specified respective age ranges) are provided. If there is no distinction in the table between adult and pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both adult and pediatric events of that type.

Determining Severity Grade

If the severity of an AE could fall under either 1 of 2 grades (eg, the severity of an AE could be either Grade 2 or Grade 3), select the higher of the 2 grades for the AE.

Laboratory normal ranges should be taken into consideration to assign gradings to a laboratory value.

Definitions

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. Young Children Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.

Intervention — Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an AE.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

MAJOR CLINICAL CONDITIONS				
CARDIOVASCULAR				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1]				
Hypertension *(with the lowest reading taken after repeat testing during a visit)*				
≥18 years of age	140 to <160 mmHg systolic OR 90 to <100 mmHg diastolic	≥160 to <180 mmHg systolic OR ≥100 to <110 mmHg diastolic	≥180 mmHg systolic OR ≥110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR Hospitalization indicated
<18 years of age	>120/80 mmHg	≥95th to <99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (eg, malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Tachycardia[o] - beats per minute	101 - 115	116 - 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia[a] - beats per minute	50 - 54	45 - 49	< 45	ER visit or hospitalization for arrhythmia
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (eg, hypoxemia) OR Intervention indicated (eg, oxygen)	Life-threatening consequences OR Urgent intervention indicated (eg, vasoactive medications, ventricular assist device, heart transplant)

[o] Modification of DAIDS toxicity table consistent with FDA guidance "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007

Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of >2 units packed RBCs (for children, packed RBCs >10 cc/kg) indicated

[1] Blood pressure norms for children <18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged PR Interval or AV Block *Report only one* *>16 years of age* *≤16 years of age*	PR interval 0.21 to <0.25 seconds 1st degree AV block (PR interval > normal for age and rate)	PR interval ≥0.25 seconds OR Type I 2nd degree AV block Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥3.0 seconds Type II 2nd degree AV block OR Ventricular pause ≥3.0 seconds	Complete AV block Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	>0.47 to 0.50 seconds	>0.50 seconds OR ≥0.06 seconds above baseline	Life-threatening consequences (eg, Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (eg, pulmonary embolism, thrombus)

[2] As per Bazett's formula.

DERMATOLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (eg, oral antibiotics, antifungals, antivirals)	IV treatment indicated (eg, IV antibiotics, antifungals, antivirals)	Life-threatening consequences (eg, sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae OR superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.

ENDOCRINE AND METABOLIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

GASTROINTESTINAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (eg, diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea *≥1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
<1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (eg, liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (eg, hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (eg, aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (eg, circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
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)

MUSCULOSKELETAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥30 years of age* *<30 years of age*	BMD t-score -2.5 to -1 BMD z-score -2 to -1	NA NA	NA NA	NA NA
Osteoporosis[6] *≥30 years of age* *<30 years of age*	NA NA	BMD t-score <-2.5 BMD z-score <-2	Pathologic fracture (eg, compression fracture causing loss of vertebral height) Pathologic fracture (eg, compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

NEUROLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (eg, stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *<18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures				
New Onset Seizure *≥18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
<18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting <5 minutes with <24 hours postictal state	Seizure lasting 5 to <20 minutes with <24 hours postictal state	Seizure lasting ≥20 minutes OR >24 hours postictal state	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (eg, severity or focality)	Prolonged and repetitive seizures (eg, status epilepticus) OR Difficult to control (eg, refractory epilepsy)
Syncope	Near syncope without loss of consciousness (eg, pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

PREGNANCY, PUERPERIUM, AND PERINATAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to <37 weeks gestational age	Delivery at 28 to <34 weeks gestational age	Delivery at 24 to <28 weeks gestational age	Delivery at <24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A delivery of a live-born neonate occurring at ≥20 to <37 weeks gestational age.
[8] Definition: A clinically recognized pregnancy occurring at <20 weeks gestational age.

PSYCHIATRIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

RESPIRATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥70 to <80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to <70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to <50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow <25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to <95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry <90%	Respiratory failure with ventilator support indicated (eg, CPAP, BPAP, intubation)

SENSORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hearing Loss *≥12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (>80 dB at 2 kHz and above) OR Non-serviceable hearing (ie, >50 dB audiogram and <50% speech discrimination)
<12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	>20 dB hearing loss at ≤4 kHz	>20 dB hearing loss at >4 kHz	>20 dB hearing loss at ≥3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medicamylasal intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SYSTEMIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[9]	Mild signs and symptoms AND Therapy (ie, antibody infusion) interruption not indicated	Therapy (ie, antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (eg, requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
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 to <104.0°F	≥40.0°C or ≥104.0°F
Pain[10] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[11]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (eg, antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (eg, steroids or IV fluids)	Life-threatening consequences (eg, requiring pressor or ventilator support)
Underweight[12] *>5 to 19 years of age* *2 to 5 years of age* *<2 years of age*	NA NA NA	WHO BMI z-score <-2 to ≤-3 WHO Weight-for-height z-score <-2 to ≤-3 WHO Weight-for-length z-score <-2 to ≤-3	WHO BMI z-score <-3 WHO Weight-for-height z-score <-3 WHO Weight-for-length z-score <-3	WHO BMI z-score <-3 with life-threatening consequences WHO Weight-for-height z-score <-3 with life-threatening consequences WHO Weight-for-length z-score <-3 with life-threatening consequences

[9] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[10] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
[11] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[12] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants >5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤5 years of age.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Weight Loss (excludes postpartum weight loss)	NA	5 to <9% loss in body weight from baseline	≥9 to <20% loss in body weight from baseline	≥20% loss in body weight from baseline OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)

URINARY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

SITE REACTIONS TO INJECTIONS AND INFUSIONS				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Injection Site Pain or Tenderness *Report only one*	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 usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[13] *Report only one* *>15 years of age*	2.5 to <5 cm in diameter OR 6.25 to <25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥5 to <10 cm in diameter OR ≥25 to <100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥10 cm in diameter OR ≥100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤15 years of age	≤2.5 cm in diameter	>2.5 cm in diameter with <50% surface area of the extremity segment involved (eg, upper arm or thigh)	≥50% surface area of the extremity segment involved (eg, upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*
≤15 years of age	Same as for **Injection Site Erythema or Redness,** *≤15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in <48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[13] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

LABORATORY VALUES				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acidosis	NA	pH ≥7.3 to <LLN	pH <7.3 without life-threatening consequences	pH <7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to <LLN *30 to <LLN*	≥2.0 to <3.0 *≥20 to <30*	<2.0 *<20*	NA
Alkaline Phosphatase, High	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Alkalosis	NA	pH > ULN to ≤7.5	pH >7.5 without life-threatening consequences	pH >7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to <1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to <5.0 x ULN	≥5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Bilirubin ***Direct Bilirubin[14], High*** *>28 days of age* *≤28 days of age* ***Total Bilirubin, High*** *>28 days of age* *≤28 days of age*	 NA ULN to ≤1 mg/dL 1.1 to <1.6 x ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates	 NA >1 to ≤1.5 mg/dL 1.6 to <2.6 x ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates	 >ULN >1.5 to ≤2 mg/dL 2.6 to < 5.0 x ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates	 >ULN with life-threatening consequences (eg, signs and symptoms of liver failure) >2 mg/dL ≥5.0 x ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) *≥7 days of age* *<7 days of age*	10.6 to <11.5 *2.65 to <2.88* 11.5 to <12.4 *2.88 to <3.10*	11.5 to <12.5 *2.88 to <3.13* 12.4 to <12.9 *3.10 to <3.23*	12.5 to <13.5 *3.13 to <3.38* 12.9 to <13.5 *3.23 to <3.38*	≥13.5 *≥3.38* ≥13.5 *≥3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	>ULN to <6.0 *>ULN to <1.5*	6.0 to <6.4 *1.5 to <1.6*	6.4 to <7.2 *1.6 to <1.8*	≥7.2 *≥1.8*
Calcium, Low (mg/dL; *mmol/L*) *≥7 days of age* *<7 days of age*	7.8 to <8.4 *1.95 to <2.10* 6.5 to <7.5 *1.63 to <1.88*	7.0 to <7.8 *1.75 to <1.95* 6.0 to <6.5 *1.50 to <1.63*	6.1 to <7.0 *1.53 to <1.75* 5.50 to <6.0 *1.38 to <1.50*	<6.1 *<1.53* <5.50 *<1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	<LLN to 4.0 *<LLN to 1.0*	3.6 to <4.0 *0.9 to <1.0*	3.2 to <3.6 *0.8 to <0.9*	<3.2 *<0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory

[14] Direct bilirubin >1.5 mg/dL in a participant <28 days of age should be graded as grade 2, if <10% of the total bilirubin.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Creatine Kinase, High	3 to <6 x ULN	6 to <10 x ULN	10 to <20 x ULN	≥20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	>1.3 to 1.8 x ULN OR Increase of >0.3 mg/dL above baseline	>1.8 to <3.5 x ULN OR Increase of 1.5 to <2.0 x above baseline	≥3.5 x ULN OR Increase of ≥2.0 x above baseline
Creatinine Clearance[15] or eGFR, Low *Report only one*	NA	<90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to <30% decrease from baseline	<60 to 30ml/min or ml/min/1.73 m^2 OR ≥30 to <50% decrease from baseline	<30 ml/min or ml/min/1.73 m^2 OR ≥50% decrease from baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)	110 to 125 *6.11 to <6.95*	>125 to 250 *6.95 to <13.89*	>250 to 500 *13.89 to <27.75*	>500 *≥27.75*
Fasting, High				
Nonfasting, High	116 to 160 *6.44 to <8.89*	>160 to 250 *8.89 to <13.89*	>250 to 500 *13.89 to <27.75*	>500 *≥27.75*
Glucose, Low (mg/dL; *mmol/L*)	55 to 64 *3.05 to 3.55*	40 to <55 *2.22 to <3.05*	30 to <40 *1.67 to <2.22*	<30 *<1.67*
≥1 month of age				
<1 month of age	50 to 54 *2.78 to 3.00*	40 to < 50 *2.22 to <2.78*	30 to <40 *1.67 to <2.22*	< 30 *<1.67*
Lactate, High	ULN to <2.0 x ULN without acidosis	≥2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
Lipase, High	1.1 to <1.5 x ULN	1.5 to <3.0 x ULN	3.0 to <5.0 x ULN	≥5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High	200 to <240 *5.18 to <6.19*	240 to <300 *6.19 to <7.77*	≥300 *≥7.77*	NA
≥18 years of age				
<18 years of age	170 to <200 *4.40 to <5.15*	200 to <300 *5.15 to <7.77*	≥300 *≥7.77*	NA
LDL, Fasting, High	130 to <160	160 to <190	≥190	NA
≥18 years of age	*3.37 to <4.12*	*4.12 to <4.90*	*≥4.90*	
>2 to <18 years of age	110 to <130 *2.85 to <3.34*	130 to <190 *3.34 to <4.90*	≥190 *≥4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to <1,000 *>5.7 to 11.4*	>1,000 *>11.4*
Magnesium[16], Low (mEq/L; *mmol/L*)	1.2 to <1.4 *0.60 to <0.70*	0.9 to <1.2 *0.45 to <0.60*	0.6 to <0.9 *0.30 to <0.45*	<0.6 *<0.30*
Phosphate, Low (mg/dL; *mmol/L*)	2.0 to < LLN *0.81 to < LLN*	1.4 to < 2.0 *0.65 to < 0.81*	1.0 to <1.4 *0.32 to <0.65*	<1.0 *<0.32*
>14 years of age				
1 to 14 years of age	3.0 to <3.5 *0.97 to <1.13*	2.5 to <3.0 *0.81 to <0.97*	1.5 to <2.5 *0.48 to <0.81*	<1.5 *<0.48*
<1 year of age	3.5 to <4.5 *1.13 to <1.45*	2.5 to <3.5 *0.81 to <1.13*	1.5 to <2.5 *0.48 to <0.81*	<1.5 *<0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to <6.0 *5.6 to <6.0*	6.0 to <6.5 *6.0 to <6.5*	6.5 to <7.0 *6.5 to <7.0*	≥7.0 *≥7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to <3.4 *3.0 to <3.4*	2.5 to <3.0 *2.5 to <3.0*	2.0 to <2.5 *2.0 to <2.5*	<2.0 *<2.0*

[15] Use the applicable formula (ie, Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).
[16] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to <150 *146 to <150*	150 to <154 *150 to <154*	154 to <160 *154 to <160*	≥160 *≥160*
Sodium, Low (mEq/L; *mmol/L*)	130 to <135 *130 to <135*	125 to <130 *125 to <135*	121 to <125 *121 to <125*	≤120 *≤120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to <10.0 *0.45 to <0.59*	10.0 to <12.0 *0.59 to <0.71*	12.0 to <15.0 *0.71 to <0.89*	≥15.0 *≥0.89*

HEMATOLOGY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *>5 years of age (not HIV infected)*	300 to <400 *300 to <400*	200 to <300 *200 to <300*	100 to <200 *100 to <200*	<100 *<100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *>5 years of age (not HIV infected)*	600 to <650 *0.600 x 10^9 to <0.650 x 10^9*	500 to <600 *0.500 x 10^9 to <0.600 x 10^9*	350 to <500 *0.350 x10^9 to <0.500 x 10^9*	<350 *<0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *>7 days of age* *2 to 7 days of age* *≤1 day of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9* 1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9* 4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9* 1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9* 3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9* 750 to 999 *0.750 x 10^9 to 0.999 x 10^9* 1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	<400 *<0.400 x 10^9* <750 *<0.750 x 10^9* <1,500 *<1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR 0.75 to <1.00 x LLN	75 to <100 *0.75 to <1.00* OR ≥0.50 to <0.75 x LLN	50 to <75 *0.50 to <0.75* OR 0.25 to <0.50 x LLN	<50 *<0.50* OR <0.25 x LLN OR Associated with gross bleeding
Hemoglobin[17], Low (g/dL; *mmol/L*)[18] *≥13 years of age (male only)* *≥13 years of age (female only)* *57 days of age to <13 years of age (male and female)* *36 to 56 days of age (male and female)* *22 to 35 days of age (male and female)* *8 to ≤21 days of age (male and female)* *≤7 days of age (male and female)*	10.0 to 10.9 *6.19 to 6.76* 9.5 to 10.4 *5.88 to 6.48* 9.5 to 10.4 *5.88 to 6.48* 8.5 to 9.6 *5.26 to 5.99* 9.5 to 11.0 *5.88 to 6.86* 11.0 to 13.0 *6.81 to 8.10* 13.0 to 14.0 *8.05 to 8.72*	9.0 to <10.0 *5.57 to <6.19* 8.5 to <9.5 *5.25 to <5.88* 8.5 to <9.5 *5.25 to <5.88* 7.0 to <8.5 *4.32 to <5.26* 8.0 to <9.5 *4.94 to <5.88* 9.0 to <11.0 *5.57 to <6.81* 10.0 to <13.0 *6.19 to <8.05*	7.0 to <9.0 *4.34 to <5.57* 6.5 to <8.5 *4.03 to <5.25* 6.5 to <8.5 *4.03 to <5.25* 6.0 to <7.0 *3.72 to <4.32* 6.7 to <8.0 *4.15 to <4.94* 8.0 to <9.0 *4.96 to <5.57* 9.0 to <10.0 *5.59 to <6.19*	<7.0 *<4.34* <6.5 *<4.03* <6.5 *<4.03* <6.0 *<3.72* <6.7 *<4.15* <8.0 *<4.96* <9.0 *<5.59*
INR, High (not on anticoagulation therapy)	1.1 to <1.5 x ULN	1.5 to <2.0 x ULN	2.0 to <3.0 x ULN	≥3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to <10.0%	10.0 to <15.0%	15.0 to <20.0%	≥20.0%

[17] Male and female sex are defined as sex at birth.

[18] The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
PTT, High (not on anticoagulation therapy)	1.1 to <1.66 x ULN	1.66 to <2.33 x ULN	2.33 to <3.00 x ULN	≥3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to <124,999 *100.000 x 10^9 to <124.999 x 10^9*	50,000 to <100,000 *50.000 x 10^9 to <100.000 x 10^9*	25,000 to <50,000 *25.000 x 10^9 to <50.000 x 10^9*	<25,000 *<25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to <1.25 x ULN	1.25 to <1.50 x ULN	1.50 to <3.00 x ULN	≥3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
>7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	<1,000 *<1.000 x 10^9*
≤7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	<2,500 *<2.500 x 10^9*

URINALYSIS				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤250 mg	2+ or >250 to ≤500 mg	>2+ or >500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to <10 RBCs per high power field	≥10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

APPENDIX A: TOTAL BILIRUBIN TABLE FOR TERM AND PRETERM NEONATES

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[19], High (mg/dL; *µmol/L*) [20]				
Term Neonate[21]				
<24 hours of age	4 to <7 *68.4 to <119.7*	7 to <10 *119.7 to <171*	10 to <17 *171 to <290.7*	≥17 *≥290.7*
24 to <48 hours of age	5 to <8 *85.5 to <136.8*	8 to <12 *136.8 to <205.2*	12 to <19 *205.2 to <324.9*	≥19 *≥324.9*
48 to <72 hours of age	8.5 to <13 *145.35 to <222.3*	13 to <15 *222.3 to <256.5*	15 to <22 *256.5 to <376.2*	≥22 *≥376.2*
72 hours to <7 days of age	11 to <16 *188.1 to <273.6*	16 to <18 *273.6 to <307.8*	18 to <24 *307.8 to <410.4*	≥24 *≥410.4*
7 to 28 days of age (breast feeding)	5 to <10 *85.5 to <171*	10 to <20 *171 to <342*	20 to <25 *342 to <427.5*	≥25 *≥427.5*
7 to 28 days of age (not breast feeding)	1.1 to <1.6 x ULN	1.6 to <2.6 x ULN	2.6 to <5.0 x ULN	≥5.0 x ULN
Preterm Neonate[21]				
35 to <37 weeks gestational age	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to <35 weeks gestational age and <7 days of age	NA	NA	10 to <14 *171 to <239.4*	≥14 *≥239.4*
28 to <32 weeks gestational age and <7 days of age	NA	NA	6 to <10 *102.6 to <171*	≥10 *≥171*
<28 weeks gestational age and <7 days of age	NA	NA	5 to <8 *85.5 to <136.8*	≥8 *≥136.8*
7 to 28 days of age (breast feeding)	5 to <10 *85.5 to <171*	10 to <20 *171 to <342*	20 to <25 *342 to <427.5*	≥25 *≥427.5*
7 to 28 days of age (not breast feeding)	1.1 to <1.6 x ULN	1.6 to <2.6 x ULN	2.6 to <5.0 x ULN	≥5.0 x ULN

[19] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.
[20] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.
[21] Definitions: Term is defined as ≥37 weeks gestational age; near-term, as ≥35 weeks gestational age; preterm, as <35 weeks gestational age; and neonate, as 0 to 28 days of age.

Attachment 2: HIV-risk Assessment

The following are intended as guidelines for the investigator to help identify potential vaccine trial participants at "low risk" for HIV infection (1) in the US and Switzerland and (2) in South Africa, respectively. Outside these countries, in addition to minimum requirements specified by the first two criteria defined below ("Have oral, vaginal or anal intercourse with an HIV-infected partner, or a partner who uses injection drugs" and "Give or receive money, drugs, gifts or services in exchange for oral, vaginal or anal sex"), low risk criteria as defined by local standards would be applicable.

HIV VACCINE
TRIALS NETWORK

HVTN Low Risk Guidelines
August 1, 2013

(1)

The following are intended as guidelines for the investigator to help identify potential vaccine trial participants at "low risk" for HIV infection in the US and Switzerland. These guidelines are based on behaviors within the last 6-12 months prior to enrollment; however, it may be appropriate to consider a person's behavior over a longer period of time than specified to assess the person's likelihood of maintaining low risk behavior. *Some volunteers may not be appropriate for enrollment even if they meet these guidelines.* These guidelines should be supplemented and interpreted with local epidemiologic information about HIV prevalence in your area and community networks. The investigator may review the risk level of any volunteer with the site PI and/or the Protocol Safety Review Team.

A volunteer may be appropriate for inclusion if he/she meets these guidelines:

1. SEXUAL BEHAVIORS

In the **last 12 months** did not:

- Have oral, vaginal, or anal intercourse with an HIV-infected partner, or a partner who uses injection drugs
- Give or receive money, drugs, gifts, or services in exchange for oral, vaginal, or anal sex

AND

In the **last 6 months** has abstained from penile/anal or penile/vaginal intercourse, OR

In the **last 6 months**:

- Had 4 or fewer partners of the opposite birth sex for vaginal and/or anal intercourse, OR

Is an MSM (person born male with partner(s) born male) who, in the **last 12 months**:

- Had 2 or fewer MSM partners for anal intercourse and had no unprotected anal sex with MSM, OR
- Had unprotected anal intercourse with only 1 MSM partner, within a monogamous relationship lasting at least 12 months (during which neither partner had any other partners). If the monogamous relationship ended, the volunteer may then have had protected anal intercourse with 1 other MSM partner (total 2 or fewer partners in the last 12 months).

Is a transgender person, regardless of the point on the transition spectrum, having sex with men (born male) and/or other transgender persons, who **in the last 12 months**:

- Had 2 or fewer partners for anal or vaginal intercourse, and had no unprotected anal or vaginal sex, OR
- Had unprotected anal or vaginal intercourse sex with 1 partner only within a monogamous relationship lasting at least 12 months (during which neither partner had any other partners). If the monogamous relationship ended, may then have had protected anal or vaginal sex with 1 other partner (total 2 or fewer partners in the last 12 months).

AND

Uses or intends to use condoms in situations which may include penile/anal or penile/vaginal intercourse with new partners of unknown HIV status, occasional partners, partners outside a primary relationship, and/or partners known to have other partners.

2. NON-SEXUAL BEHAVIORS

In the **last 12 months** did not:

- Inject drugs or other substances without a prescription
- Use cocaine, methamphetamine, or excessive alcohol, which in the investigator's judgment, rendered the participant at greater than low risk for acquiring HIV infection

The investigator's judgment should consider local epidemiologic information about HIV prevalence in the area and community networks.

A volunteer is NOT appropriate for inclusion if he/she:

Acquired an STI (ie, new infection) in the last 12 months:

- Syphilis
- Gonorrhea
- Non-gonococcal urethritis
- HSV-2
- Chlamydia
- Pelvic inflammatory disease (PID)
- Trichomonas
- Mucopurulent cervicitis
- Epididymitis
- Proctitis
- Lymphogranuloma venereum
- Chancroid
- Hepatitis B

(2)

LOW RISK GUIDELINES for SOUTH AFRICAN SITES

September 4, 2012

The following are intended as guidelines for the investigator to help identify potential vaccine trial participants at "low risk" for HIV infection. These guidelines are based on behaviors within the last 12 months prior to enrollment; however, it may be appropriate to consider a person's behavior over a longer period of time than specified to assess the person's likelihood of maintaining low risk behavior. Some volunteers may not be appropriate for enrollment even if they meet these guidelines. These guidelines should be supplemented and interpreted with local epidemiologic information about HIV prevalence in your area and community networks. The investigator may review the risk level of any volunteer with the site PI and/or protocol team.

ASSESSMENT OF SEXUAL BEHAVIORS

Consider whether a volunteer would be appropriate for inclusion if, within 12 months prior to enrollment, the person:

- Was sexually abstinent, or
- Was in a mutually monogamous relationship with a partner with a known HIV-uninfected status, or
- Had one partner believed to be HIV-uninfected with whom he/she regularly used condoms for vaginal and anal intercourse.

Exclude a volunteer if:

Within the 12 months prior to enrollment: a history of newly acquired syphilis, gonorrhea, chlamydia, trichomoniasis, active HSV lesions, chancroid, pelvic inflammatory disease (PID), genital sores or ulcers, cervicitis, genital warts of the labia minora, vagina, or cervix, or any other symptomatic genital warts.

Attachment 3: Test of Understanding[P]

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

True ☐	False ☐	1. The vaccines you will receive in this study protect against HIV.
True ☐	False ☐	2. You will need to come to the clinic for 4 scheduled visits over the next 1.5 years.
True ☐	False ☐	3. The vaccines in this study can give you HIV.
True ☐	False ☐	4. One purpose of this study is to determine if these vaccines are safe to administer to humans.
True ☐	False ☐	5. Participants in this study will need to avoid engaging in activities that may expose them to HIV infection.
True ☐	False ☐	6. You may take other experimental (test) products while you are taking part in this study.
True ☐	False ☐	7. 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.
True ☐	False ☐	8. Women participating in this study are permitted to become pregnant starting 3 months after the last vaccination.
True ☐	False ☐	9. A participant in this study may experience side effects after vaccination.
True ☐	False ☐	10. Some participants in this study may develop a positive HIV-test result, despite the fact that they are not HIV infected.

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

Attachment 4: Social Impact Questionnaire

Vaccine Research Center (VRC) Social Impact Case Report Form[q]

	Social Impact Question	Yes or No	If Yes, did you consider this to be harmful to you?
1. **Personal Relationships**	Did you have problems with family, friends, significant others or sex partners because of participation in this clinical trial?	☐ Yes ☐ No	☐ Yes ☐ No
	Comment: ☐ resolved; ☐ continuing		☐ mild; ☐ moderate; ☐ major
2. **Travel or Immigration**	Did you have problems getting legal permission to travel to or from another country, such as being denied a visa, or having problems with immigration/naturalization because of participation in this clinical trial?	☐ Yes ☐ No	☐ Yes ☐ No
	Comment: ☐ resolved; ☐ continuing		☐ mild; ☐ moderate; ☐ major
3. **Employment**	Have you been turned down for a new job, lost a job, or had other problems at work because of participation in this clinical trial?	☐ Yes ☐ No	☐ Yes ☐ No
	Comment: ☐ resolved; ☐ continuing		☐ mild; ☐ moderate; ☐ major
4. **Education**	Have you been turned down by an educational program, told to leave an educational program, or had other problems at school because of participation in this clinical trial?	☐ Yes ☐ No	☐ Yes ☐ No
	Comment: ☐ resolved; ☐ continuing		☐ mild; ☐ moderate; ☐ major
5. **Medical or Dental**	Have you been refused medical or dental care or treated negatively by a health care provider because of participation in this clinical trial?	☐ Yes ☐ No	☐ Yes ☐ No
	Comment: ☐ resolved; ☐ continuing		☐ mild; ☐ moderate; ☐ major
6. Health Insurance	Have you lost health insurance, had a problem getting new health insurance, or had other problems related to health insurance because of participation in this clinical trial?	☐ Yes ☐ No	☐ Yes ☐ No
	Comment: ☐ resolved; ☐ continuing		☐ mild; ☐ moderate; ☐ major
7. **Life Insurance**	Have you lost life insurance, had a problem getting new life insurance, or had other problems related to life insurance because of participation in this clinical trial?	☐ Yes ☐ No	☐ Yes ☐ No
	Comment: ☐ resolved; ☐ continuing		☐ mild; ☐ moderate; ☐ major
8. **Housing**	Have you had trouble getting or keeping housing, or had other problems related to housing because of participation in this clinical trial?	☐ Yes ☐ No	☐ Yes ☐ No
	Comment: ☐ resolved; ☐ continuing		☐ mild; ☐ moderate; ☐ major
9. **Military/Other Government Agency**	Have you had a problem with the military or any other government agency because of participation in this clinical trial?	☐ Yes ☐ No	☐ Yes ☐ No
	Comment: ☐ resolved; ☐ continuing		☐ mild; ☐ moderate; ☐ major
10. **Other**	Have you had any other problem not covered by the other questions because of anything related to participation in this clinical trial?	☐ Yes ☐ No	☐ Yes ☐ No
	Comment: ☐ resolved; ☐ continuing		☐ mild; ☐ moderate; ☐ major

[q] Adaptations to the social impact questionnaire are allowed for local purposes, after IRB and sponsor approval.

Attachment 5: 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

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-Oct-2021 12:46:49 (GMT)	Document Approval