Janssen Vaccines & Prevention B.V. *

Clinical Protocol

A Phase 1/2a Study to Evaluate the Safety/Tolerability and Immunogenicity of Homologous Ad26 Mosaic Vector Vaccine Regimens or Ad26 Mosaic and MVA Mosaic Heterologous Vector Vaccine Regimens, with High-Dose, Low-Dose or no Clade C gp140 Protein Plus Adjuvant for HIV Prevention

Protocol HIV-V-A004 Amendment 5 (IPCAVD009); Phase 1/2a

JNJ-55471468, JNJ-55471494, JNJ-55471520, JNJ-55471533, JNJ-55471572, JNJ55471585

*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.

This study will be conducted under US Food and Drug Administration IND regulations (21 CFR Part 312).

Status: Approved
Date: 21 December 2016
EDMS number: EDMS-ERI-102817395, 9.0

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	26 Sep 2014
Amendment 1	17 Dec 2014
Amendment 2	06 Feb 2015
Amendment 3	15 Apr 2015
Amendment 4	20 Aug 2015
Amendment 5	This document

Amendments are listed beginning with the most recent amendment.

Amendment 5 (This document)

The overall reason for the amendment: This amendment specifies the assessments to be performed in the long-term extension phase for the treatment groups selected based on the Week 28 results.

Rationale: Following results of Week 28, treatment groups 1 and 2 were selected for additional 5 years of follow up (Long Term Extension phase) from Week 96 to 336 post-vaccination to assess durability of immunologic responses.

SYNOPSIS
TIME AND EVENTS SCHEDULE
ABBREVIATIONS
2.1 Objectives
3.1 Overview of Study Design
4.3 Prohibitions and Restrictions
5 VACCINE ALLOCATION AND BLINDING
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10.4 Withdrawal from the Study
11 STATISTICAL METHODS
11.6 Interim Analysis
12.1.1 Adverse Event Definitions and Classifications
12.3.1 All Adverse Events
16.2.3 Informed Consent

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

Title Page
1 INTRODUCTION
14.1 Physical Description of Study Vaccines
INVESTIGATOR AGREEMENT

Rationale: minor corrections.

12.3.2 Serious Adverse Events	Administrative changes
16.2.2 Independent Ethics Committee or Institutional Review Board	Administrative Changes
17.5 Case Report Form Completion	Removed statement that all data should be recorded in CRF.

Amendment 4 (20 Aug 2015)

The overall reason for the amendment: To avoid unnecessary pausing of vaccination for Data Monitoring Committee (DMC) review of certain reactogenicity events, common to most vaccines.

Rationale: As vaccinations in general are expected to cause benign reactogenicity events ranging from Grade 1 to Grade 3 and up to about a maximum of 72 hours post-vaccination, it is in the opinion of the clinical team, with full support of Protocol Safety Review Team (PSRT) and DMC members, that it would make sense to concentrate the in-depth reviews by DMC with mandatory vaccination pauses for the vaccine-related Grade 3 solicited adverse events (AEs) as follows: DMC review with immediate pause in case ≥3 subjects experience a similar vaccine-related Grade 3 solicited AE that would last longer than 72 hours (Table 8; footnote 3). In addition, redaction of Table 8 has been done to enhance readability.

11.9 Study Holding Rules

Rationale: Minor changes.

4.1 Inclusion Criteria
4.2 Exclusion Criteria
Attachment 1

Amendment 3 (15 Apr 2015)

The overall reason for the amendment: A clear distinction has been made between single and double methods of contraception.

Rationale: Taking into account the very high effectiveness of long-acting reversible contraceptive methods; a single contraceptive method is deemed appropriate when using these methods. A double method should be used for all other contraceptive methods. The text has been expanded with the necessary details, and a summary table has been added.

4.1 Inclusion Criteria

Rationale: To account for values in peri-menstrual women, the blood urinalysis laboratory criterion for inclusion has been set from <1+ to <2+ for women.

4.1 Inclusion Criteria

Rationale: Depending on local collection processes, some variations may exist in blood volumes that will be collected. Therefore, the specific daily blood volume for the safety laboratory tests has been removed from the protocol. However, indicative blood volumes are included in the Study Procedures Manual. Total approximate blood volume per visit is still to be respected.

TIME AND EVENTS SCHEDULE

Rationale: It is clarified that the restriction "the vaccine administrator should have no other study function related to safety, study data evaluation, or recording of AEs" is limited to the study functions related to those subjects who received a study vaccine on that particular visit.

5 VACCINE ALLOCATION AND BLINDING

7 TREATMENT COMPLIANCE

9.1.4 Vaccination (Weeks 0, 12, 24, and 48)

14.3 Preparation, Handling, and Storage

Rationale: It is clarified that women with a history of toxic shock syndrome are excluded from the cervico-vaginal part of mucosal sampling only and that subjects who had surgical sex-reassignment are excluded from cervico-vaginal mucosal and semen sampling. It is further clarified that estradiol and progesterone levels are measured in serum. In addition, it is clarified that the female hormone tests are only for women who consent to the cervico-vaginal mucosal sampling.

TIME AND EVENTS SCHEDULE

9.1.9 Local Mucosal Sampling

Rationale: Clarification on definition of related and not related AEs is provided.

11.9 Study Holding Rules

12.1.2 Attribution Definitions

Rationale: Availability of follow-up VISP testing is extended: "Testing for a particular subject will be available as long as VISP is present for this subject".

9.4.3 Vaccine Induced Seropositivity (VISP)

Rationale: For consistency with the HIV-Risk Assessment in Attachment 2, HSV-2 has been added to exclusion criterion 2.

ABBREVIATIONS

4.2 Exclusion Criteria

Attachment 2

Rationale: To clarify that in case of the mentioned skin conditions in exclusion criterion 16, systemic corticosteroids are not allowed while topical forms are allowed, given that the former could interfere with immune outcome, not the latter.

4.2 Exclusion Criteria

Rationale: To clarify the hepatitis B and hepatitis C tests to be performed at screening, the actual tests as mentioned in the Study Procedures Manual have been added to exclusion criterion 1.

ABBREVIATIONS

4.2 Exclusion Criteria

Rationale: Typographical error.

TIME AND EVENTS SCHEDULE

Amendment 2 (06 Feb 2015)

The overall reason for the amendment: The overall reason for the amendment is to add a statement that the sponsor will reimburse post-exposure prophylaxis.

Rationale: Added post-exposure prophylaxis.

ABBREVIATIONS

8 PRESTUDY AND CONCOMITANT THERAPY

9.4.5 Post-Exposure Prophylaxis (PEP)

Rationale: It is clarified that vaccine administration can be performed by a qualified healthcare provider from the study site (including the pharmacist who prepared the study vaccine) who will have no other study function related to safety, study data evaluation or recording of AEs.

5 VACCINE ALLOCATION AND BLINDING

7 TREATMENT COMPLIANCE

9.1.4 Vaccination (Weeks 0, 12, 24, and 48)

14.3 Preparation, Handling, and Storage

Rationale: If the initial laboratory sampling occurred longer than 28 days before the Day 1 visit, this test will not be repeated. Instead, this will be considered a screen failure.

TIME AND EVENTS SCHEDULE

9.1.4 Vaccination (Weeks 0, 12, 24, and 48)

Rationale: Broadening of visit windows: For the 2nd, 3rd, and 4th vaccination visit, the window will be –1 week and +3 weeks. The 2- to 4-week post-vaccination visits will be determined relative to the actual day of vaccination. For the second year follow-up visits, the window will be ±3 weeks.

TIME AND EVENTS SCHEDULE

9.1.2 Visit Windows

10.3 Contraindications to Vaccination

Rationale: It is added that if a subject misses more than one study vaccination, he/she will be withdrawn from further study vaccination.

6 DOSAGE AND ADMINISTRATION

9.1.2 Visit Windows

10.2 Discontinuation of Study Vaccine

Rationale: It is added that subjects with major protocol violations are excluded from the per-protocol population, only if these violations impact the immunogenicity assessments.

11.1 Analysis Populations

Rationale: Based on updated recruitment projections, efforts will be made to enroll a minimum of 50 subjects per region.

SYNOPSIS

3.1 Overview of Study Design

5 VACCINE ALLOCATION AND BLINDING

Rationale: It is clarified that central ECG reading will be used.

4.2 Exclusion Criteria

9.1.3 Screening Phase (Weeks –4 to 0)

9.3.2 Evaluations

11.5 Safety Analyses

Rationale: Clarification on receipt of licensed or experimental vaccines.

4.2 Exclusion Criteria

4.4 Prohibitions and Restrictions

8 PRESTUDY AND CONCOMITANT THERAPY

10.3 Contraindications to Vaccination

Rationale: Addition of prohibition to use any experimental medication during the study.

4.4 Prohibitions and Restrictions

8 PRESTUDY AND CONCOMITANT THERAPY

Rationale: It is clarified that it is disallowed to concomitantly participate in another study without prior sponsor approval.

4.2 Exclusion Criteria

4.4 Prohibitions and Restrictions

Rationale: Pregnancy counseling will not only be provided at screening, but at several timepoints throughout the study.

TIME AND EVENTS SCHEDULE

9.1.4 Vaccination (Weeks 0, 12, 24, and 48)

9.1.6 Second Year Follow-Up Phase (Weeks 60 to 96)

9.1.7 Early Withdrawal – Early Exit Visit

Rationale: Since storage temperature of the study vaccine will be detailed in the site investigational product manual, these details have been removed from the protocol.

14.3 Preparation, Handling, and Storage

Rationale: The maximum time allowed between preparation and administration of the study vaccine is set to 3 hours.

14.3 Preparation, Handling, and Storage

Rationale: It is added that, in the case of VISP, HIV testing can be performed more frequently than every 3 months, if approved by the sponsor.

9.4.3 Vaccine Induced Seropositivity (VISP)

Rationale: It is sufficient for subjects to be observed for reactogenicity for 30 minutes after vaccination, instead of 60 minutes. It is also clarified that this observation does not necessarily mean a one to one observation.

SYNOPSIS

TIME AND EVENTS SCHEDULE

3.1 Overview of Study Design

9.1.4 Vaccination (Weeks 0, 12, 24, and 48)

Rationale: Weight will need to be measured at every visit, not only at screening.

TIME AND EVENTS SCHEDULE

9.1.4 Vaccination (Weeks 0, 12, 24, and 48)

9.1.5 Post-vaccination Follow-Up Phase (Weeks 1, 2 and 4; Weeks 14 and 16; Weeks 26, 28 and 36; Weeks 50 and 52)

9.1.6 Second Year Follow-Up Phase (Weeks 60 to 96)

9.1.7 Early Withdrawal – Early Exit Visit

9.3.2 Evaluations

Rationale: It is clarified that it is required to use a different deltoid for all study vaccine injections to be administered at one and the same visit. For visits with only one injection, either deltoid can be used.

SYNOPSIS

6 DOSAGE AND ADMINISTRATION

14.3 Preparation, Handling, and Storage

Rationale: It is added that adaptations to the Test of Understanding are allowed for local purposes, after IRB and sponsor approval.

9.1.3 Screening Phase (Weeks –4 to 0)

Attachment 3

Rationale: Minor Clarifications

SYNOPSIS 9.3.2 Evaluations	It is clarified that temperature should be measured at approximately the same time each day.
TIME AND EVENTS SCHEDULE 9.1.4 Vaccination (Weeks 0, 12, 24, and 48)	HLA testing was only mentioned in footnote 18 of the Time and Events Schedule. To avoid this being overlooked, wording on HLA testing has been added to the first column of the actual schedule instead. HLA test at baseline has also been added to Section 9.1.4 to match the Time and Events Schedule.
9.1.3 Screening Phase (Weeks –4 to 0)	Clarification on pre-screening assessment and use of non-study specific consent.
9.1.3 Screening Phase (Weeks –4 to 0)	Clarified that Test of Understanding needs to be performed during screening.
9.3.2 Evaluations	A subtitle ‘Cardiac-Related Events’ has been added in order to highlight the process to be followed for these events. The wording 'pre-dose' has been removed from the ECG assessment at Week 16. This implies pre-dose to the vaccination at Week 24, but might cause confusion since there is no vaccination planned at Week 16.
11.5 Safety Analyses	It has been clarified that a supine position is not required for a vital signs measurement.
ABBREVIATIONS 12.1.1 Adverse Event Definitions and Classifications 12.3.1 All Adverse Events	Wording on reporting of SUSARs is clarified.
10.2 Discontinuation of Study Vaccine 12.3.4 Pregnancy	It is clarified that subjects, who need to be withdrawn from study vaccine administration, will enter the follow-up phase, starting from Visit 14 onwards.

Rationale: A JNJ-compound number for the combination of gp140 DP and the adjuvant aluminum phosphate has been added.

14.1 Physical Description of Study Vaccines

Rationale: Minor errors were corrected.

ABBREVIATIONS	IVRS will not be used, so it has been removed.

5 VACCINE ALLOCATION AND BLINDING 15 STUDY-SPECIFIC MATERIALS	
TIME AND EVENTS SCHEDULE 9.1.3 Screening Phase (Weeks –4 to 0) 9.3.2 Evaluations	'Troponin I' was corrected to 'troponin'.
9.1.6 Second Year Follow-Up Phase (Weeks 60 to 96)	For consistency with the Time and Events Schedule, it is added that urine pregnancy test will also be performed at Week 60.
9.1.9 Local Mucosal Sampling	Text already mentions that mucosal sampling will not be performed if there are symptoms of active inflammation. Changed wording to: 'signs or symptoms'.
9.3.2 Evaluations 11.5 Safety Analyses 17.4 Source Documentation	There will not be a separate field in the CRF for physical examination findings. Clinically relevant physical examination findings need to be entered in the CRF as medical history/AE. In section 9.3.2, it is added that full physical examination is also performed at the final visit, to match the Time and Events schedule.
10.2 Discontinuation of Study Vaccine	The text on immunosuppressants was made consistent with text in Section 8.
11.7 Protocol Safety Review Team (PSRT)	Reference to Table 6 was corrected to reference to Table 8.
15 STUDY-SPECIFIC MATERIALS	Removed incorrect wording ‘pharmacy manual’.
Attachment 1	Correction of page reference to ‘Estimating Severity Grade’
Attachment 1	Added Induration/Swelling as parameter in the AE grading table.

Amendment 1 (17 Dec 2014)

The overall reason for the amendment: Upon request of the FDA, the requirement is included that from the baseline visit onwards, all grade 3 and grade 4 laboratory abnormalities, as well as laboratory abnormalities accompanied by clinically relevant signs and/or symptoms, will be repeated within 48 hours of receipt.

TIME AND EVENTS SCHEDULE 9.1.1 Overview 9.3.2 Evaluations 11.9 Study Holding Rules

SYNOPSIS

A Phase 1/2a Study to Evaluate the Safety/Tolerability and Immunogenicity of Homologous Ad26 Mosaic Vector Vaccine Regimens or Ad26 Mosaic and MVA Mosaic Heterologous Vector Vaccine Regimens, with High-Dose, Low-Dose or no Clade C gp140 Protein Plus Adjuvant for HIV Prevention

OVERALL RATIONALE

This study, first-in-human for Ad26.Mos.HIV[a], will assess the safety/tolerability and immunogenicity of seven prime/boost vaccine regimens. Subjects will receive four doses of study vaccine: Ad26.Mos.HIV or placebo will be given at Weeks 0 and 12; Ad.26.Mos.HIV or Modified Vaccinia Ankara (MVA)-Mosaic, both with or without glycoprotein 140 drug product (gp140 DP [low or high dose]), gp140 DP (high dose) or placebo, or placebo only will be given at Weeks 24 and 48. The goal of this study is to select a regimen for evaluation in future efficacy studies.

Study vaccines used in this study are Ad26.Mos.HIV, MVA-Mosaic and gp140 DP:

Ad26.Mos.HIV vaccine is made up of the following three drug substances in a 2:1:1 ratio:

- Ad26.Mos1.Env
- Ad26.Mos1.Gag-Pol
- Ad26.Mos2.Gag-Pol

MVA-Mosaic consists of the following two vaccine products supplied in separate vials and administered in a 1:1 ratio:

- MVA-Mosaic1 = MVA virus expressing Mosaic1 HIV-1 Gag, Pol, and Env proteins
- MVA-Mosaic2 = MVA virus expressing Mosaic2 HIV-1 Gag, Pol, and Env proteins

gp140 DP (HIV-1 Clade C glycoprotein 140) contains recombinant trimeric gp140, produced on a transformed PER.C6® cell line constructed to produce gp140 DP. In this study, gp140 DP will be dosed with aluminum phosphate as adjuvant.

The safety of two injections of high (250 mcg) and low (50 mcg) doses of gp140 DP will be established in a Phase 1 study prior to dosing with gp140 DP in the current study.

OBJECTIVES AND HYPOTHESIS

Primary Objectives

The primary objectives are:

- To assess the safety/tolerability of various prime/boost regimens containing Ad26.Mos.HIV, MVA-Mosaic, and/or gp140 DP components.
- To compare Env binding antibody responses between the different vaccine regimens.

[a] Ad26 = adenovirus serotype 26; Mos = mosaic; HIV-1 = Human Immunodeficiency Virus Type 1

Secondary Objectives

The secondary objective is:

- To assess other antibody binding, antibody effector function and antibody characterization, and cellular responses.

Exploratory Objectives

The exploratory objectives are:

- To explore immune responses to the different vaccine regimens in mucosal secretions in a subset of subjects.
- To explore gene expression patterns between the different vaccine regimens.
- To explore neutralization antibodies against the Ad26 vector.
- To assess the social impact of participation in an HIV vaccine study for subjects via a social impact questionnaire.
- To explore durability of the vaccine regimen in the groups selected for the long-term extension phase.

Hypothesis

No formal statistical hypothesis will be tested. This study will evaluate whether a prime/boost vaccine regimen consisting of Ad26.Mos.HIV with or without gp140 protein plus aluminum phosphate adjuvant, or Ad26.Mos.HIV/MVA-Mosaic with or without gp140 protein plus aluminum phosphate adjuvant is safe, well-tolerated and immunogenic, providing broad, functional and durable humoral and cellular responses.

OVERVIEW OF STUDY DESIGN

This is a multicenter, randomized, parallel group, placebo-controlled, double-blind clinical study in healthy HIV-uninfected adult men and women. Subjects will be enrolled regardless of their baseline Ad26 seropositivity, as data from Study IPCAVD003 suggest that there is little impact of baseline Ad26 neutralizing antibodies (nAbs) on the immunogenicity of this Ad26 vaccine vector, at the titers observed in that study, however regional differences are known to occur. Vaccinations are administered as shown in Table 1.

The study comprises a maximum 4-week screening period, a 48-week vaccination period during which subjects will be vaccinated at baseline, Week 12 and Week 24, with a booster at Week 48, and a 48-week follow-up period to the final visit at Week 96. Based on the analysis of the Week 28 data, a Long Term Extension (LTE) phase (approximately 5 years after Week 96) will be performed for subjects randomized to Group 1 and Group 2 and having received all 4 vaccinations. These 2 groups (including a gp140 250 mcg and a gp140 50 mcg dose, respectively) form the basis for the regimens that will be evaluated in future studies. The end of the study will be the last subject's last visit.

Table 1: Study Design HIV-V-A004

Group	N	Week 0 (baseline)	Week 12	Week 24	Week 48
Group 1*	50	Ad26.Mos.HIV	Ad26.Mos.HIV	Ad26.Mos.HIV + gp140 DP (250 mcg + adjuvant)[a]	Ad26.Mos.HIV + gp140 DP (250 mcg + adjuvant) [a]
Group 2*	50	Ad26.Mos.HIV	Ad26.Mos.HIV	Ad26.Mos.HIV + gp140 DP (50 mcg + adjuvant) [a]	Ad26.Mos.HIV + gp140 DP (50 mcg + adjuvant) [a]
Group 3	50	Ad26.Mos.HIV	Ad26.Mos.HIV	Ad26.Mos.HIV + Placebo	Ad26.Mos.HIV + Placebo
Group 4	50	Ad26.Mos.HIV	Ad26.Mos.HIV	MVA-Mosaic + gp140 DP (250 mcg + adjuvant) [a]	MVA-Mosaic + gp140 DP (250 mcg + adjuvant) [a]
Group 5	50	Ad26.Mos.HIV	Ad26.Mos.HIV	MVA-Mosaic + gp140 DP (50 mcg + adjuvant) [a]	MVA-Mosaic + gp140 DP (50 mcg + adjuvant) [a]
Group 6	50	Ad26.Mos.HIV	Ad26.Mos.HIV	MVA-Mosaic + Placebo	MVA-Mosaic + Placebo
Group 7	50	Ad26.Mos.HIV	Ad26.Mos.HIV	gp140 DP (250 mcg + adjuvant) [a] + Placebo	gp140 DP (250 mcg + adjuvant) [a] + Placebo
Group 8	50	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo

[a] Aluminum content will be 0.425 mg/0.5 mL dose
50 mcg and 250 mcg refer to total protein content
Sterilized aluminum phosphate wet gel suspension will be used as adjuvant for gp140 DP
*An optional LTE phase (approximately 5 years after Week 96) will be performed for subjects randomized to Group 1 and Group 2 and having received all 4 vaccinations.

After vaccination, subjects will remain under observation for at least 30 minutes for any reactogenicity. Subjects will use a memory aid to document any local and systemic adverse events (AEs) in the evening after each vaccination and then daily for the next 7 days. The investigator or his/her designee will document any AEs[b], and will collect blood and urine samples for safety laboratory assessment (hematology, biochemistry, and urinalysis) at each visit until Week 96. Cardiac safety surveillance monitoring will be performed by electrocardiogram (ECG) and measurement of specific cardiac enzymes (troponin) if cardiac symptoms appear. Also, subjects will be specifically asked about cardiac symptoms at each post-vaccination visit.

Blood samples will be taken at specific clinic visits to assess immune responses.

An independent Data Monitoring Committee (DMC) and an internal Protocol Safety Review Team (PSRT), composed of medical and safety representatives of the sponsor and partners will be established for this study to evaluate safety and tolerability data.

[b] At the visits at 2 weeks after each vaccination, the investigator or his/her designee should discuss information from the memory aids with subjects, and complete the relevant parts of the CRF.

PSRT and DMC Review of Sentinel Groups

There will be a pause in enrollment after 10% of the target number of subjects have received their first injection (ie, approximately 40 subjects). The PSRT will review the blinded Week 2 safety data after first injection to determine if enrollment can continue. The PSRT will also review blinded safety data (2 weeks of follow up) after 30% of subjects have received their first injection without a pause in enrollment.

To decide whether further dosing can continue, the DMC will review blinded safety data (2 weeks of follow up) after 30% of subjects have received their first injection, and unblinded data after 10% of subjects have received their third injection, and after 30% of subjects have received their third injection.

DMC Review of gp140 DP Safety in HIV-V-A003

The safety, tolerability and immunogenicity of gp140 DP will be evaluated in a separate safety study (HIV-V-A003) with interim safety results available prior to the first subject reaching Week 24 of this study, HIV-V-A004 (the time point at which subjects in certain arms will receive gp140 DP). The DMC will review the interim safety results of study HIV-V-A003 and will allow administration of the first dose of gp140 DP (third injection; Week 24 vaccination) in this HIV-V-A004 protocol only if no safety concerns are identified.

Analysis Timepoints

The primary analysis will be performed once all subjects have completed the Week 28 visit (ie, 4 weeks after the third injection) or discontinued earlier. The purpose of this analysis is to allow for an early conclusion on regimen selection for future studies, based on immunogenicity and safety. 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 study visit at Week 96 (ie, including the second year follow-up period) or discontinued earlier. The final analysis of the LTE phase (optional and only for a subset of subjects) will be performed once all included subjects have completed the last visit of the extension period (Week 336), or discontinued earlier.

SUBJECT POPULATION

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

In total, 400 subjects will be randomized equally into one of seven prime/boost vaccine regimens, consisting of Ad26.Mos.HIV with or without gp140 protein (low or high dose), Ad26.Mos.HIV/MVA-Mosaic with or without gp140 protein (low or high dose), or placebo (Table 1). Randomization will be stratified by region (United States [US], Africa, and Asia). Efforts will be made to enroll a minimum of 50 subjects per region.

DOSAGE AND ADMINISTRATION

Subjects will receive doses of study vaccine at four timepoints according to randomization, on Day 1, at Week 12, and at Week 24, with a booster at Week 48, administered by intramuscular injection into the deltoid. For visits with only one injection (ie, at Week 0 and 12), either deltoid can be used. When 2 study vaccine injections are to be given at one visit (ie, at Week 24 and 48), it is required to use a different deltoid for both injections. Exceptions are allowed only if medically indicated. Study vaccines are as follows:

- **Ad26.Mos.HIV** (Ad26.Mos.1.Env + Ad26.Mos1.Gag-Pol + Ad26.Mos2.Gag-Pol):
  - Total dose is $5x10^{10}$ viral particles (vp) per 0.5 mL injection

- **MVA-Mosaic** (MVA-Mosaic1 + MVA-Mosaic2):
  - Total dose is 10^8 plaque-forming units (pfu) per 0.5 mL injection
- **gp140 DP**:
  - Low-dose: gp140 DP with 50 mcg total protein, mixed with aluminum phosphate adjuvant (0.425 mg aluminum) at the pharmacy, per 0.5 mL injection
  - High-dose: gp140 DP with 250 mcg total protein, mixed with aluminum phosphate adjuvant (0.425 mg aluminum) at the pharmacy, per 0.5 mL injection
- **Placebo**:
  - 0.9% saline, 0.5 mL injection

SAFETY EVALUATIONS

All AEs will be recorded from the time the informed consent is signed until the Week 96 visit of the main study. During the optional LTE phase (Group 1 and 2), only SAEs (including HIV infection and abnormal pregnancy outcome) will be recorded.

On a daily basis, for 8 days post-vaccination (day of vaccination and the subsequent 7 days), subjects will be asked to record symptoms of the following AEs via a memory aid:

- Solicited local AEs: erythema, induration and swelling (measured using the ruler supplied), and pain/tenderness, itching, or warmth at the injection sites.
- Solicited systemic AEs: fatigue, headache, myalgia, arthralgia, chills, fever, nausea, vomiting, rashes, and general itching.
- Temperature should be measured at approximately the same time each day using the thermometer supplied. Fever will be recorded by the investigator for temperatures equal to or higher than 38.0°C.
- Other spontaneously reported AEs (ie, unsolicited AEs).

The investigator or his/her designee should discuss information from the memory aids with subjects, document relevant information in the clinic chart (source document) and complete the relevant parts of the case report form (CRF).

IMMUNOGENICITY EVALUATIONS

Humoral response assays will include, but are not limited to Env-specific serum binding antibody assay, nAb assays, and antibody-dependent cellular phagocytosis (ADCP) assay, as well as epitope mapping (see Table 2).

Table 2: Humoral Immune Response Assays

Objective/ endpoint	System	Assay/Method	Readout	Timepoint
Primary	Serum	Env binding antibody (ELISA)	Titer or % responders (Clade C) and breadth (Clade A, B, C)	Baseline 1 mo post-vac. 1 0.5, 1 mo post-vac. 2-4 3, 6 mo post-vac. 4
Secondary	Serum	HIV neutralizing antibody	Tier 1 and Tier 2[a] nAbs: GMT for each isolate, % responders to each isolate Breadth: # isolates neutralized	As above
Secondary	Serum	gp120 binding antibody	Anti-gp120 titer (Clade A, B, C)	As above
Secondary	Serum	ADCP	% phagocytosis	As above
Secondary	Serum	Isotyping Env binding antibody (ELISA)	Isotyping (Clade C) (IgA, IgG1, IgG2, IgG3)	As above
Exploratory	Serum	Epitope mapping	Targeted epitopes and diversity (including V2)	1 mo post-vac. 1-4 At vac. 2-4
Exploratory	Serum	Ad26 neutralization antibodies	Titers of Ad26 neutralization antibodies	1 mo post-vac. 1-4 3, 7.5, 12 mo post-vac. 4 At vac. 1-4

ADCP = antibody-dependent cellular phagocytosis; ELISA = enzyme-linked immunosorbent assay; GMT = geometric mean titer; Ig = immunoglobulin; mo = month ; nAb = neutralizing antibody; vac = vaccination

[a] Classification of HIV-1 viruses according to sensitivity to antibody-mediated neutralization: very high (tier 1A), above-average (tier 1B), moderate (tier 2), or low (tier 3) [1]. Tier 2 will only be assessed if Tier 1 shows positive results.

Evaluations of cellular immune responses will include, but are not limited to, the following assays: ELISPOT, intra-cellular cytokine staining, and multi-parameter flow cytometry (see Table 3).

Table 3: T-Cell Immune Response Assays

Objective/ endpoint	System	Assay/ Method	Readout	Timepoint
Secondary	PBMC	ELISPOT	Breadth and depth: # peptides, % responders, median response	Baseline 0.5, 1 mo post-vac. 3 & 4
Exploratory	PBMC	Intracellular cytokine staining	% of CD4 and CD8+ T cells producing IFNγ, IL-2, TNFα	Baseline 1 mo post-vac. 1 0.5, 1 mo post-vac. 2-4 3, 7.5 mo post-vac. 4
Exploratory	PBMC	Multi-parameter flow cytometry	Characterization of memory T-cell development with emphasis on follicular helper T cells	Baseline 1 mo post-vac. 1 0.5, 1 mo post-vac. 2-4 3, 7.5 mo post-vac. 4
Exploratory	PBMC	Gene expression analysis	Regulation of genes (clusters) that predict specific immune responses and HLA typing	Baseline 1 mo post-vac. 1 0.5, 1 mo post-vac. 2-4 3, 7.5 mo post-vac. 4

ELISPOT = enzyme-linked immunospot assay; HLA = human leukocyte antigen; IFNγ = interferon gamma; IL-2 = interleukin 2; mo = month; PBMC = peripheral blood mononuclear cell; TNFα = tumor necrosis factor alpha; vac = vaccination

Note: HLA only tested once (using the baseline blood sample)

Exploratory humoral and cellular immunogenicity assessments during the optional long-term extension phase (Group 1 and 2 only) may include, but are not limited to, the following assays: Env-specific serum binding antibody assay and ELISPOT. Further specification will be based on the Week 52 results.

Exploratory assessments on mucosal samples will include, but are not limited to, characterization of Env-specific binding antibodies.

OTHER EVALUATIONS

A social impact questionnaire will be administered at Weeks 24, 48, 96 and at each visit of the LTE phase.

STATISTICAL METHODS

A sample size of 50 subjects per regimen is regarded to be appropriate to assess the safety and tolerability of the different vaccine regimens and also collect sufficient data on immunogenicity. Placebo recipients are included to assess safety and will provide control specimens for immunogenicity assays.

While mild to moderate vaccine reactions (local site and systemic responses) are expected, AEs that preclude further dose administration or more serious ones that would limit product development are not anticipated. With 50 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 6%. For the combined groups with Ad26.Mos.HIV (n = 350), there would be 95% confidence that the true rate is <1% when 0 events are observed. The following table shows the probabilities of observing at least one AE at given true AE rates:

True AE rate	Probability of observing at least one AE in n subjects	
	n = 50	n = 350
0.1%	5%	30%
0.5%	22%	83%
1%	39%	97%
2.5%	72%	100%
5%	92%	100%
10%	99%	100%

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

The immunogenicity population will consist of all subjects who received at least one dose and have at least one measured post-dose blood sample collected. Anticipating a dropout rate of approximately 10%, 45 evaluable subjects per group will allow detection of 2.3-fold differences in Env-binding antibody titers, generally accepted to be biologically relevant, between groups with 80% probability, assuming a two-sided 5% Type I error and a standard deviation of 0.6 on the $\log_{10}$ scale.

Interim Safety Review

No formal interim analysis prior to the primary analysis at Week 28 is planned. The PSRT and DMC will review interim safety data.

An interim safety review by the PSRT is planned of the blinded Week 2 safety data after 10% of subjects (approximately 40 subjects) have received their first injection at which time enrollment is paused. Based on the results of this analysis, a decision will be made whether enrollment can continue. The PSRT will also review blinded safety data (2 weeks of follow up) after 30% of subjects have received their first injection without enrollment pause.

The DMC will review safety data (2 weeks of follow up) after:

- 30% of subjects have received their first injection (blinded)
- 10% of subjects have received their third injection (unblinded)
- 30% of subjects have received their third injection (unblinded)

Immunogenicity Analysis

Since the correlate of protection for an HIV vaccine is unknown, regimen selection for future studies will be based on several immunogenicity assessments aiming at the regimen that elicits a well-balanced immune response as well as broad coverage of Clades A, B, and C. Emphasis will be on strength and breadth of Env antibody responses, as co-primary endpoints. In addition, functional antibody responses, nAb responses as well as mapping of Env antibodies (including V2 loop region) will be considered. Additional consideration will be given to responses to a comprehensive package of immunogenicity testing including, but not limited to HIV nAb responses, functional antibody responses and cellular immune responses. This should be supported by strong responses in magnitude and breadth of CD8 IFNγ T-cells, CD4 T cells and functional antibodies.

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

Safety Analyses

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively (including 95% confidence intervals).

TIME AND EVENTS SCHEDULE

(see next page)

Time and Events Schedule for Treatment Phase and Follow-up Phase until Week 96

Phase	*Scr*	*Vac*		*Post-vac. FU*			*Vac*	*Post-vac. FU*			*Vac*	*Post-vac. FU*				*Vac*	*Post-vac. FU*[11]			*Second Year FU*[11]			
Visit #	**1**[1]	**2**	**2a**	**3**	**4**	**5**	**6**	**6a**[18]	**7**[18]	**8**[18]	**9**	**9a**[18]	**10**[18]	**11**[18]	**12**	**13**	**13a**[18]	**14**[18]	**15**[18]	**16**	**17**	**18**	**Exit**[12]
Visit Week	**-4 to 0**	**0**		**1**	**2**	**4**	**12**		**14**	**16**	**24**		**26**	**28**	**36**	**48**		**50**	**52**	**60**	**78**	**96**[11]	
Visit Day	**-28 to 0**	**1**	**2 to 4**[3]	**8 ±1**	**15 ±3**	**29 ±3**	**85 -1/+ 3weeks**	**86-88**[3]	**99 ±3**	**113 ±3**	**169 -1/+ 3weeks**	**170 to 172**[3]	**183 ±3**	**197 ±3**	**253 ±5**	**337 -1/+ 3weeks**	**338 to 340**[3]	**351 ±3**	**365 ±3**	**421 ±3 weeks**	**547 ±3 weeks**	**673 ±3 weeks**	
Visit Type	Screening	**VACCINE 1**	Safety	Safety	Safety and Immuno.	Safety and Immuno.	**VACCINE 2**	Safety	Safety and Immuno.	Safety and Immuno.	**VACCINE 3**	Safety	Safety and Immuno.	Safety and Immuno.	Safety	**VACCINE 4**	Safety	Safety and Immuno.	Safety and Immuno.	Safety and Immuno.	Safety and Immuno.	Safety and Immuno.	Early exit
Informed consent	●																						
Medical history	●																						
Physical exam[2]	●	❶		●	●	●	❶		●	●	❶		●	●	●	❶		●	●	●	●	●	●
Vital signs	●	❸		●	●	●	❸		●	●	❸		●	●	●	❸		●	●	●	●	●	●
HIV-risk assessment	●	●		●	●	●	●		●	●	●		●	●	●	●		●	●	●	●	●	●
Counseling on HIV	●	●		●	●	●	●		●	●	●		●	●	●	●		●	●	●	●	●	●
Test of Understanding	●																						
Cardiac risk assessment	●	❶		●	●	●	❶		●	●	❶		●	●	●	❶		●	●	●	●	●	●
12-lead ECG	●									●													
Concomitant meds	●	❶		●	●	●	❶		●	●	❶		●	●	●	❶		●	●	●	●	●	●
Review of inclusion/ exclusion criteria	●	❶																					
Enrollment/ randomization		❶																					
Vaccination		●					●				●					●							
Post-vac. reactogenicity (30 min)[17]		●					●				●					●							
AE, SAE recording	❺	●		●	●	●	●		●	●	●		●	●	●	●		●	●	●	●	●	●
8-day memory aid distribution		●					●				●					●							
8-day memory aid review by site staff				●					●				●					●					
24-72 hour contact[3]			●					●				●					●						
Social Impact Q'naire											●					●						●	●
Mucosal secretions[4,6]		●			●				●				●					●		●		●	

Female hormone testing[5]		❷			❷				❷				❷					❷		❷		❷	
Urinalysis[7]	●	❶			●	●	❶		●	●	❶		●	●	●	❶		●	●	●	●	●	●
Serum pregnancy test/pregnancy counseling[14]	●																						
Urine pregnancy test/pregnancy counseling[14]		❶					❶				❶		●[6]			❶				●		●	●
CBC with differential and platelets[8,13,19]	●	●			●	●	●		●	●	●		●	●	●	●		●	●	●	●	●	●
Serum chemistry[8,13,19]	●	●			●	●	●		●	●	●		●	●	●	●		●	●	●	●	●	●
Troponin[9]	❷																						
Hepatitis B/C serologies	❷																						
Syphilis serology	❷	❷ ❹			❷ ❹				❷ ❹				❷ ❹					❷ ❹		❷ ❹		❷ ❹	
Urine chlamydia/ gonorrhea	●	❹			❹				❹				❹					❹		❹		❹	
Trichomonas[15]	●	❹			❹				❹				❹					❹		❹		❹	
HIV EIA[19]	●	●					●				●					●					●	●	●
HIV RNA[10]	❷	❷					❷				❷					❷					❷	❷	❷
Ad26 seropositivity		❷				❷	❷			❷	❷			❷		❷		❷		❷	❷	❷	❷
HLA test		❷																					
Cellular immuno. Assays (approx mL)[13,16,18]		102				50			50	50			102	102				102	102	50	50	50	50
Humoral immuno. assays (approx mL)[13]		20			20	20	20		20	20	20		20	20		20		20	20	20	20	20	20
***Cumulative blood draw volumes*:**																							
Approx daily blood volume (mL)	13	135	0	0	27	77	33	0	77	77	33	0	129	129	7	33	0	129	129	77	83	83	83
Approx cumulative blood volume (mL)	13	148	148	148	175	252	285	285	362	439	472	472	601	730	737	770	770	899	1028	1105	1188	1271	

AE = adverse event; CBC = complete blood count; ECG = electrocardiogram; EIA = enzyme immunoassay; FU = follow up; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; ICF = informed consent form; RNA = ribonucleic acid; SAE = serious adverse event; vac = vaccination

❶ pre-dose; ❷ no extra blood required; ❸ pre- and post-dose; ❹ for subjects who consent to mucosal secretion collection; ❺ AEs will be recorded from the signing of the ICF.

[1] Screening visit may be split into multiple days/visits.

[2] Complete physical exam will be performed at the screening and final visits. 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).

[4] Baseline mucosal secretion sampling may be done at screening or baseline prior to vaccination. (Note: mucosal secretion procedures for both men and women are optional, and will only be performed on a subset of subjects who provide consent.)
[5] For female subjects who consent to the cervico-vaginal mucosal sample collection
[6] Urine pregnancy test performed prior to mucosal secretion procedure, only for females who consent to mucosal secretion collection.
[7] Microscopic reflex testing in the event of positive urinalysis
[8] If medical status and physical examination on Day 1 suggests 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 28 days of the initial screening assessment. 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), a confirmatory test should be performed within 48 hours after the results have become available. After that, laboratory tests will be repeated weekly until values are resolved or stable.
[9] Measurement of specific cardiac enzymes (troponin); will also occur at later timepoints if cardiac symptoms warrant
[10] An HIV testing algorithm will be followed (detailed in the Study Procedures Manual)
[11] Subjects randomized to Group 1 and 2 who have received all 4 vaccinations will be asked to enter the LTE phase. Signing of ICF for this phase will preferably be done at the Week 96 visit or at an unscheduled visit as soon as possible after the Week 96 visit. ICF needs to be signed at the latest at Visit 19 (before any assessment is done). See **Time and Events Schedule for the Long-Term Extension Phase**.
[12] For those subjects who are unable to continue participation in the study, an exit visit will be conducted as soon as possible
[13] Pre-dose at Visits 2, 6, 9 and 13
[14] For both male and female subjects
[15] For female subjects only
[16] For clinical reasons, eg, anemia, the investigator can decide to draw a smaller volume
[17] Observation for at least 30 minutes
[18] If a subject is not vaccinated on the given day of vaccination, the timings of visits at 2 and 4 weeks post-vaccination will be determined relative to the actual day of vaccination.
[19] Blood volumes may vary upon the local collection process. Indicative volumes are provided in the Study Procedures Manual. Total approximate volume per visit is to be respected.

Time and Events Schedule for the Long-Term Extension Phase (from Week 96 onwards, Group 1 and 2 only)											
Phase		**Long Term Extension**									
Visit #	**18 bis[1]**	**19[1]**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Visit Week		**120[1]±4**	**144±4**	**168±4**	**192±4**	**216±4**	**240±4**	**264±4**	**288±4**	**312±4**	**336±4**
Informed consent	●										
HIV-risk assessment		●	●	●	●	●	●	●	●	●	●
Counseling on HIV		●	●	●	●	●	●	●	●	●	●
Concomitant meds[2]		●	●	●	●	●	●	●	●	●	●
SAE recording		●	●	●	●	●	●	●	●	●	●
Social Impact Q'naire		●	●	●	●	●	●	●	●	●	●
HIV EIA[3]		●	●	●	●	●	●	●	●	●	●
HIV RNA[3,4]		●	●	●	●	●	●	●	●	●	●
Ad26 seropositivity		●	●	●	●	●	●	●	●	●	●
Cellular immuno. Assays (approx mL)[5]		102	102	102	102	102	102	102	102	102	102
Humoral immuno. assays (approx mL)		20	20	20	20	20	20	20	20	20	20

EIA = enzyme immunoassay; HIV = human immunodeficiency virus; RNA = ribonucleic acid; SAE = serious adverse event

[1]this visit only needs to occur if ICF is not signed at Week 96. Visit 18bis should occur as soon as possible after the Week 96 visit. ICF needs to be signed at the latest at visit 19 (before any assessment is done).

[2]restricted to concomitant therapies given in conjunction with an SAE and any chronic or recurrent use of immunomodulators/suppressors and oral or parenteral corticosteroids.

[3]Blood volumes may vary upon the local collection process. Indicative volumes are provided in the Study Procedures Manual. Total approximate volume per visit is to be respected.

[4]An HIV testing algorithm will be followed (detailed in the Study Procedures Manual)

[5]For clinical reasons, eg, anemia, the investigator can decide to draw a smaller volume

ABBREVIATIONS

Ad	adenovirus
Ad5	adenovirus serotype 5
Ad26	adenovirus serotype 26
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
β-HCG	β-human chorionic gonadotropin
BIDMC	Beth Israel Deaconess Medical Center
BMI	body mass index
CBC	complete blood count
CD4/8	cluster of differentiation 4/8
CMDR	Chiang Mai Double Recombinant
CRF	case report form
DAIDS	Division of AIDS
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DP	drug product
ECG	electrocardiogram
eDC	electronic data capture
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot assay
Env	envelope
ENVA	envelope A
FDA	Food and Drug Administration
Gag	group-specific antigen
GCP	Good Clinical Practice
gp	glycoprotein
GMT	geometric mean titer
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HSV-2	herpes simplex virus type 2
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	intracellular cytokine staining
IEC	Independent Ethics Committee
IFNγ	interferon gamma
IL-2	interleukin 2
ID	intradermal
IM	intramuscular
Ig	immunoglobulin

IPCAVD	Integrated Preclinical/Clinical AIDS Vaccine Development
IRB	Institutional Review Board
IWRS	interactive web response system
LTE	Long Term Extension
MVA	Modified Vaccinia Ankara
nAb	neutralizing antibody
PBMC	peripheral blood mononuclear cell
PEP	post-exposure prophylaxis
pfu	plaque-forming unit
PIR	post-injection reactogenicity
Pol	polymerase
PQC	Product Quality Complaint
PSRT	Protocol Safety Review Team
RNA	ribonucleic acid
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TNFα	tumor necrosis factor alpha
TOU	test of understanding
ULN	upper limit of normal
US	United States
USAMRMC	US Army Medical Research and Materiel Command
VISP	vaccine induced seropositivity
vp	viral particle

1. INTRODUCTION

Janssen Vaccines & Prevention B.V. is evaluating the potential of a prophylactic Human Immunodeficiency Virus Type 1 (HIV-1) vaccine comprising four candidate HIV-1 vaccine products that will be used in different prime-boost regimens. These products are Ad26.Mos.HIV[c], Modified Vaccinia Ankara (MVA)-Mosaic1, MVA-Mosaic2, and glycoprotein 140 drug product (gp140 DP).

Ad26.Mos.HIV vaccine is a recombinant replication-deficient Ad26 vectored vaccine and consists of three Ad26 vectors, one containing a mosaic insert of Env sequence, and two vectors containing mosaic inserts of Gag and Pol sequences.

MVA-Mosaic is a recombinant live attenuated MVA virus-vectored vaccine that has been genetically engineered to express two mosaic Gag, Pol, and Env sequences (Mosaic 1 and Mosaic 2) optimized for maximal coverage of potential T-cell epitopes.

gp140 DP (HIV-1 Clade C glycoprotein 140) contains recombinant trimeric gp140, produced on a transformed PER.C6® cell line constructed to produce gp140 DP. In this study, gp140 DP will be dosed with aluminum phosphate as adjuvant.

Funding for the manufacture of the vaccine products came from the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) program, grants AI078526/ AI096040.

For the most comprehensive nonclinical and clinical information regarding Ad26.Mos.HIV, MVA-Mosaic and gp140 DP, refer to the latest versions of the respective Investigator's Brochures [2-4].

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, these organizations are: the U.S. National Institute of Allergy and Infectious Diseases Division of AIDS (DAIDS), the U.S. Military HIV Research Program (MHRP), the Beth Israel Deaconess Medical Center (BIDMC), and the International AIDS Vaccine Initiative (IAVI).

1.1. Background

A safe and effective HIV vaccine is the presently elusive cornerstone of HIV prevention. Although the ideal vaccine would prevent infection of persons exposed to the virus, a vaccine might also attenuate infection once it has occurred. No presently available immunogen is able to induce efficient protection against HIV through neutralizing antibodies (nAbs), the mechanism by which licensed vaccines typically confer protection. The results of study RV144, "the Thai

[c] Ad26 = adenovirus serotype 26; Mos = mosaic

trial", which evaluated a recombinant canarypox vector vaccine (ALVAC-HIV [vCP1521]) prime and a recombinant gp120 subunit vaccine (AIDSVAX B/E) boost, demonstrated approximately 30% protection from infection in the absence of either CD8 or nAb to primary HIV isolates [5]. A subsequent case-control analysis of RV144 revealed the following correlates of activity of vaccines: high V_1V_2 antibody responses were associated with lower risk of HIV infection and high levels of anti-HIV-1 Env plasma immunoglobulin A (IgA) correlated with decreased vaccine efficacy [6,7]. Optimally, both a robust CD4/CD8 T-cell response and a potent humoral response with multiple effectors would be induced by a vaccine.

Recent data have shown that heterologous Ad26/MVA vaccine regimens containing Gag, Pol, and Env antigens can establish a per exposure risk reduction against acquisition of infection following repetitive, heterologous, intrarectal challenges with a neutralization-resistant virus (SIV MAC251) in rhesus monkeys [8]. These data also demonstrated that the inclusion of Env sequences is required for protection, despite an 18% difference in the Env amino-acid sequences between the vaccine and the challenge strains. Moreover, immunological correlates analyses suggest that Env-specific antibodies are critical for blocking acquisition of infection, whereas multiple cellular and humoral immune responses correlate with virological control, although the actual mechanisms of protection remain to be determined [8].

Studies of HIV vaccine subjects and infected patients suggest that a successful HIV vaccine program will need to protect against the diverse strains and clades. Recently published data demonstrated the capacity of bivalent HIV-1 mosaic antigens expressing Env, Gag, and Pol, as part of adenovirus/poxvirus and adenovirus/adenovirus vaccines, to protect rhesus monkeys against acquisition of SHIV-SF162P3 [9]. Improving the magnitude and breadth of epitope coverage is thought to be key to development of a successful T-cell based preventive HIV vaccine. Published data from studies in non-human primates indicate that the number of epitope-specific responses induced by a vaccine may be an important immune correlate of viral load control in the SIV challenge system [10].

Strategies to accomplish this include the use of vaccines containing immunogens from a number of prevalent clades or using mosaic sequences, ie, proteins assembled from natural sequences by *in silico* recombination, optimized for potential T-cell epitopes [11]. 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, as well as the qualitative complexity of the induced immune response. A second objective is to increase the breadth of response, defined as immune recognition of diverse strains of HIV to include multiple clades and multiple genes.

This study proposes to evaluate the safety/tolerability and the immunogenicity of vaccination with homologous Ad26.Mos.HIV regimens with high-dose gp140 DP/aluminum phosphate adjuvant, low-dose gp140 DP/aluminum phosphate adjuvant or no protein, as well as heterologous vector vaccine regimens with Ad26.Mos.HIV and MVA-Mosaic with high or low-dose gp140 DP/aluminum phosphate adjuvant or no protein.

Both Ad26 and MVA viral vectors with HIV deoxyribonucleic acid (DNA) inserts and HIV envelope proteins have been previously studied in clinical studies with no important or unexpected safety concerns. In three Phase 1 studies, Ad26.ENVA.01, at intramuscular (IM) doses over the range 10^9 to 10^{11} viral particles (vp), was found to induce Env-specific humoral and cell-mediated responses when given on up to three 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 to study further in this study.

In nine completed Phase 1/2 studies in approximately 350 healthy subjects, MVA-CMDR (Chiang Mai Double Recombinant) was found to be safe and immunogenic when given by either the intradermal (ID) or IM routes, either as a single agent, or when administered as a booster following appropriate priming [3]. At IM doses of 10^7 and 10^8 pfu and ID doses of 10^6 and 10^7 pfu, MVA-CMDR was found to induce robust and durable humoral and cell-mediated immune responses when given on up to three occasions, with an IM dose of 10^8 pfu being optimally immunogenic. Therefore, this is the dose of MVA with mosaic inserts to be studied in this study.

A monovalent gp120 protein (AIDSVAX B) was tested in 671 healthy subjects at three doses, 100 mcg, 300 mcg and 600 mcg. The 300 mcg dose was found to be the most effective, inducing a higher antibody response without significant side effects. In RV144, the only vaccine study to date to demonstrate efficacy in prevention of acquisition of HIV, a bivalent gp120 protein (AIDSVAX B/E) was used as a booster following a priming with a recombinant canarypox vector (ALVAC-HIV). The gp120 proteins were dosed at 300 mcg. Therefore, a similar dose (250 mcg) of trimeric gp140 was chosen for evaluation in this study. Evidence exists indicating that there is no clear correlation between dose of envelope protein and antibody response [12]. For this reason, a lower (50 mcg) dose of gp140 will also be tested.

In two previous HIV efficacy studies utilizing Ad5 a trend towards increased HIV-1 infection was observed in vaccine recipients as compared with placebo recipients [13,14]. 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. The HVTN 503/Phambili (Merck Ad5) 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. There was also differential dropout of high-risk placebos during this time period.

Additionally, a third study, the HVTN 505 (NIH VRC DNA/Ad5) study, 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.

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 [15,16].

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 SIVmac251 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 IPCAVD003, 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 enrollment. The T-cell responses by ELISPOT were slightly lower in the baseline Ad26 seropositive subjects, the intracellular cytokine staining (ICS) and enzyme-linked immunosorbent assay (ELISA) 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 vector 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.

In this study (HIV-V-A004), Ad26 with mosaic inserts will be used for the first time in a clinical study. It is not expected that the DNA insert will alter the safety of the viral vector. However, an internal Protocol Safety Review Team (PSRT) and an independent data monitoring committee (DMC) will be established and pauses in enrollment, regular safety reviews, and stringent vaccine/study pause rules will be included (see Section 11.9).

1.2. Overall Rationale for the Study

This study, first-in-human for Ad26.Mos.HIV, will assess the safety/tolerability and immunogenicity of seven prime/boost vaccine regimens. Ad26.Mos.HIV or placebo will be given at Weeks 0 and 12. Ad.26.Mos.HIV or MVA-Mosaic, both with or without gp140 DP (low or high dose), gp140 DP (high dose) or placebo, or placebo only will be given at Weeks 24 and 48. The goal of this study is to select a regimen for evaluation in future efficacy studies.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objectives

The primary objectives are:

- To assess the safety/tolerability of various prime/boost regimens containing Ad26.Mos.HIV, MVA-Mosaic, and/or gp140 DP components.
- To compare Env binding antibody responses between the different vaccine regimens.

Secondary Objective

The secondary objective is:

- To assess other antibody binding, antibody effector function and antibody characterization, and cellular responses.

Exploratory Objectives

The exploratory objectives are:

- To explore immune responses to the different vaccine regimens in mucosal secretions in a subset of subjects.
- To explore gene expression patterns between the different vaccine regimens.
- To explore neutralization antibodies against the Ad26 vector.
- To assess the social impact of participation in an HIV vaccine study for subjects via a social impact questionnaire.
- To explore durability of the vaccine regimen in the groups selected for the long-term extension phase.

2.2. Hypothesis

No formal statistical hypothesis will be tested. This study will evaluate whether a prime/boost vaccine regimen consisting of Ad26.Mos.HIV with or without gp140 protein plus aluminum phosphate adjuvant, or Ad26.Mos.HIV/MVA-Mosaic with or without gp140 protein plus aluminum phosphate adjuvant is safe, well-tolerated and immunogenic, providing broad, functional and durable humoral and cellular responses.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter, randomized, parallel group, placebo-controlled, double-blind clinical study in healthy HIV-uninfected adult men and women. A target of 400 subjects will participate in this study, with 50 subjects planned in each one of eight groups. Subjects will be enrolled regardless

of their baseline Ad26 seropositivity. Randomization will be stratified by region (US, Africa, and Asia). Efforts will be made to enroll a minimum of 50 subjects per region.

Subjects will receive four doses of study vaccine: Ad26.Mos.HIV or placebo will be given at Weeks 0 and 12; Ad.26.Mos.HIV or MVA-Mosaic (both with or without gp140 DP [low or high dose]), gp140 DP (high dose) or placebo will be given at Weeks 24 and 48, as shown in Table 4.

Table 4: Study Design HIV-V-A004

Group	N	Week 0 (baseline)	Week 12	Week 24	Week 48
Group 1*	50	Ad26.Mos.HIV	Ad26.Mos.HIV	Ad26.Mos.HIV + gp140 DP (250 mcg + adjuvant)[a]	Ad26.Mos.HIV + gp140 DP (250 mcg + adjuvant) [a]
Group 2*	50	Ad26.Mos.HIV	Ad26.Mos.HIV	Ad26.Mos.HIV + gp140 DP (50 mcg + adjuvant) [a]	Ad26.Mos.HIV + gp140 DP (50 mcg + adjuvant) [a]
Group 3	50	Ad26.Mos.HIV	Ad26.Mos.HIV	Ad26.Mos.HIV + Placebo	Ad26.Mos.HIV + Placebo
Group 4	50	Ad26.Mos.HIV	Ad26.Mos.HIV	MVA-Mosaic + gp140 DP (250 mcg + adjuvant) [a]	MVA-Mosaic + gp140 DP (250 mcg + adjuvant) [a]
Group 5	50	Ad26.Mos.HIV	Ad26.Mos.HIV	MVA-Mosaic + gp140 DP (50 mcg + adjuvant) [a]	MVA-Mosaic + gp140 DP (50 mcg + adjuvant) [a]
Group 6	50	Ad26.Mos.HIV	Ad26.Mos.HIV	MVA-Mosaic + Placebo	MVA-Mosaic + Placebo
Group 7	50	Ad26.Mos.HIV	Ad26.Mos.HIV	gp140 DP (250 mcg + adjuvant) [a] + Placebo	gp140 DP (250 mcg + adjuvant) [a] + Placebo
Group 8	50	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo

[a] Aluminum content will be 0.425 mg/0.5 mL dose
50 mcg and 250 mcg refer to total protein content
Sterilized aluminum phosphate wet gel suspension will be used as adjuvant for gp140 DP
* An optional LTE phase (approximately 5 years) will be performed for subjects randomized to Group 1 and Group 2 and having received all 4 vaccinations

An internal PSRT and an independent DMC will be established for this study. Refer to Sections 11.7 and 11.8, respectively, for details.

The study comprises a maximum 4-week screening period, a 48-week vaccination period during which subjects will be vaccinated at baseline, Week 12 and Week 24, with a booster at Week 48, and a 48-week follow-up period to the final visit at Week 96. Based on the analysis of the Week 28 data, a Long Term Extension (LTE) phase (approximately 5 years after Week 96) will be performed for subjects randomized to Group 1 and Group 2 and having received all

4 vaccinations. These 2 groups (including a gp140 250 mcg and a gp140 50 mcg dose, respectively) form the basis for the regimens that will be evaluated in future studies.

After vaccination, subjects will remain under observation for at least 30 minutes for any reactogenicity. Subjects will use a memory aid to document local and systemic adverse events (AEs) in the evening after each vaccination and then daily for the next 7 days. The investigator or his/her designee will document any AEs in the case report form (CRF), and will collect blood and urine samples for safety laboratory assessment (hematology, biochemistry, and urinalysis) at each visit until Week 96. Cardiac safety surveillance monitoring will be performed by electrocardiogram (ECG) and measurement of specific cardiac enzymes (troponin) if cardiac symptoms appear. Also, subjects will be specifically asked about cardiac symptoms at each post-vaccination visit.

Blood samples will be taken at specific clinic visits to assess immune responses.

PSRT and DMC Review of Sentinel Groups

There will be a pause in enrollment after 10% of the target number of subjects have received their first injection (ie, approximately 40 subjects). The PSRT will review the blinded Week 2 safety data after first injection to determine if enrollment can continue. The PSRT will also review blinded safety data (2 weeks of follow up) after 30% of subjects have received their first injection without a pause in enrollment. See Section 11.9 on study holding rules.

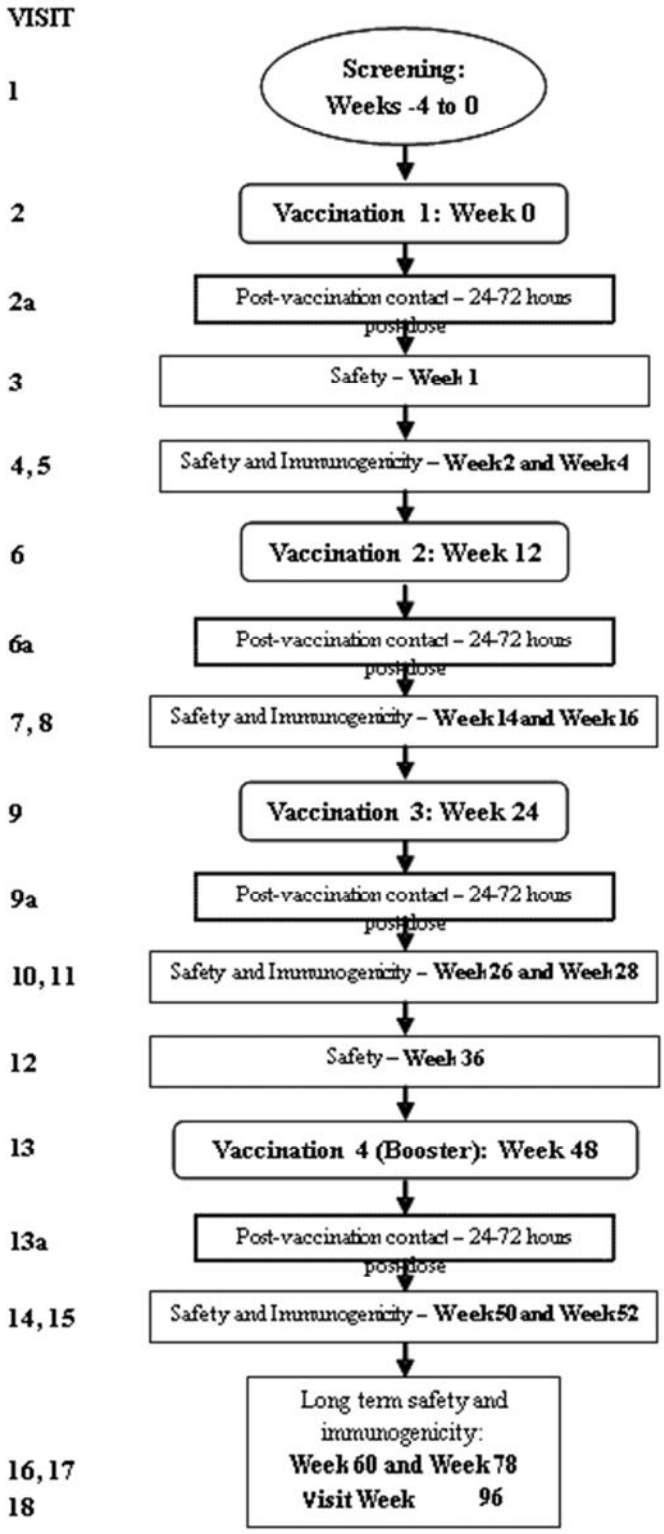
To decide whether further dosing can continue, the DMC will review blinded safety data (2 weeks of follow up) after 30% of subjects have received their first injection, and unblinded data after 10% of subjects have received their third injection, and after 30% of subjects have received their third vaccination.

DMC Review of gp140 DP Safety in HIV-V-A003

The safety, tolerability and immunogenicity of gp140 DP will be evaluated in a separate safety study (HIV-V-A003) with interim safety results available prior to the first subject reaching Week 24 of this study, HIV-V-A004 (the time point at which subjects in certain arms will receive gp140 DP). The DMC will review the interim safety results of study HIV-V-A003 and will allow administration of the first dose of gp140 DP (third injection; Week 24 vaccination) in this HIV-V-A004 protocol only if no safety concerns are identified.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



A long-term Extension Phase (approximately 5 years after Week 96) will continue for subjects randomized to Group 1 and Group 2.

3.2. Study Design Rationale

The rationale behind selection of study vaccines and doses is described in Section 1.1.

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 study vaccine will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Based on preclinical data, lack of remarkable differences in immunologic responses generated between different adjuvants tested, and its well-known safety and tolerability profile, as well as the relatively low cost of goods, aluminum phosphate has been chosen as the adjuvant. Aluminum-containing vaccines have been in use for more than 70 years and have been rarely associated with serious adverse events. However, local reactions such as redness, swelling and/or tenderness at the injection are common.

Aluminum-containing vaccines have been associated with severe local reaction such as redness, lumps under the skin, contact allergy or irritation, and swelling at the site of injection. There have also been reports, especially in patients with impaired renal function, of systemic accumulation of aluminum, which has been associated with nervous disorders and bone disease. Nonetheless, aluminum is one of the most common metals found in nature and is present in food and water. Aluminum intake from vaccines is far less than that received from dietary sources or medications such as antacids. Aluminium salts do not cause any serious or long-lasting adverse events [20,21].

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within the 4 weeks before the first administration of study vaccine at Week 0.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following two subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

4.1. Inclusion Criteria

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

1. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and is 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 physical examination, medical history, ECG and vital signs measurement performed at screening.

4. Laboratory criteria prior to enrollment*:

   - Hemoglobin: ≥11.0 g/dL, or accompanied by approval from the investigator and sponsor's study responsible physician and above the site's lower limit of normal (LLN)
   - White cell count: 2,500 to 11,000 cells/mm^3, inclusive
   - Absolute neutrophil count (ANC): >1,300 cells/mm^3, or accompanied by approval from the investigator and sponsor's study responsible physician and within the site's normal ranges
   - Platelets: 125,000 to 450,000 per mm^3, inclusive
   - Urinalysis: protein <1+, blood <1+ (men) and <2+ (women), and glucose negative
   - Alanine aminotransferase/aspartate aminotransferase (ALT/AST) <1.25 x upper limit of normal (ULN)
   - Creatinine <1.1 x 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[d].

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[e].

7. Contraceptive requirements for heterosexually active female subjects[f]:

   - 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); surgically sterile: no additional contraception required.
   - If of child-bearing potential, but has a vasectomized partner (after vasectomy, sperm count below the limit of detection must be confirmed if procedure occurred <1 year ago): no additional contraception required.
   - 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, should be practicing either:

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

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

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

– A long-acting reversible contraceptive method, including contraceptive implants, contraceptive injections, or an intrauterine system or device,) or,

– A double method of birth control, including combined contraceptive pills, progestogen-only pills, contraceptive patch, vaginal ring, diaphragm, or a cap in conjunction with either a male or female condom.

Women, who are not heterosexually active at screening, must agree to utilize an effective method of birth control if they become heterosexually active until 3 months after receiving the last dose of study vaccine.

	Woman not of Child-bearing Potential[a]	Woman of Child-bearing Potential	
Man with vasectomy[b]	NA	NA	
Man without vasectomy	NA	Single method Long-acting reversible contraceptive method, including contraceptive implants, contraceptive injections, or an intrauterine system or device	Double method Combined contraceptive pills, progestogen-only pills, contraceptive patch, vaginal ring, diaphragm, or a cap + male or female condom

[a] 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 FSH level >40 IU/L); surgically sterile

[b] Sperm count below the limit of detection must be confirmed if procedure occurred <1 year ago

8. Contraceptive requirements for heterosexually active male subjects:

   - If male subject had a vasectomy (after vasectomy, sperm count below the limit of detection must be confirmed if procedure occurred <1 year ago): no additional contraception required.
   - If male subject did not have a vasectomy or had a positive sperm count after a vasectomy procedure of <1 year ago: contraceptive methods will depend on child-bearing potential of female partner: same criteria to be followed as for female subjects in Criterion 7.

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

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.

12. Subjects are assessed by the clinic staff as being at low risk for HIV infection (see Attachment 2).

13. Passed the test of understanding (TOU) (see Section 16.1 and Attachment 3).

4.2. Exclusion Criteria

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] antibody test; if positive, HCV RNA PCR test will be used to confirm active versus past HCV infection), active syphilis infection, chlamydia, gonorrhea, or trichomonas[g]. Active syphilis documented by exam or serology unless positive serology is due to past treated infection.
2. In the 12 months prior to enrollment, subject has a history of newly acquired herpes simplex virus type 2 (HSV-2), syphilis, gonorrhea, non-gonococcal urethritis, chlamydia, pelvic inflammatory disease (PID), trichomonas, mucopurulent cervicitis, epididymitis, proctitis, lymphogranulomavenereum, chancroid, or hepatitis B.
3. Subject has any clinically significant acute or chronic medical condition that in the opinion of the investigator would preclude participation (eg, history of seizure disorders, bleeding/clotting disorder, autoimmune disease, active malignancy, poorly controlled asthma, active tuberculosis or other systemic infections).
4. Subject has had major surgery within the 4 weeks prior to study entry or planned major surgery through the course of the study.
5. Subject has a history of myocarditis, pericarditis, cardiomyopathy, congestive heart failure with permanent sequelae, clinically significant arrhythmia (including any arrhythmia requiring medication, treatment, or clinical follow up).
6. Subject has an ECG (per examination and interpretation of a central reading cardiologist) with clinically significant findings, or features that would interfere with the assessment of myo/pericarditis, including any of the following:
    a. Conduction disturbance (complete left or complete right bundle branch block or nonspecific intraventricular conduction disturbance with QRS ≥120 ms, PR interval ≥220 ms, any second or third degree AV block, or QTc[h] prolongation [>450 ms]);
    b. Significant repolarization (ST segment or T wave) abnormality;
    c. Significant atrial or ventricular arrhythmia; frequent atrial or ventricular ectopy (eg, frequent premature atrial contractions, two premature ventricular contractions in a

[g] Trichonomas testing will only be for female subjects

[h] According to Bazett's or Fridericia's formula. In the event that the value is reported by both methods, the longer of the 2 values will be considered for the exclusion criterion.

row)

d. ST elevation consistent with ischemia; or evidence of past or evolving myocardial infarction.

Note: If screening ECG parameters indicate suspicion of false positive results or user error, repeat of the ECG is permitted once

7. Subject has had a thyroidectomy, or thyroid disease requiring medication during the last 12 months.
8. 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.
9. 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/placebo.
10. 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/placebo.
11. Subject has been in receipt of any licensed vaccine within 14 days prior to the first dose of study vaccine, 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.
12. Subject has used experimental therapeutic drugs (excluding investigational vaccines) within 30 days of study entry.
13. Subject is currently in, or plans participation in, another clinical study during the study period without prior approval of the sponsor[i].
14. Subject has been in receipt of blood or immunoglobulin products in the past 3 months.
15. Subject has a history of anaphylaxis or other serious adverse reactions to vaccines or vaccine products, or neomycin or streptomycin or egg products.
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, oral or parenteral corticosteroids.
18. 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. For subjects who received an experimental vaccine (except HIV vaccine) more than 12 months ago, 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 where the vaccine received was subsequently

[i] For subjects randomized to the regimen that is subsequently selected and who enter the long-term follow-up period, this restriction will continue during this period until approximately 2 years after Week 96.

licensed (see exclusion criterion 11). Subjects with proof of having received only a placebo vaccine can also be included.

19. Subject who cannot communicate reliably with the investigator.
20. Subject is a study site employee, directly supervised by members of the study team, as well as family members of the investigator, employee of the sponsor or partners.
21. Subject is in the military.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including 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 and considered to be a screen failure. Section 17.4 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. Subjects must continue using an appropriate method of birth control (as described in Section 4.1) until 3 months after receiving the last dose of study vaccine.

   All female subjects of childbearing potential must have a negative serum pregnancy test at screening (β-hCG) and negative urine pregnancy tests immediately prior to each vaccine/placebo administration, and additionally at Weeks 26 and 60.

   Men must use an effective method of birth control as stated in Section 4.1.
2. Subjects in this study will not be able to donate blood or blood products during the time of the study due to the potential confusion with a false-positive HIV test (vaccine induced seropositivity) at blood banks. Furthermore, they may be excluded from donating blood in the future upon disclosure of their participation in a viral-vectored vaccine study and the potential false-positive HIV screening test result. For subjects randomized to the regimen that is subsequently selected and who enter the LTE phase, this restriction will continue during this period until approximately 5 years after Week 96.
3. Male subjects must agree not to donate sperm from the first administration of study vaccine until 3 months after the last dose of study vaccine.
4. Female subjects must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction until 3 months after the last dose of study vaccine.
5. Use of any experimental medication (including experimental vaccines other than the study vaccine) during the study (including the LTE phase) is disallowed. Vaccination with any licensed vaccine within 14 days prior to or after any of the study vaccinations is disallowed. However, if a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

6. Chronic or recurrent use of immunomodulators/suppressors, eg, cancer chemotherapeutic agents, oral or parenteral corticosteroids is prohibited during the main study and discouraged during the optional LTE phase and each use should be reported during clinical visits.

7. Concurrent participation in another clinical study without prior sponsor approval is disallowed. For subjects randomized to the regimen that is subsequently selected and who enter the LTE phase , this restriction will continue during this period until approximately 5 years after Week 96.

5. VACCINE ALLOCATION AND BLINDING

Study Vaccine Allocation

Procedures for Randomization

Central randomization will be implemented in this study. Subjects will be randomly assigned to one of eight 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 (US, Africa, and Asia). Efforts will be made to enroll a minimum of 50 subjects from each region.

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, clinical staff, and investigator, will be blinded to study vaccine allocation until Week 96. The sponsor will be blinded to study vaccine allocation until the Week 28 analysis (see Section 11.6). The pharmacist with primary responsibility for vaccine dispensing will not be blinded to the study vaccine.

A pharmacist will prepare study vaccine for administration and will provide it to the clinic. 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. More information and details on the preparation of vaccine and adjuvant components, as well as details on the holding time and storage conditions from the time of preparation to delivery of the study vaccine, are provided in Section 14.

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

Under normal circumstances, the blind should not be broken until the Week 96 electronic Data Capture (eDC) database is finalized. By participating to the LTE phase of the study, clinical staff, the investigator and participating subjects will be partially unblinded to their received treatment prior to full unblinding. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment. 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 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.

The sponsor, but not the investigator, will be unblinded at the time of the primary analysis at Week 28.

6. DOSAGE AND ADMINISTRATION

Each subject will receive doses of study vaccine at four timepoints according to randomization, on Day 1, at Week 12, and at Week 24, with a booster at Week 48, administered by IM injection into the deltoid. For visits with only one injection (ie, at Week 0 and 12), either deltoid can be used. When 2 study vaccine injections are to be given at one visit (ie, at Week 24 and 48), it is required to use a different deltoid for both injections. Exceptions 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 1 study vaccination, he/she will be withdrawn from further study vaccination (see Section 10.2).

Study vaccines are as follows:

- **Ad26.Mos.HIV** (Ad26.Mos.1.Env + Ad26.Mos1.Gag-Pol + Ad26.Mos2.Gag-Pol)
  - Total dose is $5x10^{10}$ vp per 0.5 mL injection
- **MVA-Mosaic** (MVA-Mosaic1 + MVA-Mosaic2):
  - Total dose is 10^{8} pfu per 0.5 mL injection
- **gp140 DP**:
  - Low-dose: gp140 DP with 50 mcg total protein, mixed with aluminum phosphate adjuvant (0.425 mg aluminum) at the pharmacy, per 0.5 mL injection
  - High-dose: gp140 DP with 250 mcg total protein, mixed with aluminum phosphate adjuvant (0.425 mg aluminum) at the pharmacy, per 0.5 mL injection

- **Placebo**:
  - 0.9% saline, 0.5 mL injection

7. TREATMENT COMPLIANCE

A pharmacist will prepare study vaccine for administration and will provide it to the clinic. 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. More information and details on the mixing and diluting of vaccine and adjuvant components, as well as details on the holding time and storage conditions from the time of preparation to delivery of the study vaccine, are provided in Section 14.3.

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

8. PRESTUDY AND CONCOMITANT THERAPY

Pre-study therapies administered up to 30 days before the screening visit will be recorded in the CRF at screening.

All concomitant therapies must be recorded on the CRF throughout the study from the signing of the ICF to the final main study visit at Week 96. Beyond Week 96, only concomitant therapies given in conjunction with an SAE will be collected, as well as any chronic or recurrent use of immunomodulators/suppressors and oral or parenteral corticosteroids (see below).

Use of any experimental medication (including experimental vaccines other than the study vaccine) during the study is disallowed. Vaccination with any licensed vaccine within the 14 days prior to or after any dose of study vaccine 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.

Study subjects can receive medications such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), 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 (Section 4.2), and these medications are prohibited during the main study and discouraged during the optional LTE phase and each use should be reported during clinical visits.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

For HIV post-exposure prophylaxis (PEP), see Section 9.4.5.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

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

From screening to the final visit at Week 96, the total blood volume to be collected from each subject will be approximately 1271 mL.

The Time and Events Schedule summarizes the frequency and timing of safety and immunogenicity measurements applicable to this study.

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), a confirmatory test should be performed within 48 hours after the results have become available. After that, laboratory tests will be repeated weekly until values are resolved or stable.

9.1.2. Visit Windows

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

- Visit 3: Day 8 ± 1 day
- Visit 4: Day 15 ± 3 days
- Visit 5: Day 29 ± 3 days
- Visit 6: Day 85 -1 week, + 3 weeks (second vaccination)
- Visit 7*: Visit 6 + 14 days (Day 99) ± 3 days
- Visit 8*: Visit 6 + 28 days (Day 113) ± 3 days
- Visit 9: Day 169 ± -1 week, + 3 weeks (third vaccination)
- Visit 10*: Visit 9 + 14 days (Day 183) ± 3 days
- Visit 11*: Visit 9 + 28 days (Day 197) ± 3 days
- Visit 12: Day 253 ± 5 days
- Visit 13: Day 337 - 1 week, + 3 weeks (fourth [booster] vaccination)
- Visit 14*: Visit 13 + 14 days (Day 351) ± 3 days

- Visit 15*: Visit 13 + 28 days (Day 365) ± 3 days
- Visits 16 to 18, inclusive: Days 421, 547, and 673 ± 3 weeks
- Visit 19 to 28 inclusive: Weeks 120, 144, 168, 192, 216, 240, 264, 288, 312, 336 ±4 weeks

*If a subject is not vaccinated on the given day of vaccination, the timings of visits at 2 and 4 weeks post-vaccination (see Time and Events Schedule) will be determined relative to the actual day of vaccination.

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 investigator and sponsor. If a subject misses more than 1 study vaccination, he/she will be withdrawn from further study vaccination.

9.1.3. Screening Phase (Weeks –4 to 0)

Only healthy subjects negative for HIV infection (if possible, the site should select an assay that is US Food and Drug Administration [FDA]-approved) and complying with the inclusion and exclusion criteria specified in Section 4 will be included into the study. The investigator 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 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 these pre-screening procedures are identical to the per protocol screening tests and are within the 28-day window 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 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[j]).

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

- Physical examination including vital signs measurement
- Medical history
- Review of pre-study medications
- HIV-risk assessment
- Cardiac risk assessment
- Review of inclusion/exclusion criteria

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

- Blood sampling for complete blood count (CBC) with differential, blood chemistries, hepatitis B and C serologies, troponin, and HIV testing
- Sexually-transmitted infection (STI) testing (syphilis, chlamydia, gonorrhea, trichomonas[k])
- 12-lead ECG, interpreted by a central reading cardiologist
- Pregnancy counseling for all subjects (men and women)
- Female subjects of childbearing potential: serum β-human chorionic gonadotrophin pregnancy testing
- Urinalysis

General eligibility for this clinical study will be dependent on results of laboratory tests and the medical assessment. Counseling related to the potential risks of becoming pregnant during this study and avoidance of HIV infection will be provided. Pre- and post-HIV test counseling will be provided to all subjects. Study subjects who qualify for inclusion based on the medical history, physical examination, and laboratory results will be contacted and scheduled for enrollment and initial vaccination (Visit 2) within 28 days.

Subjects with laboratory values or vital signs (eg, elevated blood pressure) not meeting eligibility criteria on the screening visit may have one repeat testing if the abnormality is not clinically significant and may be a testing aberrancy. The screening visit may be split into several visits.

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

Subjects who consent to mucosal secretion collection (Section 9.1.9) may have baseline samples taken at the screening visit instead of pre-vaccination on Day 1.

All AEs will be recorded on CRFs from the signing of the ICF until the subject's last study visit, together with information about any concomitant medications.

9.1.4. Vaccination (Weeks 0, 12, 24, and 48)

Visit 2: Week 0/Day of Randomization/Vaccination 1

After re-check of inclusion and exclusion criteria, a urine pregnancy test (for women of childbearing potential), abbreviated physical examination (including weight measurement), measurement of vital signs, and cardiac risk assessment, 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 28 days of

[k] Trichonomas testing will only be for female subjects

the initial screening assessments. If the initial laboratory sampling occurred longer than 28 days before the Day 1 visit, this will be considered a screen failure.

Pre-dose samples for hematology, biochemistry, urinalysis, and HIV testing will be collected. Before the first vaccination, subjects will also have blood drawn for cellular and humoral immunogenicity assays, and for assessment of Ad26 seropositivity. HLA will also be tested using the baseline blood sample. 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 vaccination, subjects will remain under observation for at least 30 minutes for reactogenicity, and vital signs measurement will be repeated.

Subjects will be provided with a memory aid, thermometer, and ruler to measure and record local solicited AEs and body temperature. Subjects will also note symptoms of unsolicited and solicited systemic AEs through the memory aid for 8 days post-vaccination (day of vaccination and the subsequent 7 days). Subjects who consent to mucosal secretion collection at this visit (Section 9.1.9) will undergo additional testing for syphilis, chlamydia, gonorrhea, and trichomonas.

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

Visit 6: Week 12/Vaccination 2

An abbreviated physical examination (including weight measurement), measurement of vital signs, and cardiac risk assessment will be performed for all subjects pre-vaccination. A pre-dose blood sample for humoral immunogenicity assessment will be drawn, and for assessment of Ad26 seropositivity. 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, urinalysis, and HIV testing will be collected.

After vaccination, subjects will remain under observation for at least 30 minutes for reactogenicity, and vital signs measurement will be repeated.

All AEs will be recorded on the CRFs, together with information about any concomitant medications.

Subjects will be provided a memory aid, thermometer, and ruler to measure and record local solicited AEs and body temperature. Subjects will also note symptoms of unsolicited and solicited systemic AEs through the memory aid for 8 days post-vaccination (day of vaccination and the subsequent 7 days).

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

Visit 9: Week 24/Vaccination 3

The procedures for Week 24 will be the same as at Visit 6 as detailed above. Additionally at Week 24, subjects will complete a Social Impact Questionnaire (Attachment 4).

Visit 13: Week 48/(Booster) Vaccination 4

The procedures for Week 48 will be the same as at Visit 6 as detailed above. Additionally, at Week 48, subjects will complete a Social Impact Questionnaire (Attachment 4).

9.1.5. Post-vaccination Follow-Up Phase (Weeks 1, 2 and 4; Weeks 14 and 16; Weeks 26, 28 and 36; Weeks 50 and 52)

Visits 2a, 3, 4, and 5 (Days 2-4, and Weeks 1, 2, and 4)

At Visit 2a (24-72 hour 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.

Visit 3 is a clinic visit that will include an abbreviated physical examination (including weight measurement), vital signs, and cardiac risk assessment, recording of any AEs and concomitant medications, and review of the memory aid for 8 days post-vaccination (day of vaccination and the subsequent 7 days).

Visit 4 is a clinic visit that will include an abbreviated physical examination (including weight measurement), vital signs, and cardiac risk assessment, recording of any AEs and concomitant medications, and collection of samples for humoral immunogenicity assay, and for safety laboratory testing (CBC, serum chemistry and urinalysis). Subjects who consent to mucosal secretion collection at this visit (Section 9.1.9) will undergo additional testing for syphilis, chlamydia, gonorrhea, and trichomonas.

Visit 5 is a clinic visit that will include an abbreviated physical examination (including weight measurement), vital signs, and cardiac risk assessment, recording of any AEs and concomitant medications, and collection of samples for cellular and humoral immunogenicity assay, assessment of Ad26 seropositivity, and for safety laboratory testing (CBC, serum chemistry and urinalysis).

At Visits 3 and 4, in addition to an HIV-risk assessment, counseling related to avoidance of HIV infection will be provided to all subjects.

Visits 6a, 7, and 8 (Days 86-88, and Weeks 14 and 16)

The procedures for Visits 6a, 7, and 8 will be the same as at Visits 2a, 4, and 5, respectively, as detailed above, with the exception that blood samples for cellular and humoral immunogenicity assay will be drawn at both Visits 7 and 8. Additionally at Visit 8 only, a 12-lead ECG will be carried out.

Visits 9a, 10, and 11 (Days 170-172, and Weeks 26 and 28)

The procedures for Visits 9a, 10, and 11 will be the same as at Visits 6a, 7 and 8, respectively, as detailed above. (Note: no ECG at Visit 11.)

Visit 12 (Week 36)

Visit 12 will be for safety follow up only, and will include an abbreviated physical examination (including weight measurement), vital signs measurement, and cardiac risk assessment, recording of any AEs and concomitant medications, and collection of samples for safety laboratory testing (CBC, serum chemistry and urinalysis).

In addition to an HIV-risk assessment, counseling related to avoidance of HIV infection will be provided to all subjects.

Visits 13a, 14, and 15 (Days 338-340, and Weeks 50 and 52)

The procedures for Visits 13a, 14, and 15 will be the same as at Visits 6a, 7, and 8, respectively, as detailed above.

9.1.6. Second Year Follow-Up Phase (Weeks 60 to 96)

Visits 16, 17, and 18 (Weeks 60, 78, and 96, respectively)

Subjects will make follow-up visits at the clinic from Week 60 until the final visit at Week 96. Each visit includes an abbreviated physical examination (including weight measurement), vital signs measurement, cardiac risk assessment, recording of any AEs and concomitant medications, and collection of samples for cellular and humoral immunogenicity assay, assessment of Ad26 seropositivity, and for safety laboratory testing (CBC, serum chemistry and urinalysis). Subjects who consent to mucosal secretion collection at Visits 16 and 18 (Section 9.1.9) will undergo additional testing for syphilis, chlamydia, gonorrhea, and trichomonas at both visits.

At Visits 17 and 18, 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. At Week 60 and Week 96, a urine pregnancy test will be carried out for women of childbearing potential and pregnancy counseling will be provide to all subjects (men and women).

Also, at Week 96, subjects will complete a Social Impact Questionnaire (Attachment 4).

9.1.7. Early Withdrawal – Early Exit Visit

In the event of early withdrawal from the study (ie, before Week 96), the following procedures will be performed: an abbreviated physical examination (including weight measurement), measurement of vital signs, and cardiac risk assessment, recording of any AEs/SAEs and concomitant medications, and collection of samples for immunogenicity assays, assessment of Ad26 seropositivity, and for safety laboratory testing (CBC, serum chemistry and urinalysis). In addition to an HIV-risk assessment, counseling related to avoidance of HIV infection, pre- and post-HIV test counseling, and pregnancy counseling will be provided to all subjects (men and women). A urine pregnancy test will be carried out for women of childbearing potential. Additionally at the early withdrawal visit, subjects will complete a Social Impact Questionnaire (Attachment 4).

9.1.8. Long-Term Extension Phase

Based on the analysis of the Week 28 data, a LTE phase (approximately 5 years after Week 96) will be performed for subjects randomized to Group 1 and Group 2 who have received all 4 vaccinations. At Week 96, these subjects will be asked to sign the ICF appendix for the LTE phase. If signing the ICF appendix is not possible at Week 96, signing should be performed at an extra visit (Visit 18bis) as soon as possible after Week 96 and at the very latest at Visit 19, before any assessment is performed.

Subjects will make follow-up visits at the clinic from Week 120 until the final visit at Week 336. Each visit includes recording of any SAEs and concomitant medications (any medication given in conjunction with an SAE, as well as any recurrent or chronic use of immunomodulators and corticosteroids), and collection of samples for cellular and humoral immunogenicity assay, and assessment of Ad26 seropositivity.

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).

9.1.9. Local Mucosal Sampling

Cervico-vaginal secretions (women), ano-rectal secretions (men and women), and ejaculate (men) will be collected from consenting subjects to assess if desirable mucosal HIV-1-specific immune responses are induced, that may be able to block or attenuate infection. These collections are optional and will be collected at all participating sites at Day 1 (baseline), 2 weeks after each vaccination, during the second year follow-up visits and at the final visit for both male and female subjects. Subjects who consent to mucosal collection will be tested for gonorrhea, chlamydia, syphilis and trichomonas at each visit where mucosal samples are collected. Collection will not take place if the woman is menstruating or has signs or symptoms of active inflammation or infection of the vagina or cervix. Serum estradiol and progesterone levels and last menstrual period will be measured/recorded at each collection visit, for women who consent to the cervico-vaginal sample collection. If, during the course of the study, a woman becomes pregnant, she will be excluded from further mucosal secretion collections. Women with

a history of toxic shock syndrome will be excluded from cervico-vaginal mucosal sampling. Subjects who have had surgical sex-reassignment will be excluded from cervico-vaginal mucosal and semen sampling. Further details on the collection of mucosal samples are provided in the Site Procedures Manual.

9.2. Immunogenicity

9.2.1. Endpoints

The primary immunogenicity endpoints will be defined as the Env-C ELISA binding antibody titer and breadth of Env-binding antibody response across Clades A, B, and C measured at Week 28.

For evaluation of humoral responses:

- Env-specific binding antibody titers (ELISA) 4 weeks after the third and fourth vaccinations, covering Clades A, B, and C.
- HIV nAb titers for Tier 1 and Tier 2 viruses covering Clades A, B, and C; note: Tier 2 will be assessed only if Tier 1 shows positive results.
- Functional antibodies as assessed by antibody-dependent cellular phagocytosis (ADCP) assay.

For evaluation of T-cell responses:

- Assays of peptide pool sets covering the Gag, Env or Pol will be evaluated by standard ELISPOT criteria [17] with additional mapping of positive pools to determine the number of positive epitopes for each individual, at baseline and at 2 and 4 weeks after the third and fourth vaccinations.

For durability of responses:

- Immunogenicity assays at 12, 30, and 48 weeks after the last vaccination. Durability of responses to be followed approximately 5 years after Week 96 in selected group(s) (see Section 9.1.8).

9.2.2. Evaluations

Venous blood samples of approximately 20 mL will be collected for the determination of humoral responses. For the determination of cellular responses, venous blood samples of approximately 102 mL will be collected. The Laboratory Manual contains further information regarding the collection, handling, labeling, and shipment of blood samples to the central laboratory. Sampling for humoral and cellular immunogenicity testing will be performed as indicated in the TIME AND EVENTS SCHEDULE.

Humoral response assays will include, but are not limited to Env-specific serum binding antibody assay, nAb assays, and antibody-dependent cellular phagocytosis (ADCP) assay, as well as epitope mapping (see Table 5).

Table 5: Humoral Immune Response Assays

Objective/ endpoint	System	Assay/Method	Readout	Timepoint
Primary	Serum	Env binding antibody (ELISA)	Titer or % responders (Clade C) and breadth (Clade A, B, C)	Baseline 1 mo post-vac. 1 0.5, 1 mo post-vac. 2-4 3, 6 mo post-vac. 4
Secondary	Serum	HIV neutralizing antibody	Tier 1 and Tier 2[a] nAbs: GMT for each isolate, % responders to each isolate Breadth: # isolates neutralized	As above
Secondary	Serum	gp120 binding antibody	Anti-gp120 titer (Clade A, B, C)	As above
Secondary	Serum	ADCP	% phagocytosis	As above
Secondary	Serum	Isotyping Env binding antibody (ELISA)	Isotyping (Clade C) (IgA, IgG1, IgG2, IgG3)	As above
Exploratory	Serum	Epitope mapping	Targeted epitopes and diversity (including V2)	1 mo post-vac. 1-4 At vac. 2-4
Exploratory	Serum	Ad26 neutralization antibodies	Titers of Ad26 neutralization antibodies	1 mo post-vac. 1-4 3, 7.5, 12 mo post-vac. 4 At vac. 1-4

ADCP = antibody-dependent cellular phagocytosis; ELISA = enzyme-linked immunosorbent assay; GMT = geometric mean titer; Ig = immunoglobulin; mo = month; nAb = neutralizing antibody; vac = vaccination

[a] Classification of HIV-1 viruses according to sensitivity to antibody-mediated neutralization: very high (tier 1A), above-average (tier 1B), moderate (tier 2), or low (tier 3) [1]. Tier 2 will only be assessed if Tier 1 shows positive results.

Evaluations of cellular immune responses will include, but are not limited to, the following assays: ELISPOT, intra-cellular cytokine staining, and multi-parameter flow cytometry (see Table 6).

Table 6: T-Cell Immune Response Assays

Objective/ endpoint	System	Assay/Method	Readout	Timepoint
Secondary	PBMC	ELISPOT	Breadth and depth: # peptides, % responders, median response	Baseline 0.5, 1 mo post-vac. 3 & 4
Exploratory	PBMC	Intracellular cytokine staining	% of CD4 and CD8+ T cells producing IFNγ, IL-2, TNFα	Baseline 1 mo post-vac. 1 0.5, 1 mo post-vac. 2-4 3, 7.5 mo post-vac. 4
Exploratory	PBMC	Multi-parameter flow cytometry	Characterization of memory T-cell development with emphasis on follicular helper T cells	Baseline 1 mo post-vac. 1 0.5, 1 mo post-vac. 2-4 3, 7.5 mo post-vac. 4
Exploratory	PBMC	Gene expression analysis	Regulation of genes (clusters) that predict specific immune responses and HLA typing	Baseline 1 mo post-vac. 1 0.5, 1 mo post-vac. 2-4 3, 7.5 mo post-vac. 4

ELISPOT = enzyme-linked immunospot assay; HLA = human leukocyte antigen; IFNγ = interferon gamma; IL-2 = interleukin 2; mo = month; PBMC = peripheral blood mononuclear cell; TNFα = tumor necrosis factor alpha; vac = vaccination

Note: HLA only tested once (using the baseline blood sample)

Exploratory humoral and cellular immunogenicity assessments during the optional long-term extension phase (Group 1 and 2 only) may include, but are not limited to, the following assays: Env-specific serum binding antibody assay and ELISPOT. Further specification will be based on the Week 52 results.

Exploratory assessments on mucosal samples will include, but are not limited to, characterization of Env-specific binding antibodies.

9.3. Safety Evaluations

9.3.1. Endpoints

Safety and tolerability endpoints:

- AEs until Week 96 and local and systemic reactogenicity rates for 8 days after each vaccination.
- Discontinuations from vaccination/from study due to AEs.
- SAEs during the course of the study.

9.3.2. Evaluations

Any clinically relevant safety-related changes that occur during the study must be recorded in the CRF.

Any clinically significant abnormalities 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.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule:

Adverse Events

AEs will be recorded from signing of ICF until the final visit of the main study (Week 96). SAEs (including HIV infection and abnormal pregnancy outcome) will be recorded for the duration of the study, including the optional LTE phase (Group 1 and Group 2 only). AEs will be followed by the investigator as specified in Section 12.
Details regarding the PSRT and the DMC are provided in Sections 11.7 and 11.8, respectively.

Cardiac-Related Events

At study visits, subjects will be specifically questioned about cardiac-related events, including chest pain/pressure, shortness of breath, and peripheral edema. Any suspicion of a cardiac event will be evaluated clinically by history and physical examination, ECG (read by a central reading cardiologist), and quantitative troponin assay. In the event of an elevation of troponin and/or pathologic ECG changes, the subject will be sent for evaluation by a local cardiologist.

Solicited Adverse Events

Solicited AEs are precisely defined events that subjects are specifically asked about and which are noted by subjects through the memory aid. The investigator or his/her designee should discuss the information from the memory aids with subjects, document relevant information in the clinic chart (source document) and complete the relevant parts of the CRF as described in the CRF Completion Guidelines.

Injection Site (Local) Reactions

Subjects will be asked to note occurrences of erythema, induration and swelling (measured using the ruler supplied), and pain/tenderness, itching, or warmth at the injection site daily for 8 days post-vaccination (day of vaccination and the subsequent 7 days). These occurrences should be recorded through the memory aid provided to serve as a reminder to the subject for the next clinic visit.

Solicited Systemic AEs

Subjects will be instructed on how to record daily temperature using a thermometer provided for home use. Subjects should record oral temperature in the evening post-vaccination, and then daily for the next 7 days through the memory aid. Temperature should be measured at approximately the same time each day. If more than one measurement is made on any given day, the highest daily temperature will be used in the CRF. Fever will be recorded by the investigator or his/her designee for temperatures equal to or higher than 38.0 °C.

Subjects will also be instructed on how to note daily symptoms through the memory aid for 8 days post-vaccination (including the day of vaccination) of the following events:

- fatigue
- headache
- myalgia
- arthralgia
- chills
- fever
- nausea
- vomiting
- rashes
- general itching

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected at times specified in the Time and Event Schedule. The investigator must review the laboratory report, 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), a confirmatory test should be performed 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 a local laboratory (*parameters only measured at screening):

- **Serum chemistry**

sodium*	alkaline phosphatase*
potassium*	phosphate*
chloride*	albumin*
calcium*	total protein*
magnesium*	bilirubin*
bicarbonate*	AST
blood urea nitrogen (BUN)*	ALT
glucose*	creatinine
creatine phosphokinase (CPK)*	troponin
	FSH (post-menopausal women only)*

- **Hematology**

  hemoglobin

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

- **Urinalysis** – dipstick for
specific gravity
pH
glucose
protein
blood
ketones

Microscopic reflex testing will be carried out in the event of positive urinalysis tests.

Laboratory values will be graded according to a modified version of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0 dated December 2004 (Clarification, August 2009) included in Attachment 1, and, if clinically significant, reported as AEs.

Additional clinical laboratory assessments to be performed are as follows:

- Serum pregnancy testing (β-hCG) for women of childbearing potential at screening
- Urine pregnancy testing for women of childbearing potential pre-dose on Day 1, Weeks 12, 24, 48, 60, 96 and at the early exit visit. A urine pregnancy test will also be carried out prior to mucosal secretion collection, for those females who have consented to this procedure.
- Troponin at screening
- Serology: hepatitis B, and hepatitis C at screening
- Syphilis, chlamydia, gonorrhea and trichomonas at screening, and additionally at Weeks 2, 14, 26, 50, 60, and 96 for subjects who consent to mucosal secretion collection
- HIV testing at screening, pre-dose on Day 1, Weeks 12, 24, and 48, and additionally at Weeks 78 and 96, at the early exit visit and at each visit of LTE phase.

Electrocardiogram (ECG)

Supine 12-lead ECGs will be performed at screening and at Week 16, and only performed again during the study if clinically indicated based on signs and symptoms.

For 30 minutes prior to the ECG, subjects should refrain from meals, hot or cold beverages and strenuous exercise, and should remain in a room with a comfortable temperature. Each ECG should be obtained after the subject has been at rest for at least 5 minutes. ECG interpretation/comparison will be provided by a central reading cardiologist.

Computer-generated interpretations of ECGs should be reviewed for data integrity, reasonableness and for immediate safety assessment by the investigator or appropriately delegated healthcare provider. Digital ECG data will be transmitted to a centralized ECG over-read service provider. Over-read of the ECGs will be transmitted back to the site within 72 hours. The centralized ECG over-read data will be considered source data.

Vital Signs

Vital sign measurements will be performed at time points specified in the Time and Events Schedule. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions.

The following measurements will be performed:

- Heart rate (beats per minutes, bpm), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg). Confirmatory vital signs measurement can be performed if inconsistent with a prior measurement
- Body temperature (oral)

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, including height and weight, will be carried out at screening and at the final visit of the main study (Week 96). At all other visits, 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. Weight will be measured at every visit.

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

9.4.1. HIV Testing

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

After screening, diagnostic HIV testing will be performed during the study as indicated in the Time and Events Schedule. An HIV testing algorithm (detailed in the Study Procedures 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 “infected” or “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 phase of the study aims to differentiate false-positive results (Vaccine Induced Seropositivity [VISP]) from true positives (HIV infection).

If a false-positive HIV test develops during the study, further HIV testing will be offered via post-study follow up. (See Section 9.4.3 for more details on VISP).

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 will (see Section 12.3.3):

- be excluded from further vaccinations
- be provided counseling and referred for medical treatment
- be informed about observational studies monitoring subjects with HIV infection

9.4.3. Vaccine Induced Seropositivity (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. VISP may become evident during the study, or after the study has been completed.

Should a subject receive a positive result in an HIV antibody test during the study, the site will carry out a follow-up testing algorithm either to exclude or confirm HIV infection. Further details of this algorithm are given in the Site Procedures Manual.

Subjects should not donate blood during the study. Blood donation options for those subjects who wish to resume blood donation 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 the site at most every three months, to confirm their HIV-status. 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, the site will provide HIV testing on request as described in the previous paragraph.

In addition to providing testing, subjects will always receive pre- and post-test 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 at Weeks 24, 48, 96, and at each visit of the LTE phase as specified in the TIME AND EVENTS SCHEDULE to evaluate any potential consequences of the subject's participation.

9.4.5. Post-Exposure Prophylaxis (PEP)

In case a subject believes he/she might have been exposed to HIV, he/she should contact the study site as soon as possible. Treatment will be determined by the investigator or his designee, in accordance with local PEP guidelines. The sponsor should be informed as soon as possible. PEP medication will be reimbursed by the sponsor during study participation. HIV prevention counseling will be provided. In case a subject has recurrent need for PEP, eligibility of the subject (with regards to HIV-risk profile) to continue in the study will be re-assessed.

9.5. Sample Collection and Handling

The actual dates of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples for immunogenicity assay are found in the Laboratory 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/WITHDRAWAL

10.1. Completion

A subject who is not participating in the long-term extension period will be considered to have completed the study if he or she has completed the assessments at Week 96. A subject who is participating in the long-term extension period will be considered to have completed the main study if he or she has completed the assessments at Week 96 and will be considered to have completed the LTE phase if he or she has completed the assessments at the last visit of the extension period (Week 336).

10.2. Discontinuation of Study Vaccine

Subjects will be withdrawn from study vaccine administration for the reasons listed below. These subjects must not receive any additional dose of study vaccine but should enter the follow-up phase, starting from Visit 14 onwards. Additional unscheduled visits may be performed for safety/tolerability reasons, if needed. These subjects are not eligible for the LTE phase.

- 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 (see Section 8)
- Missing more than 1 study vaccination (see Section 6).

*AEs deemed by the investigator to be very likely, probably, or possibly related to study vaccine.

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 time of vaccination.

10.4. 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:

- 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 and Institutional Review Board/Independent Ethics Committee (IRB/IEC) to stop or cancel the study
- Lost to follow up

- Withdrawal of consent
- Death

If a subject is lost to follow up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken for at least three efforts 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. Enrollment will be stopped when 400 subjects have received at least one vaccination. 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 96.

A subject who withdraws from the study will have the following options regarding optional research samples:

- 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.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The subject may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for future research (refer to Section 16.2.5). 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 main 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 immunogenicity and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

The primary analysis will be performed once all subjects have completed the Week 28 visit (ie, 4 weeks after the third injection) or discontinued earlier. The purpose of this analysis is to allow for an early conclusion on regimen selection for future studies, based on immunogenicity and safety. 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 study visit at Week 96 (ie, including the second year follow-up period) or discontinued earlier. The final analysis of the LTE phase (optional and only for a subset of subjects) will be performed once all included subjects have completed the last visit of the extension period (Week 336), or discontinued earlier.

11.1. 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 data from at least one post-dose blood sample.

The per-protocol population will consist of all subjects who have received at least the first three vaccinations according to the protocol-specified vaccination schedule, have at least one measured post-dose blood sample collected, and who have no major protocol violations impacting immunogenicity assessments.

11.2. Sample Size Determination

A sample size of 50 subjects per regimen is regarded to be appropriate to assess the safety and tolerability of the different vaccine regimens and also collect sufficient data on immunogenicity. Placebo recipients are included for blinding and safety purposes and will provide control specimens for immunogenicity assays.

While mild to moderate vaccine reactions (local injection site and systemic responses) are expected, AEs that preclude further dose administration or more serious ones that would limit product development are not anticipated. With 50 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 6%. For the combined groups with Ad26.Mos.HIV (n = 350), there would be 95% confidence that the true rate is <1% when 0 events are observed. The following table shows the probabilities of observing at least one AE at given true AE rates:

True AE rate	Probability of observing at least one AE in n subjects	
	n = 50	n = 350
0.1%	5%	30%
0.5%	22%	83%
1%	39%	97%
2.5%	72%	100%
5%	92%	100%
10%	99%	100%

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

The immunogenicity population will consist of all subjects who received at least one dose and have at least one measured post-dose blood sample collected. Anticipating a dropout rate of approximately 10%, 45 evaluable subjects per group will allow detection of 2.3-fold differences in Env-binding antibody titers, generally accepted to be biologically relevant, between groups with 80% probability, assuming a two-sided 5% Type I error and a standard deviation of 0.6 on the $\log_{10}$ scale.

Groups will be combined to make comparisons between different viral vectors (groups combined over the different protein doses, N=135 per group) or between different protein doses (groups combined over different viral vectors, N=90 per group). Under the same assumptions as above, this will allow detection of 1.6-fold (N=135/group) to 1.8-fold differences (N=90/group) in Env-binding antibody titers. Potential statistical interactions will be explored by means of the appropriate interaction tests.

Breadth of Env-binding antibody response will be summarized as the number of HIV clades (ranging 0-3, for Clades A, B, C) to which a subject shows an antibody response. Differences in breadth between different regimens will be compared via the Wilcoxon-Mann-Whitney test. Assuming 45 evaluable subjects per group, a two-sided 5% Type I error rate, no correlation between the different clades, and a 90% response rate for every clade (A/B/C) in one group, Table 7 below shows the power to detect a significant difference with various alternative breadths and (combined) group sizes.

Table 7: Power (%) for two-sided 5% test for difference in breadth of response, if the response towards Clade A/B/C in one group is 90%/90%/90%

N per group	45	90	135
Lower response for 3 clades			
80/80/80	61.9	88.9	97.3
75/75/75	89.0	99.4	>99.9
70/70/70	98.0	>99.9	>99.9
Lower response for 2 clades			
90/80/80	36.0	61.6	78.7
90/75/75	63.4	90.0	97.7
90/70/70	84.1	98.6	>99.9
Lower response for 1 clade			
90/90/80	13.7	22.7	31.5
90/90/75	24.4	42.9	58.7
90/90/70	38.3	64.9	81.7

11.3. Subject Information

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

11.4. Immunogenicity Analyses

No formal hypothesis on immunogenicity will be tested. The analysis of immunogenicity will be done on the immunogenicity and per-protocol populations as defined in Section 11.1.

Descriptive statistics (actual values and changes from reference) will be calculated for continuous immunologic parameters at all time points. Graphical representations of changes in immunologic parameters will be made as applicable. 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 two-sided and will be considered statistically significant if $p<0.05$.

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

Magnitude and breadth of (neutralizing) antibody 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.

11.5. Safety Analyses

No formal statistical testing of safety data is planned. Safety data will be analyzed descriptively (including 95% confidence interval).

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

Adverse Events and Reactogenicity

The verbatim terms used in the CRF by investigators to report AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs (local and systemic, solicited and unsolicited) with onset during the treatment period (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the number and percentage of subjects who experience at least one occurrence of the given event will be summarized by group, including exact 95% confidence intervals. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue vaccinations due to an AE, or who experience a severe AE or an SAE. The analysis for solicited AEs will be done on those subjects in the safety population for whom reactogenicity assessments are available in the database. The analysis of unsolicited AEs will be done based on the safety population.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics (actual values and changes from reference) will be calculated for each laboratory analyte at baseline and at each scheduled time point. Graphical presentation of changes in laboratory tests will be made as applicable. Baseline refers to the pre-dose value on Day 1. If this value is not available, the value at screening will be used as baseline value. Laboratory abnormalities will be determined according to a modified version of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0 dated December 2004 (Clarification, August 2009) included in Attachment 1, and in accordance with the normal ranges of the clinical laboratory. Laboratory abnormalities will be tabulated per treatment group.

Electrocardiogram (ECG)

All statistical analyses of ECG variables will use the centralized ECG over-read data.

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations.

Vital Signs

Descriptive statistics of pulse rate and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond pre-specified limits will be summarized.

Physical Examination

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

Social Impact Questionnaire

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

11.6. Interim Analysis

Interim safety data will be reviewed by the PSRT (see Section 11.7) and the DMC (See Section 11.8)

No formal interim analysis is planned prior to the primary analysis. The primary analysis will be performed once all subjects have completed the Week 28 visit (ie, 4 weeks after the third injection) or discontinued earlier. The purpose of this analysis is to allow for an early conclusion on regimen selection for future studies, based on immunogenicity and safety. 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 study visit at Week 96 (ie, including the second year follow-up period) or discontinued earlier. The final analysis of the LTE phase (optional and only for a subset of subjects) will be performed once all included subjects have completed the last visit of the extension period (Week 336), or discontinued earlier.

11.7. Protocol Safety Review Team (PSRT)

The internal PSRT will review all AEs on a regular basis as needed. The PSRT will also review safety data reports on a regular basis until the last subject has completed the Week 52 visit, and thereafter as needed. In addition to regular reviews of safety information, the PSRT will perform a cumulative review of blinded safety data.

The PSRT will review safety data at two specific timepoints to ensure the safety of the subjects:

- Following a pause in enrollment after 10% of the target number of subjects have received their first injection, the PSRT will review blinded Week 2 safety data of these subjects to determine if enrollment can continue.
- Review blinded safety data (2 weeks of follow up) after 30% of subjects have received their first injection (without enrollment pause).

The occurrence of any AE/SAE leading to a study holding situation may trigger a DMC meeting as outlined in Section 11.9, and the PSRT will decide by consensus whether any other AE/SAE should also be reviewed by the DMC. As per Section 11.9, any AE/SAE will be handled as indicated in Table 8, be it for a DMC meeting or for a PSRT review and consideration for a

DMC meeting. As described below, the DMC will operate according to a charter and will evaluate safety and tolerability data.

The PSRT will include, but will not be limited to, medical and safety representatives from the sponsor, site, DAIDS and BIDMC.

11.8. Data Monitoring Committee (DMC)

An independent DMC will be appointed by the sponsor before the start of the study and will operate according to its charter. The DMC may review an individual SAE or it may choose to review AEs, SAEs, and laboratory and vital sign data. The conclusions of the DMC will be communicated to the investigators and the IRB/IEC and the national regulatory authorities as appropriate. The sponsor agrees to abide by the decision of the DMC and any directives issued by the national regulatory authorities, the IRBs or IECs.

In general, the DMC may unblind any amount of safety information needed to conduct their assessment.

The DMC will review safety data at three specific timepoints to ensure the safety of the subjects:

- Review blinded safety data (2 weeks of follow up) after 30% of subjects have received their first injection to decide whether further dosing can continue;
- Review unblinded safety data (2 weeks of follow up) after 10% of subjects have received their third injection to decide whether further dosing can continue;
- Review unblinded safety data (2 weeks of follow up) after 30% of subjects have received their third injection to decide whether further dosing can continue.

The occurrence of any AE/SAE leading to a study holding situation may trigger a DMC meeting, as outlined in Section 11.9 .

The DMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The DMC responsibilities, authorities, and procedures will be documented in its charter.

11.9. Study Holding Rules

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. The AEs that may lead to a safety pause or prompt PSRT AE review are summarized below in Table 8. These study holding rules apply to AEs/SAEs occurring up to 4 weeks after the last vaccination. Related AEs are defined as AEs deemed to be very likely, probably, or possibly related to study vaccine; not related AEs are defined as AEs deemed to be doubtful or not related to the study vaccine.

Table 8: AE Notification and Safety Pause/AE Review Rules[1]

(S)AE and Relationship[2]	Severity	Site Principal Investigator Action	PSRT/DMC Action
SAE, related	Any grade	Phone Study Responsible Physician or designee AND fax SAE form to Global Medical Safety Officer, immediately and within 24 h	Immediate vaccination pause for PSRT review of safety data
SAE, not related	Grade 5	Phone Study Responsible Physician or designee AND fax SAE form to Global Medical Safety Officer, immediately and within 24 h	PSRT review and consideration of pause
AE, related	Grade 3 or Grade 4	Phone Study Responsible Physician immediately and within 24 h	PSRT review and consideration of pause
≥3 subjects with a similar related AE[3]	Grade 3 or Grade 4	Not applicable	Immediate vaccination pause for DMC review of safety data

The telephone number of the Study Responsible Physician (and designee) is in the Contact Information page(s). The Study Responsible Physician (or designee) is responsible for the immediate notification of PSRT/DMC members and coordination of a PSRT/DMC 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. Conduct of DMC review will require a confirmation of the laboratory test within 48 hours.

[2] Related: very likely, probably, or possibly related to the study vaccine; not related: doubtful or not related to the study vaccine.

[3] 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 72 hours)

After each DMC review of a similar AE, the DMC 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, pending DMC review, if, in the judgment of the PSRT, 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, as specified in Table 8, the PSRT will convene within one business day to review these AEs. The PSRT will review and determine disposition, including whether the DMC needs to review the event(s).

If a study pause is triggered by the PSRT, all enrollment and vaccinations will be held until review by the PSRT or DMC is complete. Resumption of enrollment and study treatment may be determined by the PSRT or DMC (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 DMC 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. ADVERSE EVENT 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.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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 ICF to the final visit of the main study (Week 96). During the optional LTE phase (Group 1 and 2), only SAEs will be recorded.

Serious Adverse Event

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 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.

Confirmed HIV infection in a subject during the study is considered an SAE (see Section 12.3.3).

A suspected transmission of any infectious agent via a medicinal product is always considered as an important medical event, ie, an SAE.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study vaccine and the event (eg, death from anaphylaxis), the event will be reported as a suspected unexpected serious adverse reaction (SUSAR) by the sponsor to Health Authorities and by the investigator to the IRB/IEC according to regulatory and local requirements.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Ad26.Mos.HIV, MVA-Mosaic and gp140 DP, the expectedness of an AE will be determined by whether or not it is listed in the respective Investigator's Brochures [2-4].

Adverse Event Associated With the Use of Study Vaccine

An AE is considered associated with study vaccine if the attribution is possibly, probably, or very likely related by the definitions listed in Section 12.1.2.

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 therapy). This applies to all AEs, whether serious or non-serious.

The investigator will use the following guidelines to assess the causal relationship of an AE to study vaccine:

Not related:	An AE that is not related to the use of study vaccine.
Doubtfully related:	An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.
Possibly related:	An AE that might be due to the use of study vaccine. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
Probably related:	An AE that might be due to the use of study vaccine. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).
Very likely related:	An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

Related AEs are defined as AEs deemed to be very likely, probably, or possibly related to study vaccine; not related AEs are defined as AEs deemed to be doubtful or not related to the study vaccine.

12.1.3. Severity Criteria

All AE and laboratory data will be coded for severity using a modified version of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0 dated December 2004 (Clarification, August 2009) included in Attachment 1.

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. Special Reporting Situations

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

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

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last procedure of the main study (which may include contact for follow-up of safety). During the optional LTE phase (Group 1 and 2), only SAEs will be recorded.

All SAEs, must be reported to the sponsor during the entire study period (including the optional LTE phase for Group 1 and 2) using the SAE Form. Suspected unexpected serious adverse reactions (SUSARs) are reported even after the study is over, if the sponsor, DMC or investigator becomes aware of them. The sponsor will evaluate any safety information that is spontaneously reported by the investigator beyond the time frame specified in the protocol.

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 12.1.1. 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.

Post-injection reactogenicity (PIR) includes solicited AEs related to study vaccine and therefore must be reported as such. The investigator or designee must review both PIR 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 study 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 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 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.

Subjects will 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
- Information about who should be contacted in case of emergency

12.3.2. Serious Adverse Events

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. The initial and follow-up reports of a SAE should be made by facsimile (fax) and/or e-mail.

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 study 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)

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 during the entire study period, whether or not the event is expected or associated with the study vaccine, is considered an SAE and must be reported.

12.3.3. 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, and must be negative to be entered into the study. If possible, the site should select an assay that is US FDA-approved. After screening, an HIV testing algorithm (detailed in the Study Procedures Manual) will be followed. 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 SAE and must be reported using the Serious Adverse Event Form.

12.3.4. Pregnancy

All initial reports of pregnancy 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, stillbirth, and congenital anomaly) are considered SAEs and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from further study vaccination but should continue participation in the study for follow up (see Section 10.2).

Because the effect of the study vaccine on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required to be sent to the sponsor.

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 on 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 on the Contact Information page(s), which will be provided as a separate document.

14. STUDY VACCINE INFORMATION

14.1. Physical Description of Study Vaccines

Ad26.Mos.HIV

Ad26.Mos.HIV vaccine is made up of the following three drug substances in a 2:1:1 ratio:

- Ad26.Mos1.Env (JNJ-55471468-AAA)
- Ad26.Mos1.Gag-Pol (JNJ-55471494-AAA)
- Ad26.Mos2.Gag-Pol (JNJ-55471520-AAA)

The Ad26.Mos.HIV vaccine, manufactured by Janssen Vaccines & Prevention B.V., Leiden, The Netherlands, that will be supplied for this study is formulated as a trivalent vaccine as a clear to slightly opalescent solution for IM injection. The vaccine will be supplied as a frozen liquid to be thawed prior to use, and will be essentially free from particles. The vaccine will be provided in individual dosage vials at a concentration of 1 x 10^{11} vp/mL. Each stoppered and sealed glass vial contains a volume of approximately 0.7 mL. Refer to the Investigator's Brochure for a list of excipients [2].

MVA-Mosaic

MVA-Mosaic consists of the following two vaccine products supplied in separate vials and administered in a 1:1 ratio:

- MVA-Mosaic1 = MVA virus expressing Mosaic1 HIV-1 Gag, Pol, and Env proteins (JNJ 55471533-AAA)
- MVA-Mosaic2 = MVA virus expressing Mosaic2 HIV-1 Gag, Pol, and Env proteins (JNJ 55471572-AAA)

The MVA-Mosaic vaccine, manufactured by Advanced BioScience Laboratories, Inc., Rockville, MD, USA, that will be supplied for this study is formulated for IM injection as a white to opaque, slightly to moderately cloudy solution that may contain white particles. MVA-Mosaic vaccine will be supplied as frozen liquids to be thawed prior to use. Separate MVA-Mosaic1 (MVA virus expressing Mosaic1 HIV-1 Gag, Pol and Env proteins) and MVA-Mosaic2 (MVA virus expressing Mosaic2 HIV-1 Gag, Pol and Env proteins) components will be provided in individual dosage vials at a concentration of 2x10^{8} pfu/mL. Each stoppered and sealed glass vial contains a volume of approximately 0.8 mL. Refer to the Investigator's Brochure for a list of excipients [3].

gp140 DP

The gp140 DP, manufactured by Gallus, Princeton, NJ, USA, that will be supplied for this study is formulated as a solution for IM injection. The drug product (DP) will be supplied as a colorless frozen liquid to be thawed prior to use, and will be essentially free from particles. The DP will be supplied as a 0.5 mL fill in a glass vial at a nominal strength of either 1 mg/mL or

0.2 mg/mL based on total protein content. Refer to the Investigator's Brochure for details of the components of the DP and a list of excipients [4].

Adjuvant

In this study, gp140 DP will be adjuvanted, using a commercially available aluminum salt-based adjuvant, aluminum phosphate. The adjuvant will be supplied as a formulated refrigerated liquid suspension. As supplied, the adjuvant will have a nominal aluminum content of 1.7 mg/mL. It will be mixed with gp140 DP at the site pharmacy prior to administration (JNJ-55471585-AAA: gp140 DP + aluminum phosphate adjuvant).

Placebo

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

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

Study vaccine must be stored at controlled temperatures. Guidance on storage temperature is provided in the site investigational product manual.

Vials must be stored in a secured location with no access for unauthorized personnel. The study freezer 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.

All injections should be administered in the deltoid. For visits with only one injection (ie, at Week 0 and 12), either deltoid can be used. When 2 study vaccine injections are to be given at one visit (ie, at Week 24 and 48), it is required to use a different deltoid for both injections. Exceptions are allowed only if medically indicated. No local or topical anesthetic will be used prior to the injection. To account for the product with the shortest stability time, the maximum time allowed between preparation and administration of the study vaccine will be 3 hours.

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.

Ad26.Mos.HIV Preparation

Each vial must be thawed to room temperature.

Full details on the holding time and storage conditions from the time of preparation to delivery of Ad26.Mos.HIV, are provided in the Site Investigational Product Procedures Manual.

MVA-Mosaic Preparation

Each MVA-Mosaic vial must be thawed to room temperature. MVA-Mosaic1 and MVA-Mosaic2 are intended to be mixed prior to injection. Equal volumes of MVA-Mosaic1 and MVA-Mosaic2 are transferred by syringe into an empty sterile 2 mL Type 1 glass vial with a butyl rubber stopper with a final MVA dose of 10^8. The vial is vortexed at high-speed for 60 seconds prior to withdrawal of the vaccine into the syringe.

More information the mixing of the two vaccine components, as well as full details on the holding time and storage conditions from the time of preparation to delivery of MVA-Mosaic, are provided in the Site Investigational Product Procedures Manual.

gp140 DP Preparation

The gp140 DP active pharmaceutical ingredient (API) vial must be removed from the freezer storage location and thawed with occasional gentle swirling by hand at ambient room temperature.

For the preparation of the adjuvanted high (250 mcg/0.5 mL) dose, the gp140 DP API with a nominal total protein concentration of 1 mg/mL must be diluted 1:1, by mixing 0.5 mL of the aluminum adjuvant as supplied with 0.5 mL of gp140 DP. The aluminum content in the gp140 DP-adjuvant mix will be 0.85 mg/mL (ie, 0.425 mg aluminum/0.5 mL dose).

For the preparation of the adjuvanted low (50 mcg/0.5 mL) dose, the gp140 DP API with a nominal total protein concentration of 0.2 mg/mL must be diluted 1:1, by mixing 0.5 mL of the aluminum adjuvant as supplied with 0.5 mL of gp140 DP. The aluminum content in the gp140 DP-adjuvant mix will be 0.85 mg/mL (ie, 0.425 mg aluminum/0.5 mL dose).

More information and full details on the mixing and diluting of vaccine and adjuvant components, as well as full details on the holding time and storage conditions from the time of preparation to delivery of gp140 DP, are provided in the Site Investigational Product Procedures Manual.

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. Returned study vaccine must not be dispensed again, even to the same subject. 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 Brochures for Ad26.Mos.HIV, MVA-Mosaic, and gp140 DP
- Site Investigational Product Procedures Manual/Study Procedures Manual
- Laboratory Manual
- IWRS Manual
- Electronic Data Capture (eDC) Manual/electronic CRF completion guidelines and randomization instructions
- Sample ICF
- Memory aids
- Test of Understanding
- Social Impact Questionnaire
- Rulers, thermometers

- 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.

The total blood volume drawn from each subject will not exceed the US Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP), and US FDA guidelines of 550 mL in any eight-week period.

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, prior to enrollment in the study. 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.

Risks Related to Vaccines

Subjects may exhibit general signs and symptoms associated with administration of a vaccine, or vaccination with placebo, including fever, chills, rash, aches and pains, nausea, headache, dizziness and fatigue. These side effects will be monitored, but are generally short-term and do not require treatment.

Subjects may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, hives or even difficulty breathing. Severe reactions are rare. Medications must be available in the clinic to treat serious allergic reactions.

The effect of this vaccine on a fetus or nursing baby is unknown, as well as the effect on semen, so female subjects of child bearing potential, and male subjects having sexual intercourse with females, will be required to agree to use birth control for sexual intercourse beginning prior to

the first vaccination and through 3 months after the last vaccination. Women who are pregnant or nursing will be excluded from the study.

Risks related to VISP are discussed in Section 9.4.3.

Risk of Myo/Pericarditis

The MVA vaccine used in this study is related to the vaccine to prevent smallpox. A very small number of people who received the smallpox vaccine developed myocarditis or pericarditis. The number of people who had these problems was very small (96 people out of >650,000 who received the vaccine)[18]. These side effects are not expected from the MVA vaccine because it is an attenuated virus and it cannot replicate. Myocarditis has not been reported with previous MVA use and has not been seen in Phase I/II clinical studies cited in this protocol. Subjects will be actively screened to exclude pre-existing cardiac concerns and followed-up for symptoms related to cardiac complications. The management of subjects who develop cardiac symptoms is detailed in Section 9.3.2.

Risks from Blood Draws

Blood drawing may cause pain, bruising, 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.

Participants 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.

Potential Benefits

There is no direct medical benefit to the subject for participation in this clinical study. Although study subjects may benefit from clinical testing and physical examination, they may receive no direct benefit from participation. Others may benefit from knowledge gained in this study that may aid in the development of an HIV vaccine.

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 ICFs (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- TOU
- 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 ICFs 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 study 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, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, 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). After informed consent for the study is appropriately obtained, the subject will be asked to sign and personally date the ICF appendix indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF appendix will be given to the subject.

Subjects from Group 1 and Group 2 who received all 4 vaccinations will be asked to sign an ICF addendum for the optional LTE phase.

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 (refer to 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.

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1.

16.3. USAMRMC Volunteer Registry Database

For sites with a direct affiliation with the US Army Military HIV Research Program, it is the policy of the US Army Medical Research and Materiel Command (USAMRMC) that volunteer registry data sheets are collected on all volunteers participating in this greater than minimal risk research for entry into the Command's Volunteer Registry Database (VRDS). The Volunteer Registry Database will collect the following data on volunteers:

- Names (first and last name)
- Date of birth
- Contact information, both permanent and local
- Study name and study dates, and dates of individual's participation

- SAE and unexpected AEs related to the vaccine experienced during study participation
- Details of the product received

The intent of the database is two-fold: firstly, to readily answer questions concerning an individual's participation in research supported by the USAMRMC; and secondly, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored for a minimum of 75 years at USAMRMC.

17. ADMINISTRATIVE REQUIREMENTS

17.1. 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 (and 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 (see Contact Information page(s) provided separately). 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.

17.2. Regulatory Documentation

17.2.1. 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 site may not be initiated until all local regulatory requirements are met.

17.2.2. Required Pre-study Documentation

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

17.3. 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. In cases where the subject is not randomized into the study, the date seen and date of birth 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.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; safety parameters as required by the protocol; record of all AEs and follow up of AEs; concomitant medication; vaccine receipt/dispensing/return records; study vaccine administration information; and date of study completion and reason for early discontinuation of study vaccine or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data can be recorded directly into the CRF and will be considered source data:

- Race
- Blood pressure and pulse/heart rate
- Height and weight

Information from the memory aid, given to subjects to note symptoms of unsolicited and solicited local and systemic AEs for 8 days after each vaccination, will be reviewed by the investigator or his/her designee at Visits 3, 7, 10 and 14, to complete the relevant parts of the CRF as described in the CRF Completion Guidelines.

17.5. Case Report Form Completion

CRFs are provided for each subject in electronic format.

eDC will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

Data must be entered into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in three different ways:

- 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).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. 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.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs 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.

17.8. Monitoring

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 CRFs with the hospital or clinic records (source documents). 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 documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents 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 documentation 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 be provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion

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.

17.9.2. 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 study vaccine development

17.10. 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 and comparison with the CRFs. 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.

17.11. Use of Information and Publication

All information, including but not limited to information regarding Ad26.Mos.HIV, MVA-Mosaic and gp140 DP 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.Mos.HIV, MVA-Mosaic and gp140 DP, 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 CRF data from all study sites that participated in the study. 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. 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, upon agreement with the sponsor. 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 12 months of the availability of the final data (tables, listings, graphs), 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 Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: Division of AIDS Tables for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004; Clarification August 2009 – Including Modifications

Division of AIDS table for grading the severity of ADULT AND PEDIATRIC adverse Events Version 1.0, December, 2004; clarification AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

This clarification of the DAIDS Table for Grading the Severity of Adult and Pediatric AE's provides additional explanation of the DAIDS AE Grading Table and clarifies some of the parameters.

I. Instructions and Clarifications

Grading Adult and Pediatric AEs

The DAIDS AE 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 given in the Table. 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.

> Note: In the classification of adverse events, the term "severe" is not the same as "serious." Severity is an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "serious" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

Addenda 1-3 Grading Tables for Microbicide Studies

For protocols involving topical application of products to the female genital tract, male genital area or rectum, strong consideration should be given to using Appendices I-III as the primary grading scales for these areas. The protocol would need to specifically state that one or more of the Appendices would be primary (and thus take precedence over the main Grading Table) for items that are listed in both the Appendix and the main Grading Table.

Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies - PDF
Addendum 2 - Male Genital Grading Table for Use in Microbicide Studies - PDF
Addendum 3 - Rectal Grading Table for Use in Microbicide Studies - PDF

Grade 5

For any AE where the outcome is death, the severity of the AE is classified as Grade 5.

Estimating Severity Grade for Parameters Not Identified in the Table

In order to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on top of the table on Page 96.

Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (eg, the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select

the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1
Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

Determining Severity Grade when Local Laboratory Normal Values Overlap with Grade 1 Ranges
In these situations, the severity grading is based on the ranges in the DAIDS AE Grading Table, even when there is a reference to the local lab LLN.

For example: Phosphate, Serum, Low, Adult and Pediatric > 14 years (Page 20) Grade 1 range is 2.50 mg/dL - < LLN. A particular laboratory's normal range for Phosphate is 2.1 – 3.8 mg/dL. A participant's actual lab value is 2.5. In this case, the value of 2.5 exceeds the LLN for the local lab, but will be graded as Grade 1 per DAIDS AE Grading Table.

II. Definitions of terms used in the Table:

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (eg, feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social and Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (eg, social interactions, play activities, learning tasks, etc.).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	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 Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic 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
Fatigue Malaise	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 fatigue/ malaise symptoms causing inability to perform basic self-care functions
~~Fever (nonaxillary)~~[1]	~~37.7 – 38.6 ºC~~	~~38.7 – 39.3 ºC~~	~~39.4 – 40.5 ºC~~	~~>40.5 ºC~~
Fever[1]	38.0 – 38.4 °C 100.4 – 101.1 °F	38.5 – 38.9 °C 101.2 – 102.0 °F	39.0 – 40.0 °C 102.1 – 104 °F	> 40.0 °C > 104 °F
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	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 (other than emergency room visit) indicated
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition (TPN)]

[1] 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 – strike-through text replaced by grey-highlighted text

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)
INJECTION SITE REACTIONS				
~~Injection site pain (pain without touching) Or Tenderness (pain when area is touched)~~[m]	~~Pain/tenderness causing no or minimal limitation of use of limb~~	~~Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities~~	~~Pain/tenderness causing inability to perform usual social & functional activities~~	~~Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness~~
~~Injection site reaction (localized)~~[m]				
~~**Adult >15 years**~~[m]	~~Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)~~	~~Erythema OR Induration OR Edema >9 cm any diameter (or >81 cm^2)~~	~~Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage~~	~~Necrosis (involving dermis and deeper tissue)~~
~~**Pediatric ≤ 15 years**~~[m]	~~Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter~~	~~Erythema OR Induration OR Edema >2.5 cm diameter but <50% surface area of the extremity segment (eg, upper arm/thigh)~~	~~Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage~~	~~Necrosis (involving dermis and deeper tissue)~~
Pain (without touching)[m]	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness (pain when area is touched)[m]	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization

[m] 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 – strike-through text replaced by grey-highlighted text

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Erythema/ Redness[m]	2.5 cm – 5 cm	5.1 cm – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[m]	2.5 cm – 5 cm and does not interfere with activity	5.1 cm – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with <48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	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
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of >2 units packed RBCs (for children >10 cc/kg) indicated
Hypertension				
Adult >17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	≥180 mmHg systolic OR ≥110 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Correction: in Grade 2 to ≥ 160 - 179 from >160-179 (systolic) and to ≥ 100 -109 from >100-109 (diastolic) and in Grade 3 to ≥ 180 from >180 (systolic) and to ≥ 110 from >110 (diastolic).				
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult >16 years	PR interval 0.21 – 0.25 sec	PR interval >0.25 sec	Type II 2nd degree AV block OR Ventricular pause >3.0 sec	Complete AV block
Pediatric ≤16 years	1st degree AV block (PR >normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc[n]				
Adult >16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval <0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia

[n] According to Bazett's or Fridericia's formula. In the event that the value is reported by both methods, the longer of the 2 values will be considered for the exclusion criterion.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pediatric ≤16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/ embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
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 or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or 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				
Adult and Pediatric ≥ 1 year	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 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pediatric <1 year	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	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (eg, larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (eg, circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND 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)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	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	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	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
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	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 (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	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
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	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
Seizure: (new onset) **– Adult ≥18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 **–** 4 seizures	Seizures of any kind which are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (known pre-existing seizure disorder) **– Adult ≥18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind which are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric <18 years**	Seizure, generalized onset with or without secondary generalization, lasting <5 minutes with <24 hours post-ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with <24 hours post-ictal state	Seizure, generalized onset with or without secondary generalization, lasting >20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow <25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric <14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry <90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	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 See also Arthralgia	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
Bone Mineral Loss				
Adult ≥21 years	BMD t-score -2.5 to -1.0	BMD t-score <-2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric <21 years	BMD z-score -2.5 to -1.0	BMD z-score <-2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	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	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	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
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption <25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption >75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (eg, stone)	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
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	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
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption <25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption >75% total surface
OCULAR/VISUAL				

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (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)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (eg, back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic 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	Asymptomatic	Symptomatic 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 (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute $CD4^+$ count **– Adult and Pediatric >13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	<100/mm^3 *<100/µL*
Absolute lymphocyte count **– Adult and Pediatric >13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	<350/mm^3 *<0.350 x 10^9/L*
Comment: Values in children ≤13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, >7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	<500/mm^3 *<0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	<750/mm^3 *<0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x 10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	<1,500/mm^3 *<1.500 x 10^9/L*
Comment: Parameter changed from "Infant, <1 day" to "Infant, ≤1 day"				
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	<50 mg/dL *<0.50 g/L* OR <0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)				
Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb 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 that lab.				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62–5.23 mmol/L*	6.50 – 7.4 g/dL *4.03–4.61 mmol/L*	<6.5 g/dL *<4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 - 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 - 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL *>2.79 mmol/L*	<7.0 g/dL *<4.34 mmol/L*
Comment: The decrease is a decrease from baseline				
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	<6.00 g/dL *<3.72 mmol/L*

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 - 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	<7.00 g/dL *<4.34 mmol/L*
Infant*†, ≤21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59- 6.17 mmol/L*	<9.0 g/dL *<5.59 mmol/L*
Correction: Parameter changed from "Infant <21 days" to "Infant ≤21 days"				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	>3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	>20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	>3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	>3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	<25,000/mm^3 *<25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	<1,000/mm^3 *<1.000 x 10^9/L*

CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH <normal, but ≥ 7.3	pH <7.3 without life-threatening consequences	pH <7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – <LLN *30 g/L – <LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	<2.0 g/dL *<20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	>10.0 x ULN†
Alkalosis	NA	pH >normal, but ≤ 7.5	pH >7.5 without life-threatening consequences	pH >7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	>10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	>10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – <LLN *16.0 mmol/L – <LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	<8.0 mEq/L *<8.0 mmol/L*
Comment: Some laboratories will report this value as Bicarbonate (HCO_3) and others as Total Carbon Dioxide (CO_2). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above.				
Bilirubin (Total)				
Adult and Pediatric >14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	>5.0 x ULN
Infant*†, ≤14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	>30.0 mg/dL *>513.0 µmol/L*
Infant*†, ≤14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	>25.0 mg/dL *>428 µmol/L*
Calcium, serum, high				
Adult and Pediatric ≥7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	>13.5 mg/dL *>3.38 mmol/L*
Infant*†, <7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	>13.5 mg/dL *>3.38 mmol/L*
Calcium, serum, low				
Adult and Pediatric ≥7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	<6.1 mg/dL *<1.53 mmol/L*
Infant*†, <7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	<5.50 mg/dL *<1.38 mmol/L*
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer

CHEMISTRIES	***Standard International Units are listed in italics***			
Cholesterol (fasting)				
Adult ≥18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	>300 mg/dL *>7.77 mmol/L*	NA
Pediatric <18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	>300 mg/dL *>7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	>500 mg/dL *>27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	>500 mg/dL *>27.75 mmol/L*
Glucose, serum, low				
Adult and Pediatric ≥1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	<30 mg/dL *<1.67 mmol/L*
Infant*†, <1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	<30 mg/dL *<1.67 mmol/L*
Lactate	ULN - <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
Comment: Added ULN to Grade 1 parameter				
LDL cholesterol (fasting)				
Adult ≥18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Pediatric >2 - <18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥190 mg/dL *≥4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	>5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	<0.60 mEq/L *<0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	>5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric >14 years	2.5 mg/dL – <LLN *0.81 mmol/L – <LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	<1.00 mg/dL *<0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	<1.50 mg/dL *<0.48 mmol/L*
Pediatric <1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	<1.50 mg/dL *<0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	>7.0 mEq/L *>7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	<2.0 mEq/L *<2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*

CHEMISTRIES	***Standard International Units are listed in italics***			
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	>1,200 mg/dL *>13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	>15.0 mg/dL *>0.89 mmol/L*

URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	>10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	>3,500 mg/24 h *>3.500 g/d*
Pediatric >3 mo - <10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	>1,000 mg/ m^2/24 h *>1.000 g/d*

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 in the US and Switzerland. 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

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

Attachment 3: Test of Understanding[°]

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 18 scheduled visits over the next year.
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 during the study.
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..

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

Attachment 4: Social Impact Questionnaire

Vaccine Research Center (VRC) Social Impact Case Report Form [19]

	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

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 drug, 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 US (an affiliate of Janssen Vaccines & Prevention B.V.)

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 course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

LAST PAGE

SIGNATURES

Signed by	Date	Justification
PPD	21Dec2016, 17:50:49 PM, UTC	Document Approval

Janssen Vaccines & Prevention B.V. *

Clinical Protocol

COVID-19 Appendix

Protocol Title

A Phase 1/2a Study to Evaluate the Safety/Tolerability and Immunogenicity of Homologous Ad26 Mosaic Vector Vaccine Regimens or Ad26 Mosaic and MVA Mosaic Heterologous Vector Vaccine Regimens, with High-Dose, Low-Dose or no Clade C gp140 Protein Plus Adjuvant for HIV Prevention

Protocol HIV-V-A004 (IPCAVD009); Phase 1/2a

JNJ-55471468, JNJ-55471494, JNJ-55471520, JNJ-55471533, JNJ-55471572, JNJ55471585

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Status: Approved
Date: 16 July 2020
EDMS number: EDMS-RIM-80643, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL HIV-V-A004 (EDMS-ERI-102817395 and EDMS-ERI-100065253)

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

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.[a] At each contact, participants will be interviewed to collect safety data. Key endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

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

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to applicable guidance documents and regulations. Modifications made to the study conduct as a result of the COVID-19 pandemic will be summarized in the clinical study report.

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[a] An on-site visit is defined as a visit during which the participant and the qualified 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.

Study Visits and Assessments:

- When site visits are not possible, sites should collect the assessments via remote visits, or via home visits (if possible and if the participant allows and provides consent to it). The actual visit date and the type of visit (i.e., remote or home visit) should be captured in the eCRF according to the eCRF completion guidelines.
- Procedures that can't be performed in case of remote visits (e.g., blood sampling for immunogenicity and HIV testing), should be documented as protocol deviations and labelled as "missed due to COVID-19". The protocol deviations need to be captured in the source document.

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.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-55471468, JNJ-55471494, JNJ-55471520, JNJ-55471533, JNJ-55471572, JNJ55471585
Clinical Protocol HIV-V-A004

INVESTIGATOR AGREEMENT

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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): PPD

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: _____ Date: _____
(Day Month Year)

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

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 4
Status: Approved, Date: 16 July 2020