Protocol VAC89220HTX1001 Amendment 3
RV405/SEARCH023/IPCAVD007/WRAIR#2217
Ad26.Mos.HIV/MVA-Mosaic

A Combined Phase 1/2a, Exploratory Study of a Therapeutic Vaccine Using an Adenovirus Type 26 Vector Prime and Modified Vaccinia Ankara Boost Combination With Mosaic Inserts in HIV-1 Infected Adults who Initiated Antiretroviral Treatment During Acute HIV Infection

Sponsor:

Janssen Vaccines & Prevention B.V.*

Funding Agencies:

Janssen Vaccines & Prevention B.V.*

Military HIV Research Program (MHRP, through Cooperative Agreement #W81XWH-11-2-0174)

*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.

Protocol Chair:	Jintanat Ananworanich, MD, PhD
Local Principal Investigator:	Nittaya Phanuphak, MD, PhD
Sponsor Clinical Leader:	Frank Tomaka, MD
Local Project Leader:	PPD, MD, MPH

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	7 Jan 2015
Amendment 1	12 Jun 2015
Amendment 2	1 Oct 2015
Amendment 3	This document

Amendment 3 (This document)

The overall reason for the amendment: Reduction in sample size.

Rationale: The sample size has been reduced from 36 to 27 subjects, with 18 subjects in the vaccine arm and 9 in the placebo arm instead of the original 24 and 12 subjects, respectively. The decision to stop study enrollment prior to the full anticipated recruitment is due to limitations of clinical supplies. This is in part due to unexpected delays in approvals as well as challenges in timely recruitment of subjects.

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3.1. Study Design
9.4. Sample Size Consideration

Rationale: Addition of information on the interim immunology analysis.

9.5.2. Analysis Time Points

Rationale: Clarification that volunteers for this study are participants in the study RV254 and will continue to participate in RV254 related activities during the course of the study. Updated wording on the inclusion of RV254 related activities as data points in this study.

3.1. Study Design
4.1.7. Management of Subjects After Reinitiating ART
4.1.8. Management of Subjects With Sustained Virologic Control at End of Study
4.1.9. Management of Subjects Who Become Pregnant

Rationale: Extending exceptions to ARV changes as justified by recent clinical practice.

4.3. Prior and Concomitant Treatment

Rationale: Addition of an alternative and more sensitive assay for detection of vector specific vaccine responses, reflecting experience from other studies.

3.2.5. Cohort Criteria for Proceeding to ARV ATI Phase of Study
9.5.2. Analysis Time Points

Rationale: The case definition for Acute Retroviral Syndrome has been updated, reflecting experience from other studies and consistency with other study protocols including ATI.

16.2. Case Definition for Acute Retroviral Syndrome (ARS)

Rationale: In alignment with other RV254 protocols, the location for the performance of the optional procedures, specifically lymph node biopsy and the leukapheresis, has been updated to include the PPD in addition to the PPD .

5.1.11. Optional Procedures

Rationale: From 1 June 2016 onwards, the name of Crucell Holland B.V. has been changed to Janssen Vaccines & Prevention B.V. Company logo has been updated accordingly.

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Rationale: It is clarified that neuropsychiatric evaluations and brain imaging, including MRI, MRS, and DTI are part of required continuous monitoring of the subjects from Study RV254.

5.1.10. Neuropsychiatric Examination
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Rationale: Changes are made in the fever criteria classification from 37.7ºC to 38.0ºC to align with the Division of AIDS (DAIDS) toxicity table.

5.1.2. Randomization and Vaccination 1/Day 1/Week 0 (Stage 1)
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Rationale: Minor clarifications.

3.2.5. Cohort Criteria for Proceeding to ARV ATI Phase of Study and 3.2.6. Individual Subject Criteria for ARV ATI at Week 60	Minor clarification of individual subject criteria for ARV ATI.
5.1. General Aspects	Reference to Section 5.1.8 added to footnote 4.
5.1. General Aspects	Updated references for total blood volume drawn.
5.1. General Aspects and 5.1.1. Screening	Minor clarification regarding testing for syphilis and hepatitis B.
5.1. General Aspects and 5.1.12. Visit Windows	Visit days and visit windows added.

Rationale: Minor changes.

3.2.6.1. Inclusion Criteria for ARV ATI and 3.2.6.2. Exclusion Criteria for ARV ATI	Numbering of inclusion/exclusion criteria for ARV ATI.
3.4. Method of Blinding and Unblinding	Specified that blind should not be broken before eDC (electronic data capture) database is closed.
SYNOPSIS, 4.1.1. Ad26.Mos.HIV Vaccine, 5.1.10. Neuropsychiatric Examination and 9.3.1.2. Cellular Immunogenicity	Typographical error.
4.1.9. Management of Subjects Who Become Pregnant	Administrative correction on forms to be used to report cases of pregnancy.
6.3.2 Serious Adverse Events; 5.3.2.1 Study Pausing Rules	Administrative change.
13.6. Case Report Form Completion	Removed statement that all data should be recorded in CRF.
16.4 Research Specimen Laboratory Testing	Janssen laboratory added to list.
17.1. Protocol Team Roster	Updated names and affiliations.
17.2 Study Personnel Roles and Responsibilities	Administrative update.
17.3. Collaborating Institutions and Investigators	Updated list of collaborating institutions and investigator.

Amendment 2 (1 Oct 2015)

The overall reason for the amendment: It was requested by the local Institutional Review Board (IRB) PPD and the Ethical Committee (EC) of the Ministry of Public Health (MoPH) of Thailand to clarify the language explaining:

- that all subjects will return to their usual antiretroviral therapy (ART) after Week 96 (post Stage 2)
- that a placebo group is required
- that the study consists of 2 separate stages (phases)
- the rationale for blood volume requirements
- the rationale for ATI and risks related to ATI
- the procedures for the Test of Understanding (TOU)
- the compensation for the subjects

Rationale: It is clarified that after week 96 (post Stage 2) all study participants will resume ART.

4.1.8 Management of Subjects With Sustained Virologic Control at End of Study

Rationale: It is clarified that the study will occur in 2 stages (Stage 1/Phase 1: vaccination period; Stage 2/Phase 2a: ART interruption [ATI]). It is further clarified that placebo only refers to the vaccine component of the trial (Stage 1). Subjects in both arms (vaccine, placebo) will receive standard ART:

- For HIV treatment during the first 60 weeks of the trial prior to ATI (Stage 1)
- If they meet any of the criteria to restart ART listed in Section 4.1.6 (Stage 2)
- At the end of the trial at Week 96 (post Stage 2)

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Rationale: It is clarified by an additional table (Appendix 16.4) that several types of biological samples will (optionally) be collected to address study objectives. Additionally, blood volumes are reduced during Stage 2 of the study (see Table 5). Minor textual changes are made conform MoPH guidelines for blood handling.

Table 5
5.4 Laboratory Evaluations
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Rationale: Rationale for ATI and clinical studies (new safety results) are updated. The risk of ATI is added in a separate Section 5.5.4.

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Rationale: The TOU is explained in more detail (as part of the consent procedure).

11.4 Subject Information and Informed Consent

Rationale: The compensation for the subjects is explained in more detail.

11.8 Compensation

Rationale: To align language among HIV vaccine protocols, in accordance with FDA, Study Holding Rules are adapted to avoid unnecessary pausing of vaccination for DSMC review of certain reactogenicity events, common to most vaccines.

5.3.2.1 Study Pausing Rules

Rationale: To align language among HIV vaccine protocols, wording is added to exclusion criterion 22 to exclude employees of the sponsor or its partners from enrollment.

3.2.2 Exclusion Criteria

Rationale: To allow more flexible scheduling of the visits to administer last dose of study vaccine, without expected impact on immunogenicity, the visit window of the last vaccination is extended from ±1 week to ±2 weeks.

5.1.3 Vaccinations 2 – 4 / Weeks 12, 24, 48 (Stage 1)

Rationale: Minor changes.

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Amendment 1 (12 Jun 2015)

This amendment is considered nonsubstantial in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: It was requested by the local Institutional Review Board (IRB) PPD to clarify the language explaining how subjects will be followed after the study end and how they may return to their usual antiretroviral therapy (ART), and to align the storage time of blood samples in the protocol with the information in the Informed Consent Form (ICF). The protocol was updated accordingly. In addition, the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) has recently been updated. Therefore, in the protocol, the reference to this table was updated.

Rationale: In response to a question from the local IRB, the language explaining how subjects will be followed after the study end and how they may return to their usual ART was clarified. It was specified that after study completion (96 weeks), subjects will be offered enrollment in study RV412 for continued observation, followed by a return to the RV254 parent protocol afterwards. In these follow-up studies, all subjects will have access to ART, and those subjects who are not on ART can decide to resume their treatment at any time.Thus, subjects enrolled in the RV405 protocol will have access to long-term treatment and monitoring.

4.1.7 Management of Subjects After Reinitiating ART
4.1.8 Management of Subjects With Sustained Virologic Control at End of Study

Rationale: In response to a question from the local IRB, the language explaining the storage time of blood samples in the protocol was clarified and aligned with the ICF. It was specified that samples can be stored for up to 10 years for future testing, unless there would be scientific merit in additional testing or storage beyond 10 years. Then, permission for continued storage should be requested from both the relevant IRBs and the subjects (if possible).

11.7 Future use and Storage of Blood Samples

Rationale: The reference to the DAIDS AE Grading Table Version 1.0 dated December 2004 (Clarification, August 2009) was updated to Version 2.0 dated November 2014.

6.3.5 Severity of Adverse Events

LIST OF ABBREVIATIONS

Ad26	adenovirus serotype 26
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotranferase
ALVAC-HIV	canary pox Avipox vectored HIV vaccine candidate
ART	antiretroviral therapy
ARV	Antiretroviral
AST	aspartate aminotransferase
ATI	analytical treatment interruption
BUN	blood urea nitrogen
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CD4+	a functional subclass of helper T lymphocytes that are necessary for augmentation and coordination of innate and adaptive effector responses, humoral and cellular
CD8+	cytotoxic T-Cells that destroy host cells, which have become infected by viruses or other intracellular pathogens
CFR	Code of Federal Regulations
CMDR	Chiang Mai Double Recombinant
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
DoD	Department of Defense (US)
DP	drug product
DSMC	Data and Safety Monitoring Committee
EC	ethical committee
ECG	electrocardiogram
(e)CRF	(electronic) case report form
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
Env	Envelope
FDA	US Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
HAART	highly active antiretroviral therapy
HIV and HIV-1	human immunodeficiency virus, type 1
HLA	human leukocyte antigen
HVTN	HIV Vaccine Trials Network
IB	investigator's brochure
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	intracellular cytokine staining
ID	intradermal
IFN	Interferon
IM	intramuscular
IP	investigational product

IPCAVD	Integrated Preclinical/Clinical AIDS Vaccine Development
IQR	inter-quartile range
IRB	Institutional Review Board
LTR	long terminal repeats
MHRP	(US) Military HIV Research Program
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MoPH	Ministry of Public Health
MVA	Modified Vaccinia Ankara
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
ORP	Office of Research Protection
PBMC	peripheral blood mononuclear cell
pfu	plaque forming units (equivalent to International Units)
PI	principal investigator
PIR	post-injection reactogenicity
PQC	product quality complaint
PSRT	Protocol Safety Review Team
QVOA	quantitative viral outgrowth assay
RAC	Recombinant DNA Advisory Committee
RBC	red blood cell
rMVA	recombinant MVA
RNA	ribonucleic acid
SAE	serious adverse event
SIV	simian immunodeficiency virus
SMC	Safety Monitoring Committee
SOE	schedule of evaluations
SUSAR	suspected unexpected serious adverse reaction
TILDA	Tat/Rev Induced Limiting Dilution Assay
TOU	Test of Understanding
TULDA	Tat/Rev Uninduced Limiting Dilution Assay
UCSF	University of California San Francisco
ULN	upper limits of normal
US	United States
USP	US Pharmacopeia
USAMRMC	US Army Medical Research and Materiel Command
vp	viral particles
WBC	white blood cell
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

SYNOPSIS

Protocol Number

Janssen Vaccines & Prevention B.V. protocol VAC89220HTX1001 Amendment 3

Protocol Numbers of Collaborators:

MHRP RV 405
SEARCH 023
IPCAVD 007

A Combined Phase 1/2a, Exploratory Study of a Therapeutic Vaccine Using an Adenovirus Type 26 Vector Prime and Modified Vaccinia Ankara Boost Combination With Mosaic Inserts in HIV-1 Infected Adults who Initiated Antiretroviral Treatment During Acute HIV Infection

Clinical Phase

Phase 1/2a

Study Vaccine

Vaccines used in this study are adenovirus serotype 26 mosaic human immunodeficiency virus (Ad26.Mos.HIV) and Modified Vaccinia Ankara-Mosaic (MVA-Mosaic):

Ad26.Mos.HIV vaccine contains the following drug substances in a 2:1:1 ratio:

- Ad26.Mos1.Env: recombinant, replication-incompetent adenovirus serotype 26 expressing a mosaic 1 Human Immunodeficiency Virus Type 1 (HIV-1) Envelope (Env) protein
- Ad26.Mos1.Gag-Pol: recombinant, replication-incompetent adenovirus serotype 26 expressing mosaic 1 HIV-1 Gag and Pol proteins,
- Ad26.Mos2.Gag-Pol: recombinant, replication-incompetent adenovirus serotype 26 expressing mosaic 2 HIV-1 Gag and Pol proteins.

MVA-Mosaic contains the following vaccine products, supplied in separate vials and administered in a 1:1 ratio:

- MVA-Mosaic1: Modified Vaccinia Ankara virus expressing Mosaic 1 HIV-1 Gag, Pol and Env proteins
- MVA-Mosaic2: Modified Vaccinia Ankara virus expressing Mosaic 2 HIV-1 Gag, Pol and Env proteins

Study Design

This is a combined Phase 1/2a randomized, double-blind, placebo-controlled study to investigate the safety, immunogenicity and effect on viremic control after antiretroviral (ARV) analytical treatment interruption (ATI) of a vaccine regimen consisting of an Ad26.Mos.HIV prime and an MVA-Mosaic boost. The study will include subjects who started on antiretroviral therapy (ART) during acute HIV infection, who are on a current stable ART and who have achieved absence of viremia (HIV ribonucleic acid [RNA] <50 copies/ml) for ≥48 weeks prior to initiation of vaccine/placebo. The study will be carried out in two stages (Phases). During the first stage (Phase 1), each subject will receive a total of

four vaccinations or four placebo injections. During the second stage of the study (Phase 2a), ATI will be started and all ARV drugs will be discontinued in all subjects.

Treatments

Subjects in the vaccine arm will receive Ad26.Mos.HIV at Weeks 0 and 12, and MVA-Mosaic at Weeks 24 and 48 (Stage 1). Subjects in the placebo arm will receive placebo at Weeks 0, 12, 24 and 48 (Stage 1). At Week 60, ATI will be started and all ARV drugs will be discontinued at that time in both arms (Stage 2).

Objectives and Hypothesis

Primary Objectives

1. Determine the safety and tolerability of Ad26 prime/MVA boost versus placebo in subjects on suppressive ART that was initiated during acute HIV infection
2. Measure the frequency and duration of sustained viremic control after receiving Ad26 prime/MVA boost or placebo, defined as greater than 24 weeks with plasma HIV RNA <50 copies/ml after ARV ATI

Secondary Objectives

1. Determine the immunogenicity of Ad26 prime/MVA boost in subjects on suppressive ART that was initiated during acute HIV infection
2. Characterize biomarkers of HIV reservoir at baseline, after vaccine therapy prior to ARV ATI (Week 48-60) and after ARV ATI (Week 60-96)
3. Compare the duration of viremic control (HIV RNA <50 copies/ml) between vaccine and placebo recipients who failed to achieve sustained viremic control (undetectable plasma HIV RNA [<50 copies/ml] at Week 24 after ARV ATI)
4. Describe the frequency, magnitude, specificity and functional capacity of humoral and cellular immune responses to vaccine and other immunogens
5. Describe the molecular sequence sieve effects of vaccine therapy on breakthrough rebound viremia before and after cessation of therapy
6. Describe the peripheral blood mononuclear cells (PBMC) phenotype, pattern of soluble factors and immune functional responses before and after ARV ATI in both the vaccine and placebo arms and compared to historical untreated acute infection cases in RV217
7. Describe the clinical outcomes in terms of the frequency, severity, duration and treatment for acute retroviral syndrome post ARV ATI.
8. Evaluate and characterize HIV resistance to ARV drugs in subjects who experience rebound viremia after ARV ATI.

Exploratory Objectives

1. Analyze the markers of HIV reservoir as predictors of sustained viral suppression
2. Analyze the markers of HIV specific immune responses as predictors of sustained viral suppression.
3. Analyze the expression profiles and transcriptome analysis of sorted and/or unsorted lymphocytes and monocyte/macrophages in the different arms of the study
4. Compare the mucosal immunity (vaginal and rectal for humoral and gut mucosa for cellular immunogenicity) in vaccine versus placebo arms

5. Describe the markers of immune activation in the peripheral blood and various reservoirs
6. Describe the viral load response to resumption of ART and impact on markers of HIV reservoir among those who fail to suppress HIV RNA off therapy.

Hypothesis

This is an exploratory study to collect preliminary data and establish sufficient experience to inform and develop subsequent studies to address the following hypothesis: Vaccine therapy administered in the form of Ad26 vector with mosaic inserts for gag/pol and env genes of HIV-1 at 0 and 12 weeks (Stage 1), boosted with the MVA vector with homologous mosaic inserts for gag/pol and env genes at 24 and 48 weeks (Stage 1), among individuals with fully suppressed HIV will be safe and well-tolerated, will result in a measurable immune response, and will result in over 50% of vaccine recipients achieving sustained viremic control after ATI (Stage 2).

Study Center

PPD Thailand

Study duration Planned

The total duration for each subject will be 96 weeks, including 48 weeks for the vaccination period (Stage 1), 12 weeks between the final vaccination and ARV ATI (Stage 1), and 36 weeks of follow-up (Stage 2).

Number of Subjects

Up to 27 subjects are planned to be enrolled. Subjects will be randomly assigned in a 2:1 schedule to either receive Ad26.Mos.HIV and MVA-Mosaic (total of 18 subjects) or placebo (total of 9 subjects).

Population

HIV-infected adults who started ART during acute infection, who are on a current stable ART for at least 4 weeks prior to screening, who are clinically stable while on treatment and who have undetectable plasma HIV RNA (<50 copies/ml) for at least 48 weeks.

Safety Monitoring

A Protocol Safety Review Team (PSRT) and an independent Data and Safety Monitoring Committee (DSMC) will oversee the conduct and safety monitoring of the study.

Endpoints/Criteria for Evaluation of Safety, Immunogenicity, and Efficacy

Safety and Tolerability:

- For safety and tolerability: adverse events (AEs) during the course of the study and reactogenicity for 1 week after each study vaccination.

Immunogenicity:

- This is an exploratory study; the main criteria for evaluation of immunogenicity will include but are not limited to the frequency, magnitude, and breadth of epitope recognition by enzyme-linked immunospot (ELISPOT), polyfunctinality of T-cell responses, binding antibody to various HIV-1 Env regions and neutralization of a variety of HIV strains (tier 1, 2).

Efficacy:

- The main endpoint for efficacy is the proportion of subjects with undetectable plasma HIV RNA (<50 copies/ml) at 24 weeks after ARV ATI.

Statistical Methods

The primary outcomes of the study are safety and efficacy of the vaccine. The sample size is within the range of subjects recommended in the Code of Federal Regulations (CFR 312.21) for each of the products in this investigation and will allow evaluation of epitope enumeration between arms. Placebo recipients are included for blinding purposes, safety and efficacy analyses, and will provide additional 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 18 subjects in the vaccine arm, the observation of 0 such reactions would result in a two-sided exact 95% confidence interval with an upper limit of 18. 50%.

Immunogenicity

Blood and genital secretions for the determination of systemic and local cellular and humoral immune responses will be collected at the time points as described in the schedule of evaluations. In a subset of consenting subjects, sigmoid biopsy, lymph node biopsy and cerebrospinal fluid (CSF) samples will also be collected to evaluate immune responses in gastro-intestinal and other reservoirs. Leukapheresis will be an optional procedure to collect a larger number of cells for analysis. Brain magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) will also be performed as optional procedures.

Reviewing Institutional Review Board (IRB):

PPD

1. INTRODUCTION

HIV Epidemiology

Globally, an estimated 35.3 million people were living with HIV in 2012, an increase from previous years as a result of the wider availability of life-saving ART. There were 2.3 million new HIV infections globally, showing a 33% decline in the number of new infections from 3.4 million in 2001. At the same time the number of acquired immunodeficiency syndrome (AIDS) deaths is also declining with 1.6 million AIDS deaths in 2012, down from 2.3 million in 2005. From 1996 to 2012, ART averted 6.6 million AIDS-related deaths worldwide, including 5.5 million deaths in low- and middle-income countries (UNAIDS Report on the Global AIDS Epidemic 2013). The world is within reach of providing ART to 15 million people by 2015. In 2012, 9.7 million people in low- and middle-income countries received ART, representing 61% of all who were eligible under the 2010 World Health Organization (WHO) HIV treatment guidelines. However, under the 2013 WHO guidelines, the HIV treatment coverage in low- and middle-income countries represented only 34% of the 28.3 million people eligible in 2013.

Despite its proven success at saving lives, there are significant challenges to initiating and maintaining ART for all of those that need it in the world. ART must be taken life-long with near perfect adherence in order to be effective. This places extreme pressure and costs on international donors and over-taxed health systems in developing countries where HIV prevalence rates are highest. ART has both short-term and long-term side effects for users, and drug resistance rates rise as more people are on treatment for longer periods of time. Alternative or complementary treatments, including a therapeutic vaccine, which could induce a true or "functional" cure of HIV infection and lessen or eliminate the need for lifelong ART for HIV infected individuals, would therefore be of great benefit.

HIV Vaccines

A Phase 3 community-based study conducted in Thailand (RV144) provided the first evidence that an HIV-1 vaccine could provide protective efficacy against HIV-1 acquisition. The prime-boost vaccine regimen consisted of a recombinant canarypox vector, ALVAC-HIV prime (vCP1521, expressing *gag, protease* subtype B (LAI) and *env* gp120 CRF01_AE with a gp41 subtype B (LAI) transmembrane anchor) and a bivalent AIDSVAX® gp120 B/E MN and CRF01_AE (A244) boost. The vaccine regimen was safe and well tolerated (Pitisuttithum 2011). A modified intent-to-treat analysis showed an estimated 31.2% efficacy after 42 months of follow-up (Rerks-Ngarm 2009; Gilbert 2011). Post hoc analysis of the interaction of risk status and acquisition efficacy was significant with greater benefit in low-risk individuals (Robb 2012). Vaccine efficacy appeared to be higher (60%) at 12 months post vaccination than at later timepoints, suggesting an early, but nondurable, vaccine effect. There was no effect on early post-infection HIV-1 RNA viral load or CD4+ T-cell count. Vaccination did not affect the

clinical course of HIV-1 disease after infection, though there was evidence of reduction in seminal fluid viral load (Rerks-Ngarm 2013).

The RV144 study provided a unique opportunity to perform a case control study of correlates of risk. Plasma IgG antibody binding to scaffolded gp70 V1V2 Env proteins correlated inversely with risk, while Env plasma IgA correlated directly with risk, raising the hypotheses that IgA responses against Env and IgG responses directed against V1V2 may be mechanistically associated with protection. Neither low levels of V1V2 antibodies nor high levels of Env-specific IgA antibodies were associated with higher rates of infection than in the placebo group. In vaccinees, low levels of Env-specific IgA antibodies, IgG avidity, antibody-dependent cell-mediated cytotoxicity (ADCC), neutralizing antibodies, and Env-specific CD4+ T cells, were inversely correlated with risk of infection (Haynes 2012; Karasavvas 2012; Zolla-Pazner 2013). Two weeks post last vaccination, 97% of RV144 studied plasma samples from vaccine recipients contained antibodies to V2 region synthetic peptides, falling to 19% at 48 weeks, suggesting that waning vaccine efficacy may be correlated to waning V2 antibody response (serum IgG). Interestingly, gp70 V1V2 antibodies were lower in HVTN 505 compared to RV144. The response to V3 CRF01_AE also inversely correlated with the risk of HIV infection in vaccine recipients with lower levels of Env-specific plasma IgA and neutralizing antibodies. In Vax003 and Vax004 (no protection), serum IgG responses targeted the same epitopes as in RV144 with the exception of an additional C1 reactivity in Vax003 and infrequent V2 reactivity in Vax004. These results along with a recent sieve analysis (Rolland 2013) generate the hypothesis that IgG to linear epitopes in the V2 and V3 regions of gp120 are part of a complex interplay of immune responses that contributed to protection in RV144 (Gottardo 2013).

1.1. Overall Rationale of Study Design

Studies of HIV vaccine in HIV-uninfected and infected subjects suggest that a successful HIV vaccine program will need to induce immunity against the diverse strains and subtypes predominating in the target populations. Improving magnitude, breadth and depth of epitope coverage is thought to be a key to development of a successful T-cell based preventive HIV vaccine. Published primate data indicate that the number of epitope specific responses induced by a vaccine may be an important immune correlate of viral load control in the simian immunodeficiency virus (SIV) challenge system (Chen 2001). Strategies to accomplish this include using multivalent vaccines containing immunogens from a number of prevalent subtypes or using mosaic sequences, proteins assembled from natural sequences by in silico recombination, which are optimized for potential T-cell epitopes.

The enhancement of host-mediated clearance of residual virus represents a new additional approach to HIV functional cure (Carcelain 2013). Findings of several studies have shown the importance of cellular immunity in the control of HIV reservoir size. HIV-1 Gag-specific CD8+ T cells isolated from elite controllers, but not from patients given ART, were shown to kill

autologous resting CD4+ T cells in which the virus was reactivated with vorinostat. Moreover, functional anti-viral CD8 T cells are associated with reduced size of the central memory CD4 T cell reservoir in patients controlling their virus without ART. High-avidity multifunctional CD8 cytotoxic T lymphocytes (CTL) that target vulnerable regions in Gag are especially important in limiting virus diversity and reservoirs in individuals infected with HIV who have protective human leukocyte antigen (HLA) class I alleles. Therapeutic vaccines could re-stimulate CD8+ CTL to prevent or control virus relapses and re-establish latent infection in CD4+ T cells after treatment interruptions. A few therapeutic vaccine studies such as the Ad5 HIV-1 gag vaccine (ACTG A5197 NCT00080106), and infusions of dendritic cells pulsed with inactivated HIV particles have shown transient viral suppression after treatment interruption. Eramune-02 is testing whether a deoxyribonucleic acid (DNA) prime, replication defective, recombinant adenovirus serotype-5 boost strategy, with the Vaccine Research Center's polyvalent HIV-Gag, Pol, Nef, and Env vaccine can reduce the viral reservoir in patients undergoing an ARV-intensification regimen (Katlama 2013).

Liu et al. (Liu 2009) showed that a heterologous rAd26 prime/rAd5 boost vaccine regimen expressing SIV Gag elicited cellular immune responses with augmented magnitude, breadth and polyfunctionality as compared with the homologous rAd5 regimen. After SIVmac251 challenge, monkeys vaccinated with the rAd26/rAd5 regimen showed a 1.4 log reduction of peak and a 2.4 log reduction of setpoint viral loads as well as decreased AIDS-related mortality as compared with control animals. These data demonstrate that durable partial immune control of a pathogenic SIV challenge for more than 500 days can be achieved by a T-cell-based vaccine in Mamu-A*01-negative rhesus monkeys in the absence of a homologous Env antigen.

Recently Barouch et al. (Barouch 2012) have shown that heterologous Ad26/MVA vaccine regimens containing Gag, Pol, and Env antigens, can protect against acquisition of infection following repetitive, heterologous, intrarectal challenges with a neutralization-resistant virus (SIV_{MAC251}) in rhesus monkeys. Moreover, immunological correlates analyses suggested that multiple cellular and humoral immune responses correlate with virological control, although the actual mechanisms of protection remain to be determined.

This study will explore a combination prime-boost vaccine regimen. Here we propose to evaluate the regimen in HIV-infected individuals who began suppressive ART during very early acute HIV infection and therefore have minimal viral reservoir and more intact immune systems. While previous vaccine-based immunotherapy strategies failed to control viral load in chronically HIV-infected subjects, we hypothesize that vaccine-induced immune responses may continue to control viral replication after ART stop in subjects treated very early during acute infection. This setting provides an optimal opportunity to demonstrate the concept of vaccine therapy to achieve sustained control of HIV without ART (functional cure).

1.1.1. Rationale for Modified Vaccinia Ankara (MVA)

The use of live attenuated MVA virus recombinants as expression vectors for HIV genes either alone or in various prime-boost combinations has been shown to be safe and immunogenic in humans (Cebere 2006; Currier 2010; Excler 2013; Jaoko 2008; Peters 2007; Ramanathan 2009; Vasan 2010). In particular, MVA-based recombinants have been shown to induce antibodies and specific cellular immune responses mediated by CTLs. The Walter Reed Army Institute of Research (WRAIR) and National Institutes of Health (NIH) have produced live recombinant poxvirus vectors, MVA-A/C/E, that are genetically engineered to express Gag, Pol, and Env from HIV-1 subtypes A, C, and E.

1.1.2. Rationale for Adenovirus Type 26 Vector

All three of the HIV-1 vaccine efficacy studies utilizing Ad5 and DNA/Ad5 vaccines (HVTN 502, HVTN 503, HVTN 505) showed no efficacy against HIV-1 infection. In the first two studies increased HIV-1 infection was observed in vaccinees as compared with placebo subjects. 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.

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 stringent 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 healthy HIV-uninfected humans following vaccination in a randomized, double-blinded, placebo-controlled clinical study (IPCAVD003).

Biological Differences Between Ad5 and Ad26

Ad5 seroprevalence is nearly universal with high titers in the developing world, whereas Ad26 seroprevalence is lower with substantially lower titers in the developing world (Barouch 2011, Mast 2010). Baseline Ad5 neutralizing antibodies have been shown to suppress the immunogenicity of Ad5-based vaccines in both pre-clinical and clinical studies. International seroepidemiology studies have demonstrated a much lower prevalence of antibodies to Ad26, Ad35, and Ad48 compared to Ad5 (Barouch 2011, Mast 2010). For example, Ad26 seroprevalence in adults in South Africa, Kenya, Uganda, and Thailand were 43%-53%, 66%, 68%, and 55%, respectively, compared to Ad5 seroprevalence of 88%-90%, 91%, 86%, and 82% in the same cohorts, respectively. The majority (61%-79%) of adults in these regions also demonstrated high Ad5 neutralizing antibody titers, whereas only 5%-18% of adults had high Ad26 neutralizing antibody titers.

Ad5 utilizes the coxsackievirus and adenovirus receptor as its primary cellular receptor, whereas Ad26 utilizes CD46 (Li 2012). Ad5 exhibits primarily liver tropism *in vivo*, whereas Ad26 exhibits no liver tropism (Waddington 2008). Moreover, Ad5 and Ad5 immune complexes are more stimulatory to human dendritic cells than are Ad26 and Ad26 immune complexes (Perreau 2012).

Ad5 and Ad26 also exhibit profoundly different innate immune profiles following vaccination of human subjects, as demonstrated by differential gene expression profiles on Days 1, 3, and 7 after immunization. Certain genes are up- or down-regulated by Ad5 but not Ad26, whereas others are up- or down-regulated by Ad26 but not Ad5. Genes associated with general inflammation and interferon (IFN) pathways were up-regulated by both Ad5 and Ad26, as expected, but this effect was substantially more robust and more durable with Ad5 as compared with Ad26. These data demonstrate that Ad5 and Ad26 trigger phenotypically very distinct innate inflammatory profiles, and that Ad5 stimulates more robust and more durable common inflammatory pathways than does Ad26.

Ad5 and Ad26 vectors also exhibit profoundly different adaptive immune phenotypes. In mice, Ad5 vectors elicited high magnitude but dysfunctional and exhausted T cells, characterized by low levels of CD127, CD62L, and IFN-gamma, and high levels of PD-1, whereas Ad26 vectors elicited polyfunctional T cells characterized by high levels of CD127, CD62L, and IFN-gamma, and low levels of PD-1 (Penaloza-MacMaster 2013, Tan, 2013). Moreover, Ad26-induced T cells expanded more robustly than did Ad5-induced T cells upon re-exposure to antigen and afforded superior protective efficacy in murine challenge models (Penaloza-MacMaster 2013, Tan, 2013).

Taken together, these data show that Ad5 and Ad26 are biologically substantially different in terms of key aspects of seroepidemiology, basic virology, innate immune profiles, and adaptive immune phenotypes.

Improved Protective Efficacy of Ad26 Compared With Ad5 in Rhesus Monkeys

Consistent with the results of the HVTN 505 clinical study, DNA/Ad5 vaccines afforded no protective efficacy against stringent, repetitive, intrarectal challenges with the neutralization-resistant virus SIVmac251 in rhesus monkeys (Letvin 2011). In contrast, DNA/Ad5 vaccines afforded partial protective efficacy against less stringent, neutralization-sensitive SIVsmE660 challenges, indicating that the low stringency SIVsmE660 challenge model was not predictive of the clinical results observed in HVTN 505. In contrast, the lack of protection in the high stringency SIVmac251 challenge model was consistent with the lack of efficacy observed in HVTN 505. Ad5 only vaccines also did not afford protection against SIVmac239 (Casimiro 2005), consistent with the results of the Step study.

In contrast, Ad26/MVA and Ad26/Ad35 vaccine regimens afforded substantial protective efficacy against repetitive, intrarectal challenges with the neutralization-resistant virus SIVmac251 in rhesus monkeys (Barouch 2012). Thus, Ad26/MVA vaccines afforded partial protection (76-83% reduction in the per-exposure risk of infection) in the stringent SIVmac251 challenge model in which DNA/Ad5 failed.

No Activation of Mucosal Total or Vector-Specific CD4+ T Lymphocytes Following Ad26 Vaccination in Humans

The mechanism for the possible increase in HIV-1 acquisition risk in individuals who received Ad5-based vaccines remains unclear, but a leading hypothesis involves the potential activation of total or vector-specific CD4+ T lymphocytes at mucosal surfaces following Ad5 vaccination, which theoretically could result in increased targets for HIV-1 infection. To assess the possibility that this effect may occur with Ad26 vectors, we performed a randomized, double-blinded, placebo-controlled clinical study (IPCAVD003) to determine whether vaccination of healthy human subjects with an Ad26 vector expressing HIV-1 Env would result in increased numbers or activation status of total or vector-specific CD4+ T lymphocytes in colorectal mucosa. As shown below, 24 subjects were enrolled in this study. Group 1 (N = 16) consisted of individuals who were baseline Ad26 seronegative. Group 2 (N = 8) consisted of individuals who were baseline Ad26 seropositive. Subjects were randomly allocated to receive vaccine or placebo in a 3:1 ratio. All subjects received a single intramuscular (IM) injection of vaccine ($5x10^{10}$ viral particles [vp] Ad26.ENVA.01) or placebo on Day 0. Blood samples, colorectal biopsies, and colorectal weck-cel sponges were collected prior to immunization and at Weeks 2 and 24 following vaccination. Of 72 planned biopsies, 71 were performed.

HIV-1 Env-specific humoral and cellular immune responses were observed in both peripheral blood and colorectal mucosa following Ad26 vaccination (data not shown). Ad26 vector-specific CD4+ T-lymphocyte responses were substantially lower in colorectal mucosa than in peripheral blood and did not appear to increase following vaccination. The degree of inflammation in colorectal mucosa was also assessed. Normal histology was observed in 71/71 biopsies. No increases in CD4, CD8, CD3, or CD25 cells were observed in colorectal mucosa following Ad26 vaccination. Moreover, no increases in Ki67 or HLA-DR activation were observed in colorectal mucosa following Ad26 vaccination. The activation status of total and vector-specific CD4+ T lymphocytes in colorectal mucosa was assessed by flow cytometry. No increased Ki67 activation or CCR5 expression was observed on total or vector-specific CD4+ T lymphocytes in colorectal mucosa following Ad26 vaccination. These data demonstrate that Ad26 vaccination did not result in increased numbers or activation status of total or vector-specific CD4+ T cells in colorectal mucosa in human subjects.

1.1.3. Rationale for Mosaic Sequence Inserts

Multiple studies have supported the necessity of an HIV vaccine to elicit CD8+ T-cell responses in order to control or clear HIV infection (Bhattacharya 2007, Brumme 2008, Borrow 1997, Betts 2006, Fellay 2007). A global HIV vaccine will have to elicit CD8+ T-cell responses to a diverse group of viruses. HLA class I-presented epitopes are usually 9-mers and each HIV genome contains thousands of potential T-cell epitopes. The ideal sequence to use in a global vaccine would be one that would match all 9-mers in the M group of HIV viruses; however, given the diversity of strains, the best natural strain only matches approximately one-quarter of the 9-mers in Env and one-half in Pol (Korber 2009). In order to increase the coverage of potential T-cell epitopes, mosaic sequences have been created. Mosaic sequences are in silico-derived recombinants optimized to match the most potential T-cell epitopes of M-group virus. Studies in rhesus monkeys have shown that mosaic sequences increase the breadth and depth of immune response compared with consensus or natural sequences (Barouch 2010, Santra 2010).

1.1.4. Rationale for Heterologous Vectors

Heterologous, as opposed to homologous viral vectors in a prime boost immunization strategy have been shown to increase magnitude, breadth and polyfunctionality of cellular immune responses to core protein epitopes. Ratto-Kim et al. characterized prime-boost vaccine regimens using heterologous and homologous vector and gene inserts. Heterologous regimens offer a promising approach that focuses the cell-mediated immune response on the insert and away from vector-dominated responses (Ratto-Kim 2012). Ad35-GRIN/ENV (Ad35-GE) vaccine is comprised of two vectors containing gene sequences from HIV-1 subtype A *gag, rt, int, nef* (Ad35-GRIN) and *env* (Ad35-ENV). MVA-Chiang Mai Double Recombinant (CMDR), MVA-KEA (MVA-K) and MVA-TZC (MVA-T) vaccines contain *gag, env* and *pol* genes from HIV-1 subtypes CRF01_AE, A and C, respectively. Balb/c mice were immunized with different heterologous and homologous vector and insert prime-boost combinations. HIV and vector-specific immune responses were quantified post-boost vaccination. Gag-specific IFN-gamma ELISPOT, intracellular cytokine staining (ICS) (CD107a, IFN-gamma, TNF-a, and IL-2), pentamer staining and T-cell phenotyping were used to differentiate responses to inserts and vectors. Ad35-GE prime followed by boost with any of the recombinant MVA constructs (rMVA) induced CD8+ Gag-specific responses superior to Ad35-GE-Ad35-GE or rMVA-rMVA prime-boost combinations. Notably, there was a shift toward insert-focus responses using heterologous vector prime-boost regimens. Gag-specific central and effector memory T cells were generated more rapidly and in greater numbers in the heterologous compared to the homologous prime-boost regimens. These results suggest that heterologous prime-boost vaccination regimens enhance immunity by increasing the magnitude, onset and multifunctionality of the insert-specific cell-mediated immune response compared to homologous vaccination regimens. This approach has also resulted in reduced viral load and improved survival in subsequently infected non-human primates. Furthermore, the magnitude

of these effects varies by vector. Specifically, the combination of Ad26/Ad5 has been shown to be superior to Ad35/Ad5, which is superior to the homologous Ad5/Ad5 (O'Brien 2009). Early phase human studies with heterologous vectors are currently in progress (VRC 012, HVTN 083).

1.2. Rationale for ARV ATI

ATI is not the standard of care for HIV infection. The Thai National HIV Treatment Guidelines, recently revised in 2014, now recommend lifelong ART for all persons living with HIV (PLHIV). However, the possibility of safely stopping ART would hold great benefit both for patients, who are inconvenienced by having to take medications that require strict adherence and have a number of proven short-term and long-term toxicities, and by national health programs, which are committed to providing medications to hundreds of thousands or even millions of patients for decades to come.

ATI studies are an integral and necessary part of an international research agenda to find a "cure" for HIV, or at the minimum a treatment regimen that would provide an "HIV remission" in which the body could control HIV infection without the need for daily medication (Volberding 2014; Li 2015). Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases at the United States National Institutes of Health and recipient of the 2013 Prince Mahidol Award, has written that clinical trials of HIV-cure therapies, including ATI trials, are promising and are feasible to implement (Fauci 2014). HIV-cure trials have also been deemed ethical to conduct (Sugarman 2013). The Bangkok RV254/SEARCH010 cohort is an ideal study population for ATI studies because, as explained in the following paragraph, there is evidence that patients who start ART very early in HIV infection may have a lower chance of viral rebound after stopping ART.

In contrast to patients begun on ART in the course of chronic HIV infection, many patients who begin ART at the time of acute HIV infection demonstrate blunted or delayed rebound viremia after ATI (Gianella 2011; Goujard 2012; Hamlyn 2012; Lodi 2012; Saez-Cirion 2013). Several studies have shown sustained viremic control after treatment interruption in 5- 16% of patients initiated on ART at the time of acute infection (Gianella 2011; Goujard 2012; Grijsen 2012; Lodi 2012; Saez-Cirion 2013). In these studies, factors associated with successful viremic control included shorter duration from HIV onset to ART initiation, longer duration on ART and low PBMC-associated HIV DNA (Williams 2014). In the RV254/SEARCH010 study in Thailand, early initiation of ART significantly restricted integration of HIV DNA in PBMCs, including central memory CD4+ T cells (Ananworanich 2012; Ananworanich 2013; Ananworanich 2014). Total blood HIV DNA at initiation of therapy predicted reservoir size after 24 weeks of aggressive ART, underscoring the importance of early initiation of ART. Prior evidence has shown that reservoir distribution in shorter-lived cells is associated with elite control status (Buckheit 2013; Fonseca 2011; Shacklett 2011). Patients in RV254/SEARCH010

demonstrated this favorable pattern of reservoir distribution. For these reasons, patients who have received ART early in acute HIV infection are ideal candidates for the evaluation of novel therapies that seek to achieve a functional cure of HIV.

During ARV ATI, subjects will be monitored closely for clinical and laboratory indications to resume ART. These criteria are designed to protect the subjects as much as possible from any possible clinical, immunological, or virological adverse effects of ATI. Frequent virological monitoring after ATI, up to two times per week during the first 6 weeks when rebound viremia is most likely to occur, will minimize risk for the subjects. In the event that rebound viremia above 1,000 copies/ml does occur, the frequency of monitoring will allow for early re-initiation of ART as soon as possible and before clinical or immunological adverse effects would be expected. Moreover, the safety of this approach is proven in a recent study of chronically infected adults, many of who had low pre-ART CD4+ count. With twice-weekly viral load monitoring, rapid resumption of ART and viral suppression was demonstrated. No subjects had clinical adverse events due to ATI and CD4+ counts remained stable (Rothenberger 2015).

1.3. Description of Ad26.Mos.HIV

Ad26.Mos.HIV vaccine was developed as part of the National Institute of Allergy and Infectious Diseases-sponsored U19 AI078526 Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) program at Beth Israel Deaconess Medical Center and Janssen Vaccines & Prevention B.V. It is a recombinant replication-incompetent live Ad26 virus-vectored vaccine that is comprised of 3 adenoviruses, each of which has been genetically engineered to express one of 2 mosaic *gag, pol* genes or one mosaic *env* gene, each optimized for maximal coverage of potential T-cell epitopes. The Ad26.Mos.HIV vaccine will be used as the prime at 0 and 12 weeks. For comprehensive information refer to the most recent version of the Ad26.Mos.HIV Investigator's Brochure (IB).

1.4. Description of MVA-Mosaic Sequence

Modified Vaccinia Ankara Mosaic Sequence (MVA-Mosaic sequence) is a recombinant live attenuated modified vaccinia virus vector that has been genetically engineered to express 2 mosaic Gag, Pol, and Env sequences optimized for maximal coverage of potential T-cell epitopes. The MVA-Mosaic vaccine will be used as the booster at Week 24 and 48. For comprehensive information refer to the most recent version of the MVA-Mosaic Vaccines IB.

1.5. Preclinical Studies

Safety of Ad26 and MVA-Vectored Vaccines in Preclinical Studies

The safety of the MVA-vectored vaccines is supported by the comprehensive preclinical studies conducted previously with an identical vector and similar inserts. The safety of MVA-HIV expressing *gag, pol,* and *env* inserts derived from an HIV-1 CRF01_AE isolate (CM235

env/CM240 gag/pol), from Chiang Mai, Thailand (referred to as MVA-CMDR) has been established based on a repeat-dose toxicity study conducted in rabbits and based on human clinical data from study RV158 (Currier 2010).

A repeated-dose Good Laboratory Practice (GLP) toxicity and local tolerance study in New Zealand white rabbits with different combinations of Ad26.ENVA.01 and MVA-Mosaic or MVA-Natural given by the IM route, including a 14-day reversibility period, was performed (Table 1).

Table 1: Study Design: Repeated-Dose GLP Toxicology Study in New Zealand White Rabbits

Group	Treatment	Dose	Total dose volume (mL)	Dose interval (Days)	Number of animals		
					Treatment[a]	Necropsy	
					Total (M/F)	Terminal (M/F)[b]	Recovery (M/F)[c]
1	Placebo	0	1.0	1, 22, 43, 64, 85, 106	14/14	4/4	3/3
2	MVA-Natural	$1x10^8$ pfu/mL	1.0	1, 22, 43, 64, 85	10/10	5/5	5/5
3	MVA-Mosaic	$1x10^8$ pfu/mL	1.0	1, 22, 43, 64, 85	10/10	5/5	5/5
4	Ad26ENVA.01 MVA-Natural	$5x10^{10}$ vp/dose $1x10^8$ pfu/mL	0.5 1.0	1, 22, 43 64, 85, 106	10/10	5/5	5/5
5	Ad26ENVA.01 MVA-Mosaic	$5x10^{10}$ vp/dose $1x10^8$ pfu/mL	0.5 1.0	1, 22, 43 64, 85, 106	10/10	5/5	5/5

M/F: male/female; pfu: plaque-forming units
[a] The skin over the hind legs was shaved free of hair at least 24 hours prior to dose administration.
[b] Terminal necropsies occurred on Day 87 for Groups 1-3 and on Day 108 for Groups 4 and 5.
[c] Recovery necropsies occurred on Day 99 for Groups 1-3 and on Day 120 for Groups 4 and 5.

Vaccine-related changes in body temperatures, clinical pathology parameters and pathology data were generally resolved and/or were trending toward recovery, were not deemed to be adverse, and were considered a normal immunologic/inflammatory response to the vaccine administration. None of the effects noted during the study for animals receiving any of the test articles were adverse to the health of the animal.

Barouch, et al (Barouch 2010) evaluated cellular immune responses to mosaic HIV-1 vaccines in rhesus monkeys immunized with a single dose of recombinant adenovirus serotype 26 (rAd26) expressing mosaic, consensus, or natural HIV-1 Gag, Pol, and Env sequences. The breadth of immune responses was greatest for the mosaic antigens; however there was no difference in magnitude of CD4+ and CD8+ T-cell responses between the groups. The depth of immune response (defined as the number of simultaneously elicited variant T-cell epitopes for a particular region) was greatest with the mosaic antigens. Humoral immune responses after a heterologous vector boost with the same insert as initial vaccination were also measured and the mosaic Env immunogens elicited non-inferior antibody responses as compared with the consensus or natural sequence Env antigens. This study showed that 2-valent mosaic HIV-1 Gag, Pol, and Env antigens expanded cellular immune breadth and depth in rhesus monkeys as compared with consensus or natural sequence antigens without compromising the magnitude of

antigen-specific T lymphocyte responses as compared with consensus or natural sequence HIV-1 antigens in rhesus monkeys.

A 4-cycle IM repeated-dose toxicity study (TOX10873, see IB of Ad26.Mos.HIV) was performed with prime-boost combinations of Ad26.Mos.HIV, MVA-Mosaic and Clade C gp140 drug product (DP). The objective of this study was to assess potential toxicity and local tolerance of the vaccines when administered to New Zealand white rabbits by IM injection once every 3 weeks up to 9 weeks (ie, a total of 4 injection days) and to evaluate the reversibility, persistence or delayed occurrence of any adverse effects on the vaccines during a 21-day recovery observations period following the last injection. In this study, the full human doses are being tested. Details concerning the dose groups and regimen are given in Table 2.

Table 2: Design of a 4-cycle IM Repeated Dose Toxicity Study With Prime-Boost Combinations of Ad26.Mos.HIV, MVA-Mosaic, and Clade gp140 DP

Group	Treatment(s)	Dose Levels	Dose Volume (mL)	Dosing Day/Dosing Site[a] 1	22	43	64	Number of Animals[b] Male	Female
				Caudal			Cranial		
1	Placebo (Saline)	0	0.5 or 0.75	ADM 1	ADM 2	ADM 3; ADM 4	ADM 5; ADM 6	10	10
2	Ad26.Mos.HIV[c]	$5x10^{10}$ vp	0.5	ADM 1	ADM 2	ADM 3	ADM 5	10	10
	gp140/AdjuPhos	250 mcg/425 mcg	0.5	--	--	ADM 4	ADM 6		
3	Ad26.Mos.HIV	$5x10^{10}$ vp	0.5	ADM 1	ADM 2	--	--	10	10
	gp140/AdjuPhos	250 mcg/425 mcg	0.5	--	--	ADM 4	ADM 5		
4	Ad26.Mos.HIV	$5x10^{10}$ vp	0.5	ADM 1	ADM 2	--	--	10	10
	MVA Mosaic	$1x10^{8}$ pfu	0.75	--	--	ADM 3	ADM 5		
	gp140/AdjuPhos	250 mcg/425 mcg	0.5	--	--	ADM 4	ADM 6		
5	Ad26.Mos.HIV	$5x10^{10}$ vp	0.5	ADM 1	ADM 2	--	--	10	10
	MVA Mosaic	$1x10^{8}$ pfu	0.75	--	--	ADM 3	ADM 6		
6	Ad26.Mos.HIV	$5x10^{10}$ vp	0.5	ADM 1	ADM 2	ADM 3	ADM 6	10	10

Note:
Day 1 is the first day of dosing
MVA-Mosaic is a 1:1 combination of MVA-Mosaic 1 and MVA-Mosaic 2

[a] Doses were administered to either the left (ADM 1, 3 and 5) and/or right (ADM 2, 4 and 6) thigh (caudal and/or cranial muscle) via IM bolus injection.

[b] Five animals/sex/group were maintained for a 21-day recovery period. Terminal animals were necropsied on Day 66, while recovery animals were necropsied on Day 85.

[c] On Days 43 and 64 control animals received 2 injections, 1 in left and 1 in right thigh, to provide appropriate controls for Groups 2 and 4

AdjuPhos = aluminum phosphate = established adjuvant; ADM = administration site; gp140 = Clade C gp140 DP

The different dose regimens were well tolerated when administered once every 3 weeks for up to 9 weeks (ie, 4 injections). The initial immune response, which was triggered after 2 injections with Ad26.Mos.HIV, was increased after the next 2 injections for all tested vaccine regimens shortly after the last injection and 3 weeks later. The observed increases in C-reactive protein, fibrinogen, globulin and body temperature and the transient decrease in food consumption are considered to reflect a normal, non-adverse response to the vaccine

administration. Non-adverse test article-related findings were seen in iliac lymph nodes, in the spleen, and at the injection sites. Injection-site lesions had recovered after 3 weeks while the findings in lymph nodes and spleen (ie, immunogenic response) were still present after recovery.

Immunogenicity and Protective Efficacy Against SHIV-SF162P3 Challenge of Ad/MVA and Ad/Ad Regimens Expressing HIV-1 Mosaic Gag,Pol and Env Antigens in Rhesus Monkeys

To provide maximal coverage of potential T-cell epitopes, bivalent Mosaic HIV-1 Gag, Pol and Env antigens were developed. The goal of this study was to determine the immunogenicity of these vectors expressing mosaic antigens and the protective efficacy of these vaccine regimens against repetitive, low-dose, intrarectal challenges with the heterologous, neutralization-resistant virus SHIV-SF162P3 (Barouch 2013). In particular, the study assessed whether the synthetic HIV-1 mosaic Env would elicit Env-specific antibody responses and afford protection. Adult Rhesus monkeys (N=6/group) were primed at Week 0 with Ad26 or Ad35 vectors and boosted at Week 12 with Ad26, Ad35 or MVA vectors expressing HIV-1 mosaic Gag, Pol and Env immunogens, by the IM route. The dose was $4x10^{10}$ vp for Ad26 and Ad35 vectors and 10^7 pfu for MVA vectors. Starting at Week 52, all monkeys received 6 low-dose, intrarectal challenges with SHIV-SF162P3. All vector regimens induced comparable magnitude and breadth of cellular immune responses against matched Mos1 and Mos2 peptides as well as against global potential T-cell epitope peptides. All vector regimens induced binding antibody responses against multiple Env strains from clades A, C, D, F and M (namely UG37, UG92, CN54, ZA9, UG21, BR29 and Mosaic 1 respectively). Both the Ad/MVA and Ad/Ad vaccines afforded partial protection against acquisition of SHIVSF162P3 infection, corresponding to an 87-90% reduction of per exposure acquisition risk, although the majority of the vaccinees became infected by the end of the challenge series. The vaccinated monkeys also exhibited a modest but significant 0.64 log reduction of setpoint viral loads, which was measured 84 days after infection, as compared with the controls.

Recently, a non-human primate challenge study addressed correlates of protection by interrogating virus sequences and vaccine-induced immune responses. Animals were vaccinated with DNA and Ad5 expressing either mosaic Gag or mosaic heterologous Env, or heterologous Env based on a natural SIVmac239 sequence. Env-elicited immune response is necessary and sufficient to provide protection from acquisition from intrarectal SIVsmE660 with a strong sieving effect of Env immunization, selecting for minor variants in the challenge swarm. In addition, a sequence signature in the SIV Env, possibly shared by HIV, was identified that programs the neutralization phenotype of the viruses. There was no association between protection from infection and protection from pathogenesis, suggesting that humoral responses that effectively block acquisition are not necessarily correlated with cellular responses that control pathogenesis. The Env-induced CTL suppressed acute viraemia better than Gag CTL,

but suppressed chronic viraemia less effectively, resulting in reduced transmitted-founder viruses in breakthrough infections (Roederer 2013).

Taken together, both rhesus monkey studies demonstrated increased breadth and depth of CD8+ T-cell responses to mosaic HIV-1 vaccines. This increased immune response may protect against infection by diverse viruses and may limit the formation of variant "escape" viruses.

1.6. Clinical Studies

Several Phase 1 studies have evaluated Ad26 vectored HIV-1 vaccines under the IPCAVD NIH-sponsored program (see Ad26.Mos.HIV IB). IPCAVD001 is a phase 1 randomized, double-blind, placebo controlled dose escalation study to evaluate the safety and immunogenicity of recombinant Ad26.ENVA.01 in healthy, non-HIV-infected adults. The study is now completed (N=60) and overall, the Ad26.ENVA.01 vaccine has been generally safe and well tolerated at all doses tested ($1x10^9$, $1x10^{10}$, $5x10^{10}$, and $1x10^{11}$ vp) and up to 3 vaccinations. There were no vaccine-related serious adverse events (SAEs). Minimal reactogenicity was seen at the $5x10^{10}$ dose. At the 10^{11} dose, reactogenicity (fatigue, myalgias, and chills) was seen 12 hours after the 1st vaccination, which usually resolved within 24 hours. These symptoms were not seen after the 2nd vaccination. Regarding immunogenicity, consistent Env antibody titers and Env T cell responses were seen following the prime, which increased after the 6-month boost and were durable at 1 year in vaccinated subjects. There was a dose response effect observed for Ad26 neutralizing antibody responses and EnvA enzyme-linked immunosorbent assay (ELISA) responses with 10^9 vp $<10^{10}$ vp $\sim10^{11}$ vp. These results were the basis for the choice of the selected dose of Ad26.ENVA.01 ($5x10^{10}$vp) used in the following and in the current study.

IPCAVD003 was a phase 1 randomized, double-blind, placebo-controlled study to evaluate the safety, mucosal immunogenicity, and innate immune responses of Ad26.ENVA.01 in 24 healthy, HIV-1 uninfected adults. The vaccinations were generally well tolerated. The majority of subjects reported mild or no tenderness at the vaccination site overall (21 subjects or 88%). Two vaccine recipients noted moderate and 1 vaccine recipient noted severe local reactogenicity over the week post vaccination. Four out of 18 vaccine recipients experienced at least 1 systemic reactogenicity symptom with a maximal grade of moderate; 5 vaccine recipients experienced at least 1 systemic reactogenicity symptom with a maximal grade of severe. In the latter group, the severe reactogenicity symptoms largely occurred between Day 0 to 1 and were typically a combination of headache, chills, joint pain, myalgia, and malaise/fatigue. There were no study product related SAEs. Immunology results demonstrated that all subjects developed detectable Ad26-specific NAbs by 8 weeks. 16 of the 18 subjects who received Ad26.ENVA.01 had detectable peripheral EnvA IgG ELISA titer by 2 weeks with persistence in most subjects at 24 weeks. Mucosal EnvA-specific IgG ELISA responses were detected 2 weeks post vaccination in 11 of 18 subjects receiving Ad26.EnvA. This response rate

increased slightly at 24 weeks to 14 of 17 subjects having a detectable response. EnvA-specific CD8+ T-cell response increased post vaccination to 0.25%-0.43% at 2 weeks and 0.18%-0.26% at 24 weeks. A similar pattern was seen with EnvA CD4+ T-cell responses. 12 of 18 vaccinated subjects had detectable systemic IFN-gamma EnvA-specific ELISPOT responses by Week 2 and 16 of 18 vaccinated subjects had a detectable response by Week 24. Mucosal EnvA-specific IFN-gamma CD8+ T-cell responses were undetectable at baseline in all 3 groups and remained undetectable in the placebo group at all time points. In Ad26- subjects, responses were detected in half of subjects at 2 weeks and 24 weeks with mean responses of 0.07% and 0.13% at 2 and 24 weeks, respectively. In Ad26+ subjects, similar mean responses of 0.05% and 0.06% at 2 weeks and 24 weeks were observed. Mucosal EnvA-specific IFN-gamma CD4+ T-cell responses were 0%, 0.02% and 0% (Ad26-, Ad26+, and placebo) at baseline; 0.03%, 0.14%, and 0% at 2 weeks; and 0.03%, 0.03 and 0% at 24 weeks. There were stable levels of Ki67+ cellular activation in total and vector specific CD4+ T lymphocytes following Ad26.ENVA.01 vaccination. There was no increase in CCR5 expression in total or vector specific CD4+ T lymphocytes in PBMCs or colorectal mucosa following vaccination.

A third Phase 1 randomized, double blind, placebo controlled study (IPCAVD004 – IAVI B003) was conducted in the United States (US) and in South and East Africa to evaluate the safety and immunogenicity of Ad26.ENVA.01 and Ad35Env HIV vaccines in 217 healthy HIV-uninfected adult subjects. There was no pre-screening of Ad26 or Ad35 serology and the dose of each vaccine was $5x10^{10}$vp. The study assessed different prime boost regimens including 3- vs. 6-month intervals, prime boost directionality, and homologous versus heterologous vector regimens. The majority of reported local reactogenicity reactions was graded as mild or moderate (mild 65.0%; moderate 12.4%) and resolved spontaneously. Similarly, the majority of systemic reactogenicity reactions was graded as mild or moderate (mild 43.2%; moderate 29.6%) and resolved spontaneously. The majority of AEs were mild (75.5%) or moderate (23.2%) in severity. There were three unrelated SAEs. 4 weeks post-second vaccination T-cell response rate (by IFN-gamma ELISPOT) was 44 -100%. There was induction of Ad26 NAbs in the majority of vaccinees 4 weeks after two Ad26.ENVA immunizations. EnvA ELISA response rate was 97-100% after the second injection.

A large body of clinical experience was acquired when non-recombinant MVA was used for primary vaccination against smallpox by intradermal (ID), subcutaneous, and IM routes in over 120,000 humans in southern Germany and Turkey. The original idea of using an attenuated vector such as MVA was to sequentially immunize first with MVA and then boost with the classical vaccinia vaccine to offer protection against smallpox with fewer complications. During these extensive field studies no serious side effects were associated with the use of the MVA vaccine.

Several rMVA vaccines (e.g. MVA-malaria, MVA-HIV) are currently in Phase 1 and early phase 2 international studies. For example, protocol HVTN 055 [A Phase I Trial to Evaluate the

Safety and Immunogenicity of rMVA-HIV (rMVA-HIV env/gag+rMVA-HIV *tat/rev/nef*-RT) and rFPV-HIV (rFPV-HIV env/gag+rFPV-HIV *tat/rev/nef*-RT) Vaccines, Alone or in Combination, in Healthy, Vaccinia-Naïve HIV-1 Negative Participants] assessed the safety and immunogenicity of the simultaneous administration of two modified vaccinia Ankara (MVA)-vectored HIV vaccines as priming doses (one containing *env/gag* and the other containing *tat/rev/nef*-RT), followed by boosting doses of two fowlpox-vectored HIV vaccines containing identical inserts. Overall, the vaccines were well tolerated and there were no SAEs. One or more AEs were reported by 91% of study subjects; however 97% of these were mild or moderate and they were infrequently considered to be definitely/probably (6%) or possibly (4%) related to the vaccine. Pain at the injection site was common but was usually mild with only one vaccinee reporting severe pain. Six subjects had systemic symptoms; 3 experienced them after the fowlpox vaccination and 3 after the MVA vaccination. There was no evidence that any subject developed subclinical or overt myo/pericarditis (Keefer 2011).

Another group based in Germany gave an rMVA-HIV (Bavarian Nordic) to HIV infected patients in an effort to 'boost' their immune responses (ie, therapeutic vaccination). The patients tolerated the injections well and enhanced immune responses were observed (Harrer 2005). This study in HIV-infected individuals provided very important data, because the subjects were immune suppressed; yet they tolerated the live attenuated MVA vaccine quite well and may have benefitted from the immunization as it boosted their immune responses.

A third group, GeoVax, developed an MVA-HIV vaccine to follow a DNA prime. Data on the combination of clade B products, JS7 DNA followed by MVA/HIV62 also demonstrate this combination to be safe (local and systemic symptoms were mild or moderate) and that T-cell responses not detected with available assays from seemingly non-immunogenic priming regimens are enhanced by MVA recombinant vectors (Goepfert 2005).

Another MVA construct, MVA-CMDR was tested by the Military HIV Research program (MHRP as a single agent in a Phase 1 study (RV158) and administered by IM or ID route in HIV-uninfected adults (Currier 2010). A total of 51 healthy, HIV-negative, young adult subjects were enrolled in the study and randomized 5:1 to receive vaccine or placebo. Subjects were vaccinated with up to 10^7 pfu of MVA-CMDR by the ID route (0.1 mL into the volar aspect of forearm) or with up to 10^8 pfu by the IM route (1 mL into the deltoid). Three doses of vaccine were given on Days 0, 28 and 84. Safety data at all three sites show the vaccine to have an excellent safety profile, with the majority of reactogenicity being due to local cutaneous reactions in the group administered vaccine by the ID route (Grade 1 erythema, induration, pain, and tenderness). A few subjects experienced mild systemic reactions such as fatigue, headaches, myalgias, and arthralgia. One subject had a Grade 2 fever (38.7°C), lasting one day after vaccination. No significant laboratory abnormalities were associated with vaccination. No subjects showed signs/symptoms of myo/pericarditis (clinical or subclinical) despite intensive monitoring with regularly scheduled electrocardiograms (ECGs), cardiac enzymes, and AE

solicitation of cardiac symptoms and diary cards. Cell-mediated immune responses were moderate in magnitude but high in response rate. Immune responses were predominantly HIV Env-specific CD4+T cells and were durable for at least 6 months. Binding antibodies against gp120 and p24 were detectable in all vaccination groups. The high dose (10^8 pfu) delivered by IM route was the most immunogenic.

Preliminary Safety Data From Healthy Adult Subjects

The following candidate vaccine components are currently being studied in 2 first-in-human (FIH) studies in HIV-1 uninfected subjects: MVA-Mosaic and Ad26.Mos.HIV.

HIV-V-A002

HIV-V-A002 is a single-center, randomized, parallel-group, placebo-controlled, double-blind FIH Phase 1 study to evaluate safety, tolerability, and immunogenicity of MVA-Mosaic, both in previously unvaccinated healthy adult subjects and in subjects previously vaccinated with Ad26.ENVA.01.

A prototype of MVA-Mosaic, referred to as MVA-CMDR, has previously been found to be immunogenic, safe, and well tolerated.

The independent Safety Monitory Committee (SMC) has performed a safety evaluation (unblinded to group level for SMC members only) at Week 16 (4 weeks after all of the 25 enrolled subjects had received their second vaccination). MVA-Mosaic was well tolerated and no safety concerns were identified. Most AEs were of mild and moderate severity. At the time of this SMC evaluation, there were no withdrawals or discontinuations. One SAE was reported, assessed as not related to study vaccine. The SMC concurred with proceeding with the clinical development as planned and with administration of MVA-Mosaic in HIV-V-A004.

HIV-V-A004

HIV-V-A004 is a multi-center, randomized, parallel-group, placebo-controlled, double-blind Phase 1/2a study to evaluate safety, tolerability, and immunogenicity of various prime/boost regimens containing Ad26.Mos.HIV, MVA-Mosaic, and/or Clade C gp140 (with aluminum phosphate adjuvant) components in healthy HIV-uninfected adult subjects. For Ad26.Mos.HIV, this is a FIH study.

A prototype of Ad26.Mos.HIV, called Ad26.ENVA.01, has previously been found to be immunogenic, safe, and well tolerated.

As pre-specified in the protocol, enrollment was paused when approximately 10% of subjects had received their first injection (Ad26.Mos.HIV) and the Protocol Safety Review Team

(PSRT) has reviewed blinded safety data of 2 weeks after this first injection to determine if enrollment could continue. The PSRT has reviewed blinded 2 week safety follow-up data of 39 subjects and on 18 Jun 2015 all members agreed that the study could resume enrollment. Most AEs were of mild and moderate severity. Three grade 3 AEs were reported that were considered related to vaccination: headache, chills, and myalgia. At the time of the PSRT review, there were no SAEs, withdrawals, or discontinuations.

Preliminary Data From the Acute HIV Infection Cohort

RV254 has extensive feasibility data for enrolling and retaining subjects, and performing specimen collection, processing, storage, international shipping and laboratory studies. Screening for acute HIV infection is performed in real-time by pooled nucleic acid testing. RV254 has an accompanying ARV protocol in which all subjects are offered immediate ART. Enrollment in the cohort is ongoing with an average of 30-50 new enrollees per year.

Table 3 shows characteristics of the first 150 enrolled subjects in RV254. All except two elected to initiate ART, and the mean time from enrollment to ART initiation was 2 days. The RV254 follow-up schedule includes visits at 12-week intervals until a maximum of 416 weeks, and offers additional optional intensive studies (leukapheresis, lumbar puncture, sigmoid biopsy, inguinal lymph node biopsy).

Table 3: Characteristics of 150 Subjects Enrolled in the RV254/SEARCH010 Acute Infection Cohort

Characteristics	Acute HIV Cohort
Age, Median (IQR)	28 (24 - 32)
Male gender	141 (94%)
Infection duration, days (n=123)	
Min-Max	3 - 48
Median (IQR)	17 (12 - 22)
Fiebig, n(%)	
I	51 (35%)
II	24 (16%)
III	59 (40%)
IV	8 (5%)
V	6 (4%)
CD4 (cells/mm^3), median (IQR)	361 (267 - 496)
HIV RNA (log_{10}cps/mL), median (IQR)	5.7 (5.0 - 6.6)
Treatment arm (n=147)	
HAART	68 (46%)
megaHAART	79 (54%)
CRF_01AE (n=62)	47 (76%)
R5 tropism (n=39)	38 (97%)

IQR: inter-quartile range

Relevant to HIV functional cure, RV254 has demonstrated limited seeding of the viral reservoir in early acute HIV infection with subsequent decrease following ART initiation

(Ananworanich 2012). Subjects evaluated during Fiebig I exhibit lower total and undetectable integrated HIV DNA compared to those sampled during Fiebig stage III. More importantly, after 24 weeks of ART, Fiebig I subjects display an extremely low frequency of infected cells, comparable to historical controls including elite controllers and much lower than in subjects who have initiated ART in chronic infection, despite 4 years of viral suppression. These results suggest that very early ART (Fiebig I) may limit the initial seeding of the HIV reservoir (Figure 1).

These preliminary data indicate that the subjects in the RV254 cohort have a lower HIV viral reservoir than patients who initiate ART at a later time after HIV infection. This study is based on the hypothesis that the vaccine regimen will boost the immune system enough that it will be able to control HIV replication in the absence of ART after ATI.

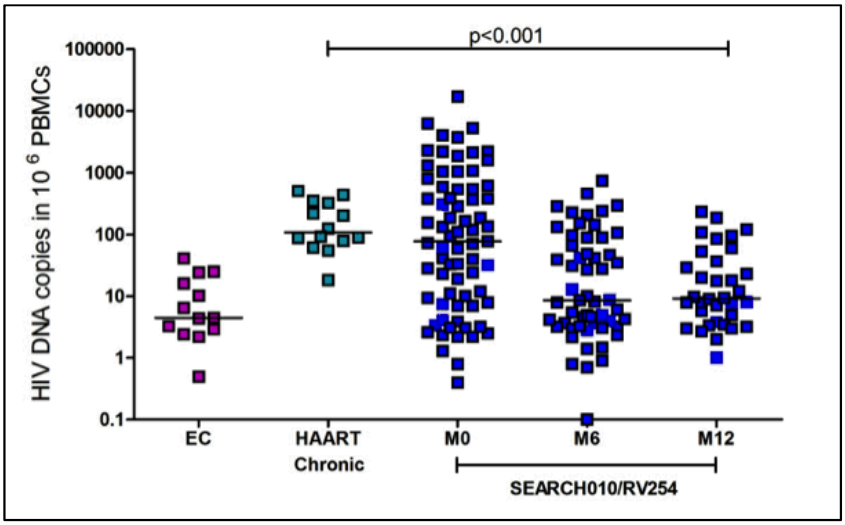

Figure 1: After 6 Months of HAART, RV254/SEARCH010 Subjects Have Very low Levels of HIV DNA in PBMCs, Similar to Levels Seen in Elite Controllers (Ananworanich, 2012)

We propose to evaluate safety and efficacy of a therapeutic vaccine administered in the form of Ad26 vector with mosaic inserts for *gag/pol* and *env* genes of HIV-1, boosted with the MVA vector with homologous mosaic inserts. These vaccine products have been shown to be immunogenic and safe. The vaccine population will be HIV-infected adults who began ART during acute HIV infection and have undetectable plasma HIV RNA (<50 copies/ml) for at least 48 weeks. Patients in this unique cohort have been shown to have very low HIV viral reservoirs and therefore have a high chance for maintained viral suppression in the absence of ART (functional cure of HIV infection).

2. STUDY HYPOTHESIS AND OBJECTIVES

2.1. Hypothesis

This is an exploratory study to collect preliminary data and establish sufficient experience to inform and develop subsequent studies to address the following hypothesis: Vaccine therapy administered in the form of Ad26 vector with mosaic inserts for gag/pol and env genes of HIV-1 at 0 and 12 weeks (Stage 1), boosted with the MVA vector with homologous mosaic inserts for gag/pol and env genes at 24 and 48 weeks (Stage 1), among individuals with fully suppressed HIV will be safe and well-tolerated, will result in a measurable immune response, and will result in over 50% of vaccine recipients achieving sustained viremic control after ATI (Stage 2).

2.2. Primary Objectives

1. Determine the safety and tolerability of Ad26 prime/MVA boost versus placebo in subjects on suppressive ART that was initiated during acute HIV infection
2. Measure the frequency and duration of sustained viremic control after receiving Ad26 prime/MVA boost or placebo, defined as greater than 24 weeks with plasma HIV RNA <50 copies/ml after ARV ATI

2.3. Secondary Objectives

1. Determine the immunogenicity of Ad26 prime/MVA boost in subjects on suppressive ART that was initiated during acute HIV infection
2. Characterize biomarkers of HIV reservoir at baseline, after vaccine therapy prior to ARV ATI (Week 48-60) and after ARV ATI (Week 60-96)
3. Compare the duration of viremic control (HIV RNA <50 copies/ml) between vaccine and placebo recipients who failed to achieve sustained viremic control (undetectable plasma HIV RNA [<50 copies/ml] at Week 24 after ARV ATI)
4. Describe the frequency, magnitude, specificity and functional capacity of humoral and cellular immune responses to vaccine and other immunogens
5. Describe the molecular sequence sieve effects of vaccine therapy on breakthrough rebound viremia before and after cessation of therapy
6. Describe the PBMC phenotype, pattern of soluble factors and immune functional responses before and after ARV ATI in both the vaccine and placebo arms and compared to historical untreated acute infection cases in RV217
7. Describe the clinical outcomes in terms of the frequency, severity, duration and treatment for acute retroviral syndrome post ARV ATI
8. Evaluate and characterize HIV resistance to ARV drugs in subjects who experience rebound viremia after ARV ATI

2.4. Exploratory Objectives

1. Analyze the markers of HIV reservoir as predictors of sustained viral suppression.
2. Analyze the markers of HIV specific immune responses as predictors of sustained viral suppression.
3. Analyze the expression profiles and transcriptome analysis of sorted and/or unsorted lymphocytes and monocyte/macrophages in the different arms of the study.
4. Compare the mucosal immunity (vaginal and rectal for humoral and gut mucosa for cellular immunogenicity) in vaccine versus placebo arms.
5. Describe the markers of immune activation in the peripheral blood and various reservoirs.
6. Describe the viral load response to resumption of ART and impact on markers of HIV reservoir among those who fail to suppress HIV RNA off therapy.

3. STUDY DESIGN AND POPULATION

3.1. Study Design

This is a combined Phase 1/2a randomized, double-blind, placebo-controlled study to investigate the safety, immunogenicity and effect on HIV viremic control after ARV ATI of a vaccine regimen consisting of an Ad26.Mos.HIV prime and an MVA-Mosaic boost. The study will include subjects who started on ART during acute HIV infection, who are on a current stable ART for at least 4 weeks prior to screening and who have achieved absence of viremia (HIV RNA <50 copies/ml) for ≥ 48 weeks prior to initiation of vaccine/placebo.

The study will be conducted at one study site in PPD Thailand PPD . Volunteers for this study will be participants on RV254. The RV254 cohort is largely composed of men who have sex with men and transgender subjects and has a limited number of women (Table 3). Participants for this study will continue to participate in other RV254 related activities in parallel. This will include regular and unscheduled visits. No research blood draws or invasive procedures are scheduled during the RV254 related visits performed in parallel with this study. Laboratory tests in RV254 for HIV clinical care, such as screening and monitoring for co-infection may be performed. In addition, blood draws for clinical care may be performed. The results of the activities/procedures specific for RV254 will only be reported if relevant to this study. Data from RV254 will be shared with the current study as needed to assess endpoints and objectives. As an example, sequences for the founder virus from the RV254 study would be available for analysis within this study.

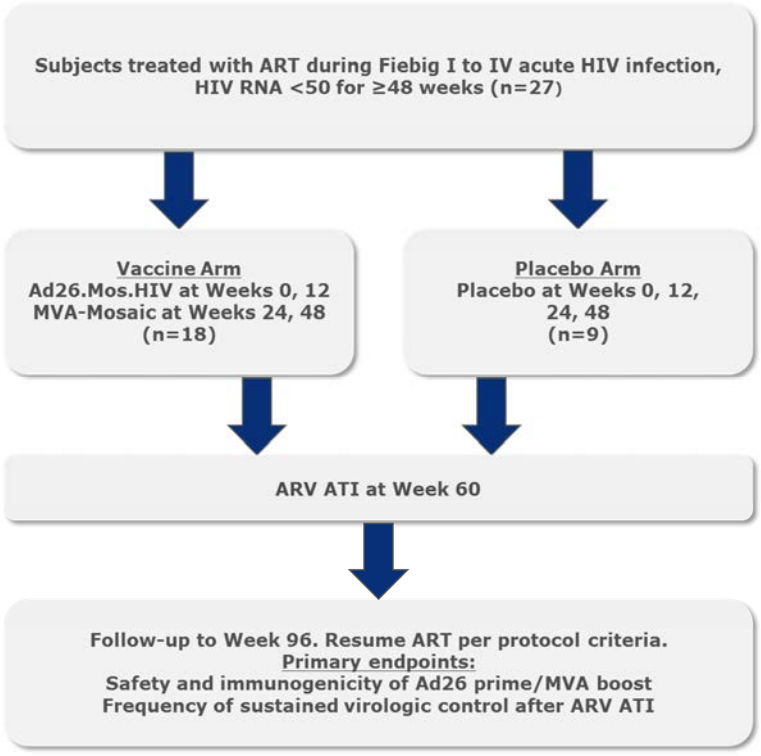

Figure 2: Study Design

The study will enroll 27 subjects in a 2:1 ratio of vaccine to placebo (Figure 2). The study will occur in two stages. Before the first stage, recruitment, consent and baseline assessments of subjects who meet the entry criteria of sustained absence of viremia for at least 48 weeks and of initiation of ART during acute HIV infection will take place. It is anticipated that enrollment will be rapid as the RV254 study has over 100 early-treated patients with viral suppression. The first stage is administration of the vaccine or placebo, and observation after vaccination and prior to ARV ATI (Phase 1). The second stage will be ARV ATI with frequent assessment of viral load for rebound viremia (Phase 2a). In this period, the duration of viral control will be determined, and follow-up for those subjects who resume therapy, ie, fail to maintain viremic control will be performed. Durability of immunogenicity will be evaluated during the ARV ATI period.

An independent DSMC will be involved in addition to a PSRT, which will have representatives from the sponsor and protocol team.

Measured outcomes include:

1) Safety endpoints
2) HIV specific antibody and cellular immune responses in blood and mucosal compartments
3) Viremic control
4) Biomarkers for HIV expression and reservoir in blood and mucosal compartments
5) Markers for immune status, including phenotype and activation markers in blood and mucosal compartments

The subjects will receive 4 single injections of the respective vaccine or placebo. Subjects, clinical staff, investigators and the sponsor are blinded to treatment allocation. The subjects receiving placebo serve as a control for safety, efficacy and immunogenicity assessments. Placebo only refers to the vaccine component of the study (Stage 1). Subjects in both the vaccine and placebo arms will receive standard ART:

- For HIV treatment during the first 60 weeks of the trial prior to ATI (Stage 1)
- If they meet any of the criteria to restart ART listed in Section 4.1.6 (Stage 2)
- At the end of the trial at Week 96 (post Stage 2)

To assess the safety of the administered vaccines, subjects will be observed for reactogenicity in the clinic for a minimum of 30 minutes after each vaccination. Vital signs will be taken and qualified study personnel will evaluate for any signs or symptoms of local or systemic reactions. The subjects will document local and systemic reactions 6 hours after each vaccination and then daily for the next 7 days and investigators will document any reported AEs at each visit throughout the study. Rebound in viral replication post ARV ATI (HIV RNA >50 copies/ml) will not be considered an AE/SAE as it is a study endpoint. To assess the subjects' cellular and humoral immune response, blood samples will be taken during the clinic visits. Safety, efficacy and immunogenicity visits will be conducted as outlined in the study Schedule of Evaluations (SOE) in Table 4 and Table 5.

The study will last approximately 96-100 weeks per subject, including up to 6 weeks for screening, 48 weeks for the vaccination period (Stage 1), 12 weeks between the final vaccination and ARV ATI (Stage 1), and 36 weeks of follow up after ARV ATI (Stage 2). End of study is defined as the last visit of the last subject undergoing the study.

All subjects in this study are participants in RV254 and will continue to participate in other RV254 activities in parallel which include regular and scheduled visits. No research blood draws are scheduled during this visits, but blood draws or procedures scheduled for clinical care

may be performed. The results of the activities/procedures specific for the RV254 will only be reported if relevant to the current study.

In addition, all subjects will be offered enrollment in study RV412 (Safety and Virologic Outcomes after Analytic Treatment Interruption in Thai Patients who Initiated Antiretroviral Therapy During Early Acute HIV Infection). This requires a separate consent process. RV412 is a protocol that will enroll all subjects who complete any clinical study that includes ARV ATI at SEARCH. The protocol provides regular clinical, immunological and virogical monitoring for at least 48 weeks or until HIV-1 RNA is undetectable on 2 consecutive assessments after reinitiating ART. RV412 provides a transition period of more frequent monitoring for safety and clinical endpoints before subjects return to routine follow-up visits of every 12 weeks under the RV254 study protocol. Data from RV412 will be shared with the current study as needed.

3.2. Subject Selection and Withdrawal

3.2.1. Inclusion Criteria

1. Confirmed HIV-1 infected and started ART during acute infection (Fiebig stages I, II, III or IV)
2. Treatment with current stable ART (no changes to treatment) for at least 4 weeks prior to screening.
3. HIV RNA <50 copies/ml for at least 48 weeks at screening.
    a. One blip of HIV RNA >50 and <200 copies/ml within 48 weeks is acceptable, provided that the most recent (before screening) HIV RNA <50 copies/ml.
4. Each subject must have voluntary signed an informed consent form indicating that he/she understands the purpose of and procedures required for the study and is willing to participate in the study.
5. Age 18 to 50 years old at the time of study enrollment.
6. Laboratory criteria during screening:
    a. Hemoglobin: Women: ≥11 g/dL; Men ≥12.5 g/dL
    a. White cell count: 2,500 to 11,000 cells/mm^3
    b. Platelets: 125,000 to 450,000 per mm^3
    c. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤1.5x institutional upper limits of normal (ULN)
    d. Creatinine ≤1.5x institutional ULN
    e. CD4 > 400 cells/mm^3
    f. Troponin ≤1 x ULN

7. All female subjects of childbearing potential must have a negative serum pregnancy test (β-human chorionic gonadotropin) at the screening visit, and a negative urine pregnancy test prior to vaccination on Day 1[1].
8. A woman must be either:
   a. 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 stimulation hormone [FSH] level >40 IU/L); surgically sterile; or
   b. Of child-bearing potential and practicing an effective double method of birth control (e.g. prescription oral contraceptives, contraceptive injections, intrauterine device, contraceptive patch, or vaginal ring, in conjunction with either a female condom or one of the methods for male contraception indicated in Inclusion Criterion 9, before entry[2] and through 3 months after the last vaccination.
9. A man who is sexually active with a woman of child-bearing potential and has not had a vasectomy, must agree to use an adequate contraception method as deemed appropriate by the investigator (e.g. condom, sterilization [after vasectomy, zero sperm must be confirmed if procedure occurred less than 1 year ago]) in conjunction with one of the methods for female contraception indicated in Inclusion Criterion 8.
10. Available and willing to participate for the duration of the study visits and follow up.
11. Pass the Test of Understanding (TOU) (See Appendix 16.3)

3.2.2. Exclusion Criteria

1. A woman who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study, or within 3 months after the last vaccination.
2. Subject is a man who plans to father a child while enrolled in this study, or within 3 months after the last vaccination.
3. Any clinically significant acute or chronic medical condition that in the opinion of the investigator would preclude participation (e.g., history of seizure disorders, bleeding/clotting disorder, autoimmune disease, active malignancy, poorly controlled asthma, active tuberculosis or other systemic infections, etc).
4. Any history of HIV-related illness under Centers for Disease Control and Prevention (CDC) category C.
5. Major surgery within the 4 weeks prior to study entry or planned major surgery through the course of the study.

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

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

6. History of myocarditis, pericarditis, cardiomyopathy, congestive heart failure with permanent sequelae, clinically significant arrhythmia (including any arrhythmia requiring medication, treatment, or clinical follow-up).
7. ECG with cardiology reading showing 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 2nd or 3rd degree AV block, or QTc prolongation [> 450 ms]);
    b. Significant repolarization (ST segment or T wave) abnormality;
    c. Significant atrial or ventricular arrhythmia; frequent atrial or ventricular ectopy (e.g., frequent premature atrial contractions, 2 premature ventricular contractions in a row)
    d. ST elevation consistent with ischemia; or evidence of past or evolving myocardial infarction.
8. History of diabetes mellitus type 1 or type 2, including cases controlled with diet alone. (Not excluded: history of isolated gestational diabetes.)
9. Chronic active hepatitis B or active hepatitis C (eg, positive serology with confirmatory positive polymerase chain reaction) or active syphilis infection. Active syphilis documented by examination or serology unless positive serology is due to past treated infection.
10. Thyroidectomy, or thyroid disease requiring medication during the last 12 months.
11. Hypertension:
    a. If a subject has been diagnosed with hypertension during screening or previously, exclude for hypertension that is not well controlled. Well-controlled hypertension is defined as blood pressure consistently ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic, with or without medication, with only isolated, brief instances of higher readings
    b. If a subject has NOT been diagnosed with hypertension during screening or previously, exclude for systolic blood pressure ≥ 150 mm Hg at enrollment or diastolic blood pressure ≥ 100 mm Hg at enrollment.
12. Major psychiatric illness and/or substance abuse problems during the past 12 months that in the opinion of the investigator would preclude participation
13. Receipt of any vaccine within 30 days prior to the first vaccination or plans to receive within 30 days post-vaccination. In the case of medically indicated vaccines, the vaccination should be given at least 2 weeks before or after the first vaccination. However, if a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.[3]

[3] The same rules will apply for the second, third and fourth vaccinations.

14. Use of experimental therapeutic agents within 30 days of study entry.
15. Receipt of blood products or immunoglobulin in the past 3 months.
16. History of anaphylaxis or other serious adverse reactions to vaccines or vaccine products, or neomycin or streptomycin or egg products.
17. History of chronic urticaria (recurrent hives).
18. Chronic or recurrent use of medications which modify host immune response, e.g. cancer chemotherapeutic agents, parenteral corticosteroids (short course oral steroids given for non-chronic conditions not expected to recur is not an exclusion criteria, topical steroid use is not an exclusion criteria), etc. but not including ART.
19. Recipient of an HIV vaccine candidate at any time, receipt of a pox-virus vaccine in the last 10 years, and receipt of other experimental vaccine(s) within the last 5 years.
    a. Exceptions may be made for vaccines that have subsequently undergone licensure by the US Food and Drug Administration (FDA). For potential subjects who have received placebo or experimental vaccine (greater than 5 years ago), documentation of the identity of the study placebo or vaccine must be provided to the PSRT, who will determine eligibility on a case-by-case basis.
20. Subjects who cannot communicate reliably with the Investigator.
21. Subjects who are, in the opinion of the Investigator, unlikely to cooperate with the requirements of the study.
22. A study site employee directly supervised by members of the study team, as well as family members of the investigator, or an employee of the sponsor or its partner(s).

NOTE: The investigator should ensure that all study enrollment criteria have been met when the subject is screened. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first administration of study vaccine such that they now meet an exclusion criterion, they should be excluded from participation in the study.

3.2.3. Prohibitions and Restrictions

Vaccination with any vaccine within 30 days prior or after any of the study vaccinations is disallowed. Medically indicated vaccines, other than those described above, (e.g. influenza, tetanus, Hepatitis A, Hepatitis B or rabies) are not exclusionary but should, if possible, be given at least two weeks before or two weeks after any study vaccination to avoid potential confusion of adverse reactions. However, if a vaccine is indicated in the post-exposure setting (e.g. rabies or tetanus), it must take priority over the study vaccine.

3.2.4. Withdrawal or Elimination Criteria

Under certain circumstances, a subject will be terminated from participating in further vaccinations or further study visits. These specific experiences are outlined in Section 5.2 and Section 5.3, respectively.

A subject who discontinues will not be replaced, unless the subject did not yet receive any study vaccine. Replacement of these subjects will only be allowed until the end of the recruitment period.

3.2.5. Cohort Criteria for Proceeding to ARV ATI Phase of Study

ICS or ELISPOT will be performed on cryopreserved PBMC using peptide pools for gag, env and pol matching the vaccine inserts. Participants will be considered to have a positive response following vaccination if after the third vaccination (2 injections of Ad26 and a single MVA injection) there is ≥2-fold increase in magnitude of IFN-gamma producing cells relative to baseline for any one of the matching peptide pools. If the baseline response is negative, then any detectable response is considered a positive response. Placebo recipients will be evaluated to maintain blinding. The ARV ATI (Stage 2) will proceed if at least 50% of subjects who received the active vaccine have a positive response (as evaluated by an independent, unblinded statistician).

Individual subject criteria for proceeding to ARV ATI are provided in Section 3.2.6 below.

3.2.6. Individual Subject Criteria for ARV ATI at Week 60

Subjects who complete 4 vaccine/placebo injections and remain in the study through Week 58 will undergo ARV ATI at Week 60 if they meet all of the criteria listed in Section 3.2.6.1. Subjects will be excluded from ARV ATI if they meet one of the criteria listed in 3.2.6.2.

3.2.6.1. Inclusion Criteria for ARV ATI

1. HIV-1 RNA <50 copies/mL for previous 52 weeks (blips <200 copies/ml are allowed, provided that the most recent result is <50 copies/ml)
2. Most recent (within 3 months) peripheral blood CD4 count > 400 cells/mm^3
3. No CDC Category B or C HIV-related illness within the last 6 months (Appendix 16.1)

3.2.6.2. Exclusion Criteria for ARV ATI

1. Pregnancy or breast-feeding.
2. New hepatitis B surface antigen positive since enrollment.
3. New hepatitis C antibody positive since enrollment.
4. Serious medical or psychiatric illness that, in the opinion of the site investigator, would interfere with the ability to adhere to study requirements.

5. Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

3.3. Treatment Arm Allocation

Subjects will be randomly assigned to one of the vaccine and placebo arms based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. A list of treatment allocation assignments will be sent to the designated pharmacist at the study site.

Distribution and randomization will be 2:1 in the vaccine and placebo arms, respectively.

A subject who discontinues will not be replaced, unless the subject did not yet receive any study vaccine. Replacement of these subjects will only be allowed until the end of the recruitment period.

3.4. Method of Blinding and Unblinding

The subjects, the clinical staff, the Principal Investigator (PI) and the sponsor will be blinded to treatment allocation. The pharmacist with primary responsibility for vaccine dispensing will not be blinded to the treatment and maintains the randomization code and completes assignments of subjects according to the randomization allocation.

The blind will be broken only if, in the opinion of the site PI, PSRT or DSMC, immediate unblinding is necessitated by an acute safety concern in order to make medical management decisions. Whenever possible, the sponsor and PSRT should be contacted before breaking the blinded emergency code. Emergency unblinding, without prior notification to the sponsor and PSRT, should occur only if necessary to make urgent medical management decisions. The sponsor's Pharmacovigilance Department (Global Medical Safety) has to be informed of unblinding within 1 working day.

Accidental unblinding (e.g., investigator sees the investigational product [IP] administration logs) must be reported within 1 working day to the sponsor who then advises on the next corrective and preventative steps to be taken.

Subjects for whom the code was broken will be withdrawn from further vaccination. If less than 4 study injections were received then they will not receive further injections and will not undergo ARV ATI. These subjects will continue follow-up through Week 50, which will be considered the final study visit and all investigations scheduled for the exit visit (Week 96) will be completed at that time. If unblinding occurs after all 4 study injections were received then the subject will continue participation in the study per protocol.

Routine unblinding of treatment allocations may occur only after all subjects have had their last study visit and the eDC database is finalized.

4. TREATMENTS

4.1. Study Treatments

Detailed instructions for study treatment management including preparation, storage and documentation are provided under separate cover in the IP Management Manual. Additional information is also provided in the IBs for Ad26.Mos.HIV and MVA-Mosaic.

4.1.1. Ad26.Mos.HIV Vaccine

Ad26.Mos.HIV is a trivalent vaccine containing the following three active pharmaceutical ingredients pre-mixed in a 1:1:2 vp ratio:

- Ad26.Mos1.Gag-Pol = recombinant, replication-incompetent Adenovirus Serotype 26 expressing mosaic 1 HIV-1 Gag and Pol proteins, manufactured in PER.C6® Cells (JNJ-55471494-AAA).
- Ad26.Mos2.Gag-Pol = recombinant, replication-incompetent Adenovirus Serotype 26 expressing mosaic 2 HIV-1 Gag and Pol proteins, manufactured in PER.C6 Cells (JNJ-55471520-AAA).
- Ad26.Mos1.Env = recombinant, replication-incompetent Adenovirus Serotype 26 expressing a mosaic 1 HIV-1 Env protein, manufactured in PER.C6 Cells (JNJ-55471468-AAA).

The trivalent Ad26.Mos.HIV vaccine will be manufactured and provided under the responsibility of the sponsor. It is formulated 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 1×10^{11} vp/mL. Each 2 mL DIN 2R vial contains a volume of approximately 0.75 mL, with an extractable volume of 0.5 mL for a dose of 5×10^{10} vp. See IP Management Manual for further details.

4.1.2. MVA-Mosaic Vaccine

Modified Vaccinia Ankara Mosaic Sequence is comprised of the following 2 vaccine products supplied in separate vials and administered in a 1:1 ratio:

- MVA Mosaic 1 = Modified Vaccinia Ankara virus expressing Mosaic 1 HIV-1 Gag, Pol and Env proteins (JNJ-55471533-AAA)
- MVA Mosaic 2 = Modified Vaccinia Ankara virus expressing Mosaic 2 HIV-1 Gag, Pol and Env proteins (JNJ-55471572-AAA)

Each vaccine is provided in individual dosage vials at the concentration of 2 x 10^8 pfu/mL. Each stoppered and sealed 2 mL glass vial contains a volume of approximately 1.2 mL. They are supplied as white to opaque, slightly to moderately cloudy liquids. Each of the MVA products is mixed at the site research pharmacy in a 1:1 ratio and a 0.5 mL dose withdrawn to deliver a net dose of MVA mosaic-1 and MVA mosaic-2 of 1 x 10^8 pfu. See IP Management Manual for further details.

4.1.3. Placebo

Sodium Chloride Injection US Pharmacopeia (USP), 0.9% will be used as the placebo for Ad26.Mos.HIV and MVA-Mosaic vaccinations. See the IP Management Manual for further details.

4.1.4. Vaccine Administration Schedule

The schedule of follow up is shown in Table 4 (schedule from screening to completion of vaccinations; Stage 1) and Table 5 (schedule from ARV ATI to the end of the study; Stage 2). Subjects will receive Ad26.Mos.HIV or placebo at Weeks 0 and 12, and will receive MVA-Mosaic or placebo at Weeks 24 and 48. In subjects who are on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based treatment, a boosted protease inhibitor (lopinavir/ritonavir or atazanavir/ritonavir or darunavir/ritonavir) will be given instead of the NNRTI from Weeks 58 to 60 to reduce the risk for NNRTI resistance. At Week 60, all ARV drugs will be discontinued.

4.1.5. Monitoring During ARV ATI

During ARV ATI (Stage 2), subjects will be monitored frequently for clinical and laboratory indications to resume ART (Section 4.1.6). These criteria are designed to protect the subjects from any possible clinical, immunological, or virological adverse effects during the ARV ATI.

Prior investigation has shown that virologic controllers may experience transient low-level viremias after ARV ATI and that these reversible low-level viremias do not always indicate viral rebound (saez-Cirion 2013). Therefore transient viremia <1,000 copies/mL is not considered an indication for resumption of ART. This low level of viremia is also unlikely to produce clinical disease or CD4 decline within the time interval of ARV ATI in this study.

4.1.6. Criteria to Reinitiate ART During ARV ATI

Subjects will require re-initiation of ART after ATI using the same regimen as their previous treatment (before Week 60) for any of the following reasons:

1. HIV-1 RNA above 1,000 copies/mL on 2 consecutive determinations at least 1 week apart.
2. CD4+ T-cell counts below 350 cells/mm^3 on 2 consecutive determinations at least 2 weeks apart.

3. CD4+ T-cell count decline of > 50% from Week 60 prior to ATI (as reference/baseline).
4. Clinical progression to CDC Category B or C disease (see Appendix 16.1).
5. Diagnosis of Acute Retroviral Syndrome (ARS, see Appendix 16.2).
6. Pregnancy
7. Subject requests re-initiation of ART.

4.1.7. Management of Subjects After Reinitiating ART

If the decision is made to reinitiate ART for any reason (except pregnancy), the subject will continue the planned visits as in Table 5. Management of subjects who become pregnant is detailed in Section 4.1.9.

If ART is reinitiated due to rebound viremia with HIV-1 RNA >1,000 copies/mL, then HIV genotype testing will be performed at the time of ART resumption. The results of genotype testing will be available within seven days and will be used to guide ART selection. The final regimen will be determined by discussion between the subject and the treating physician.

Subjects will undergo quantitative HIV-1 RNA testing every two weeks for the first four weeks and then every four weeks until the end of the study.

After 96 weeks, the protocol will be completed and all subjects will remain on ART. They will be offered enrollment in protocol RV412, which provides frequent and intensive clinical and laboratory monitoring, as noted in Section 3.1.

All subjects who complete enrollment in study RV412 will continue to participate in the RV254 parent protocol. Therefore, subjects enrolled in this VAC89220HTX1001/RV405 protocol will have access to long-term treatment and monitoring.

4.1.8. Management of Subjects With Sustained Virologic Control at End of Study

Subject can request re-initiation of ART at any time during the study, regardless of their virologic control.

After 96 weeks, the protocol will be completed and subjects will be asked to resume ART. ART will be provided by the study site. They will be offered enrollment in protocol RV412 for continued observation. The RV412 protocol will help to ensure the safety of the subjects with frequent and intensive viral load and safety laboratory monitoring.

ART regimens are based on the subject's last known ART regimen or another empiric regimen as determined by discussion with the subject's medical provider.

All subjects who complete enrollment in RV412 will continue to participate in the RV254 parent protocol. Therefore, subjects enrolled in this VAC89220HTX1001/RV405 protocol will have access to long-term treatment and monitoring.

4.1.9. Management of Subjects Who Become Pregnant

Subjects who become pregnant during the study period will complete all procedures scheduled for study end at the time the pregnancy is diagnosed. If the subject was scheduled to receive additional vaccine or placebo, these injections will not be administered after pregnancy has been determined. The visit at which pregnancy is diagnosed or immediately following the diagnosis (if diagnosed outside the study) will be considered the subject's last study visit. Pregnant subjects will subsequently be offered enrollment in RV412 for continued observation. They will be advised to resume ART as soon as possible in consultation with the study investigator, PI and an obstetrician/gynecologist experienced with the management of HIV during pregnancy. If the subject completes participation in RV412 before the pregnancy is completed, she will subsequently continue her participation in the RV254 parent study. Pregnant subjects prescribed ART will also be advised to enroll in the ARV pregnancy registry (http://www.apregistry.com/who.htm).

The site PI or designated associate investigator will be responsible for reporting any pregnancy to the PSRT and the study sponsor. This information will be reviewed by the PSRT regularly in aggregate with other safety data. The PSRT will forward notification as necessary to IRBs, study sponsor, and regulatory agencies.

A pregnancy should be followed to term, any premature terminations reported, and the health status of the mother and child including date of delivery should be reported to the sponsor after delivery. Pregnancy outcomes will be recorded via a standardized form. Information documented on this form will include date of last menstrual period, date pregnancy confirmed, history of complications during prior pregnancies (such as congenital abnormalities or spontaneous abortions), and the outcome of the pregnancy including date of termination or delivery, any complications of pregnancy, and the status of the child. A separate form will be completed for the delivered child to document date of delivery, gender, weight, presence of any congenital abnormalities, APGAR score, HIV status, and any other complication of delivery. Any abnormality considered related to the study vaccine by the responsible physician during pregnancy and delivery, and health of mother and baby must be reported through an expedited report.

4.2. Handling of Study treatments

4.2.1. Packaging and Labeling

The Ad26.Mos.HIV vaccine and MVA-Mosaic vaccines will be manufactured and vialed under supervision of the sponsor. Sodium Chloride Injection USP, 0.9% will be purchased commercially.

All study vaccines will be manufactured and packaged in accordance with Current Good Manufacturing Practice.

Further details for the packaging and labeling for both the study vaccine and placebo can be found in the IP Management Manual.

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

4.2.2. Shipment and Storage

Authorization to ship the IP to the site will be provided in writing by the sponsor, upon confirmation that all required critical documents for shipment authorization are completed. The IP will be shipped to the site according to the required storage conditions.

Upon receipt of study treatment supplies, the pharmacist must immediately inspect all vials for damage, temperature recorded during shipment, packaging and labeling, and inventory compared to the packing list. The study drug will be shipped with a continuous temperature monitoring device. The condition of the vials and the temperature of the shipment must be documented. Any deviations or problems identified must be documented. The sponsor should be immediately notified of any temperature excursion and/or damage to vials in shipment and/or storage of IP.

Study vials must be stored in a secured location with no access for unauthorized personnel. Guidance on storage temperature is provided in the pharmacy manual/study site investigational product manual. Storage temperature must be monitored daily and a log of the monitored temperature maintained. The study freezer must be equipped with a continuous temperature monitor and alarm. Study freezers should be equipped with back-up power systems. Complete storage instructions are provided in the IP Management Manual. In the event that study product is out of temperature range, all relevant data will be sent to the sponsor to determine if the affected study product will be used or replaced. Dosing should be halted until further instruction from the sponsor, and during that period the affected IPs must be quarantined.

4.2.3. Dose Preparation and Administration

To prepare the MVA-Mosaic vaccines, the vials must be thawed to room temperature and then mixed using a high-speed vortex, as per instructions in the IP Management Manual.

To prepare the Ad26.Mos.HIV vaccine, each vial must be thawed to room temperature and then prepared as per instructions in the IP Management Manual.

For MVA-Mosaic, a 0.5 mL injection (10^8 pfu) will be administered IM.

For Ad26.Mos.HIV, a 0.5 mL injection (5×10^{10} vp) will be administered IM.

For placebo, a 0.5 mL injection of normal 0.9% saline will be administered IM.

All injections may be administered in either deltoid. It is not necessary to use the same deltoid at each visit. No local or topical anesthetic will be used prior to the injection via any route of administration. The study vaccine will be prepared by the site pharmacist and administered by the clinic staff. The IP Manual specifies the maximum time allowed between preparation and administration.

Site pharmacists will prepare all doses for administration and dispense to the clinic. All other staff members and subjects will remain blinded to the treatment administered. In order to preserve blinding, the pharmacist will place an overlay on the syringes.

4.2.4. Accountability

The site pharmacist will be responsible for maintaining an accurate record of the randomization codes, inventory, and accountability of vaccine supplies for this study. At any time, the numbers of supplied, used, and remaining vials have to match. It must be possible to reconcile delivery records with those of used and unused stocks. Account must be given of any discrepancies.

The site pharmacist will also be responsible for ensuring the security of these documents.

Partially used vials will not be administered to other subjects or used for in vitro experimental studies. Any unused portion of entered vials and expired syringes should be disposed of in a biohazard container and incinerated or autoclaved. After the study is completed or terminated, the site will receive instruction regarding the final disposition of any remaining study products.

4.3. Prior and Concomitant Treatment

Concomitant medications are recorded from day of initial screening to first vaccination and at every study visit. All subjects are HIV-infected and on suppressive ART. Study vaccinations will be administered in addition to ART. The ART cannot be modified, with the following exceptions:

— Switches within an ARV class will be allowed for well documented tolerability/toxicity reasons (linked to an AE or SAE) and after sponsor approval. A switch to a different

formulation of the same ARV is allowed. Switches between lamivudine (3TC) and emtricitabine (FTC) are allowed.

— If subject fails to comply with the ARV regimen, a change that will prevent efficacy and tolerability issues will be allowed for well documented reasons and after sponsor approval.

— At Week 58, NNRTIs will be replaced by protease inhibitors (see Section 5.1.6).

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

4.4. Investigational Product Compliance

The study products will be administered intramuscularly to subjects in the clinic by trained and qualified study personnel. Study site personnel will keep a log of all study treatment administered.

5. CONDUCT OF THE STUDY

5.1. General Aspects

Evaluation of the safety of the vaccine regimens will include clinical laboratory tests, physical assessments 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. 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.

Potential adverse reactions will be further evaluated prior to continuing the vaccination schedule. Total blood volume drawn from each subject will not exceed 550 mL in any eight-week period which is considered acceptable based upon the NIH and US FDA guidelines (NIH clinical center guidelines; https://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/guidancesinformationsheetsandnotices/ucm118099.htm). The schedule for evaluations for the study is completely detailed in Table 4 and Table 5.

This study is one of the few studies in the world to follow a unique cohort of acutely treated HIV infected patients with extremely low HIV-reservoir size. Recent data have shown that HIV mainly resides in lymphoid tissues and other tissue compartments. In chronically treated

patients, the viruses in tissues are the sources of viral rebound when ART is interrupted (Rothenberger 2015). In RV254 study participants who are treated in acute HIV infection, remarkably low cell-associated HIV DNA have been observed in the blood and in the gut, as well as low HIV RNA in the CSF and genital compartments (Ananworanich 2012, Valcour 2012). The levels of these markers of HIV reservoir are undetectable in most patients and lower than those previously reported (Goujard 2012, Hocqueloux 2010). However, it is not known whether replication competent HIV is present in the compartments and whether it could be a source of viral rebound.

Moreover, in this study, it will be important to understand HIV-specific immune responses that are pre-existing and those that are generated after vaccination. HIV-specific immune responses in tissue may be key to controlling viremia following treatment interruption (Barouch 2012; Hansen 2013). The RV144 study conducted in Thailand study also illustrated the importance of HIV V1/V2 antibody in the mucosa in blocking/promoting infection (Haynes 2012). Therefore, it is important that we understand the interactions between the virus and the immune system in the tissue compartments as well as in the peripheral blood.

The biological samples collected in the study have been selected as the body compartments most likely to harbor quiescent HIV virus: CSF from the central nervous system, lymph node tissue, and lymphoid tissue in the gut mucosa. Genital secretions are collected because sexual contact is the most common way in which HIV is transmitted and the results of this testing has important implications for HIV prevention.

Measuring HIV and the immune responses against HIV in the compartments will afford us the ability to identify predictors for successes and failures in controlling viremia. This will be a major advance for the field in that it will provide measures to help select patients in the future who may have the highest probabilities to control viremia without long-term ART (ie, HIV remission).

Table 4: Schedule of Follow-Up and Testing From Screening to After all Vaccinations and Prior to ARV ATI (Stage 1)

Visit Number	**1**	**2[10]**	**3**	**4**	**5[10]**	**6**	**7**	**8**	**9**	**10**	**11**	**12[10]**	**13**
Visit Week	**Screening**	**Wk 0**	**Wk 4**	**Wk 12**		**Wk 16[13]**	**Wk 24[10]**	**Wk 26[13]**	**Wk 30[13]**	**Wk 36[13]**	**Wk 48**		**Wk 50[13]**
Visit Day and Window	**-45 to -3**	**1**	**29 ± 5**	**85 ± 7**	**88 ± 2**	**113 ± 5**	**169 ± 7**	**183 ± 5**	**211 ± 5**	**253 ± 5**	**337 ± 14**	**340 ± 2**	**351 ± 5**
Eligibility criteria, Consent	X												
Randomization		X											
Ad26 or placebo		**X**		**X**									
MVA or placebo							**X**				**X**		
AE and concomitant medications recording[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
1-week memory aid distribution		X		X			X				X		
Memory aid return and review			X			X		X					X
History, PE, vital signs	X	X	X	X		X	X		X	X	X		X
ECG[9]	X					X							
CBC[11]	6	6		6			6			6	6		6
CD4 and CD8	NB	NB		NB			NB			NB	NB		NB
HIV RNA	NB	NB		NB			NB			NB	NB		NB
Chemistry[1,11]	10			6			6			4	10		
Troponin	NB												
Serum or urine pregnancy test[7]	NB	4		NB			NB				NB		
Hepatitis B surface antigen, HCV, VDRL,TPHA[12]	NB										NB		
Binding Ab, Neutralizing Ab, ADCC		6	6	6		6	6	6	(X)[4]	6	6		6
ELISPOT, ICS, epitope mapping		170	(X)[4]	(X)[4]		(X)[4]	(X)[4]	170	(X)[4]	(X)[4]	(X)[4]		170
PBMC, plasma storage[2,4]			25.5	25.5		25.5	51		25.5	25.5	51	25.5	X
Neuropsychiatric examination		X											X
Optional procedures[3]		(X)											(X)
Soluble immune activation markers		6	(X)[4]	6		(X)[4]	6	(X)[4]	(X)[4]	6	(X)[4]		6
Gene array		8.5	(X)[4]		8.5	(X)[4]	8.5	(X)[4]	(X)[4]	8.5	(X)[4]	8.5	X
Cell-associated RNA		8.5	(X)[4]	8.5		(X)[4]	8.5	(X)[4]	(X)[4]	8.5	(X)[4]		8.5
Total, integrated HIV DNA, 2 LTR circles		8.5	(X)[4]	8.5		(X)[4]	8.5	(X)[4]	(X)[4]	8.5	(X)[4]		8.5
QVOA[5,6]		(X)[6]		(X)[6]			(X)[6]						
TILDA[5]		8.5		8.5			8.5						
TULDA[5]		8.5		8.5			8.5						
Single copy HIV RNA[5]		8.5	(X)[4]	8.5		(X)[4]	8.5	(X)[4]	(X)[4]	8.5	(X)[4]		(X)[4]
Tissue phenotyping, RNA/DNA		(X)											(X)
Approx daily vol (ml)	16	243	32	92	9	32	126	176	26	82	73	34	205

Approx cumulative vol (ml)	16	259	291	383	392	424	550	726	752	834	907	941	1,146

NB: no additional blood required; CBC: complete blood count; S = safety; S + I = safety + immunogenicity; scr = screening; vac = vaccination

[1]Chemistry including electrolytes, glucose, blood urea nitrogen (BUN), creatinine, Total/direct bilirubin, ALT, AST, gamma-glutamyl transpeptidase (GGT).

[2]Blood draw for PBMC and plasma storage, ELISPOT, ICS epitope mapping and flow cytometry will not be performed at visits for which leukapheresis is done.

[3]Optional procedures include leukapheresis, sigmoid biopsy, inguinal lymph node biopsy, lumbar puncture, MRI, MRS and DTI.

[4]Testing may be performed on selected samples of interest depending on cell yields and at the discretion of the protocol chair or PI. Not all assays listed will be done on all timepoints.

[5]QVOA: quantitative viral outgrowth assay; TILDA, Tat/Rev Induced Limiting Dilution Assay; TULDA, Tat/Rev Uninduced Limiting Dilution Assay; and single copy RNA: will be performed only if plasma HIV-1 RNA viral load <50 copies/mL.

[6]QVOA will only be performed on subjects undergoing leukapheresis or when cells yields are sufficient

[7]Women of childbearing potential only. Serum test at screening, urine test at all other visits.

[8] AEs are to be collected from signing of informed consent onwards until the end of the study.

[9] ECGs are to be taken before blood sampling.

[10] Subjects will be contacted (methods of contact may vary and may include but are not limited to phone calls, clinic visits, home visits, or email communications) 24 – 72 hours after each vaccination (contacts will be recorded as Visits 2a, 4a, 7a, and 11a as appropriate). The subjects will need to come for a clinic visit at Week 12 +3 days and at Week 48 +3 days for the planned blood sampling. For the gene array testing ideally the visit should take place exactly at +3 days after the vaccination.

[11] 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.

[12]For hepatitis C: PCR has to be done when Ab are positive and for syphilis: TPHA needs to be done when VDRL is positive.

[13]Timing of the visit will be determined relative to the actual day of vaccination.

Table 5: Schedule of Follow-Up and Testing From ARV ATI to the end of the Study (Stage 2)

Visit Number	**14**	**15**	**16-21**[16]	**22**[16]	**23-26,26a**[16]	**27**[16]	**28**[16]	**29-31**[16]	**32**[16]	**33-35**[16]	**36**[16]	**37-39**[16]	**40**[16]	**41-43**[16]	**44**[16]	**45**[16]	**46**[16]	**47**[16]	**48**[16]	**49**[16]	**50**[16]
Visit Week	**Wk 58**	**Wk 60**		**Wk 64**		**Wk 67**	**Wk 68**	**Wk 69-71**	**Wk 72**	**Wk 73-75**	**Wk 76**	**Wk 77-79**	**Wk 80**	**Wk 81-83**	**Wk 84**	**Wk 86**	**Wk 88**	**Wk 90**	**Wk 92**	**Wk 94**	**Wk 96 Exit visit Study End**
Visit Day and Window	**407 ± 5**	**421 ± 7**	**428 to 446**	**449 ± 2**	**452 to 467**	**470 ± 2**	**477 ± 3**	**484 to 498 ± 3**	**505 ± 3**	**512 to 526 ± 3**	**533 ± 3**	**540 to 554 ± 3**	**561 ± 3**	**568 to 582 ± 3**	**589 ± 3**	**603 ± 5**	**617 ± 5**	**631 ± 5**	**645 ± 5**	**659 ± 5**	**673 ±5**
Protease inhibitor replacement for NNRTI[1]	X																				
ART interruption		**X**																			
ART resumption[2]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV genotype[2]																					6
AE and concomitant medications recording[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
History, PE, vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC[3,15]	6	6		6			6		6		6		6		6		6		6		6
CD4 and CD8[3]	NB	NB		NB			NB		NB		NB		NB		NB		NB		NB		NB
HIV RNA[4]	NB	NB		NB			NB		NB		NB		NB		NB		NB		NB		NB
Qualitative RNA 2x per week			1x6		1x4																
Qualitative RNA 1x per week						1		1x3		1x3		1x3		1x3		1		1		1	
Chemistry[5,15]		4							4						4						4
Urine pregnancy test[13]		X							X						X						X
Binding Ab, Neutralizing Ab, ADCC[6]		6		6			6		6		6		6		6		6		6		6
ELISPOT, ICS, epitope mapping[6]		(X)[11]		(X)[11]			(X)[11]		(X)[11]		(X)[11]		(X)[11]		(X)[11]		(X)[11]		(X)[11]		(X)[11]
PBMC, plasma storage[7,11]		51		51			51		51		51		25.5		25.5		25.5		25.5		51
Neuropsychiatric examination									X												X
Optional procedures[8]									(X)												(X)
Soluble immune activation markers		6		(X)[11]			(X)[11]		6		(X)[11]		(X)[11]		6		(X)[11]		(X)[11]		6
Gene array		8.5		(X)[11]			(X)[11]		8.5		(X)[11]		(X)[11]		8.5		(X)[11]		(X)[11]		8.5
Cell-associated RNA		8.5		(X)[11]			(X)[11]		8.5		(X)[11]		(X)[11]		8.5		(X)[11]		(X)[11]		8.5
Total, integrated HIV		8.5		(X)[11]			(X)[11]		8.5		(X)[11]		(X)[11]		8.5		(X)[11]		(X)[11]		8.5

Table 5: Schedule of Follow-Up and Testing From ARV ATI to the end of the Study (Stage 2)

Visit Number	14	15	16-21[16]	22[16]	23-26,26a[16]	27[16]	28[16]	29-31[16]	32[16]	33-35[16]	36[16]	37-39[16]	40[16]	41-43[16]	44[16]	45[16]	46[16]	47[16]	48[16]	49[16]	50[16]
Visit Week	**Wk 58**	**Wk 60**		**Wk 64**		**Wk 67**	**Wk 68**	**Wk 69-71**	**Wk 72**	**Wk 73-75**	**Wk 76**	**Wk 77-79**	**Wk 80**	**Wk 81-83**	**Wk 84**	**Wk 86**	**Wk 88**	**Wk 90**	**Wk 92**	**Wk 94**	**Wk 96 Exit visit Study End**
Visit Day and Window	**407 ± 5**	**421 ± 7**	**428 to 446**	**449 ± 2**	**452 to 467**	**470 ± 2**	**477 ± 3**	**484 to 498 ± 3**	**505 ± 3**	**512 to 526 ± 3**	**533 ± 3**	**540 to 554 ± 3**	**561 ± 3**	**568 to 582 ± 3**	**589 ± 3**	**603 ± 5**	**617 ± 5**	**631 ± 5**	**645 ± 5**	**659 ± 5**	**673 ±5**
DNA, 2 LTR circles																					
QVOA[9,10]		(X)[10]							(X)[10]						(X)[10]						(X)[10]
TILDA[9]		8.5		(X)[11]			(X)[11]		8.5		(X)[11]		(X)[11]		8.5		(X)[11]		(X)[11]		8.5
TULDA[9]		8.5		(X)[11]			(X)[11]		8.5		(X)[11]		(X)[11]		8.5		(X)[11]		(X)[11]		8.5
Single copy HIV RNA[9]		8.5		(X)[11]			(X)[11]		8.5		(X)[11]		(X)[11]		8.5		(X)[11]		(X)[11]		8.5
Tissue[12] phenotyping, RNA/DNA																					(X)
Approx daily vol (ml)	6	124	6	63	4	1	63	3	124	3	63	3	38	3	99	1	38	1	38	1	130
Approx cumulative vol (ml)	1,150	1,274	1,280	1,343	1,347	1,348	1,411	1,414	1,538	1,541	1,604	1,607	1,645	1,648	1,747	1,748	1,786	1,787	1,825	1,826	1,956

LTR: long terminal repeats; NB: no additional blood required

[1]For subjects who are on NNRTI, the NNRTI will be discontinued at Week 58 and replaced with a protease inhibitor for 2 weeks prior to interrupting all drugs at week 60. This is to prevent possible NNRTI resistance.

[2]ART will be resumed if subjects meet any of the criteria listed in section 4.1.6. HIV genotype will be done before restarting ART.

[3]After ARV ATI, CBC and CD4 are performed every 4 weeks. A repeat CD4 will be performed when CD4 is <350 cells/mm^3 and ART will be resumed if CD4 is confirmed to be < 350 cells/mm^3 continuously for 2 weeks.

[4] From Week 61 to 66 HIV RNA testing will be done twice per week and then subsequently once per week during Week 67 to 84 and once every 2 weeks during Week 86 to 96. On visits where no venous blood draw is scheduled, testing will be performed via qualitative RNA testing from fingerstick. In case of detectable HIV RNA results, refer to Section 5.1.8 for detailed assessment timings. Upon restarting ART, subjects will undergo quantitative HIV-1 RNA testing every two weeks for the first four weeks and then every four weeks until the end of the study.

[5]Chemistry including electrolytes, glucose, BUN, creatinine, Total/direct bilirubin, ALT, AST, GGT.

[6]In patients who fulfill ART resumption criteria and no immunogenicity testing is planned at the visit that ART will be re-initiated, additional blood will be drawn for immunogenicity tests prior to ART start according to the blood draw schedule of Week 60.

[7]Blood draw for PBMC and plasma storage will not be performed at visits for which leukapheresis is done.

[8]Optional procedures include leukapheresis, genital mucosal secretions, sigmoid biopsy, inguinal lymph node biopsy, lumbar puncture, MRI, MRS and DTI. For subjects who need to resume ART prior to Week 96, optional procedures would be considered prior to ART initiation in replace of the 96-week time point.

[9]QVOA, TILDA, TULDA; and single copy RNA: will be performed only if plasma HIV-1 RNA viral load <50 copies/mL.

[10]QVOA will only be performed on subjects undergoing leukopheresis or when cells yields are sufficient

[11]Testing may be performed on selected samples of interest depending on cell yields and at the discretion of the protocol chair or PI. Not all assays listed will be done on all timepoints.

[12]Tissues/samples are obtained through optional procedures that include sigmoid biopsy, inguinal lymph node biopsy and lumbar puncture (CSF).

[13]Women of childbearing potential only

[14]AEs are to be collected from signing of informed consent onwards until the end of the study.

[15] 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.
[16]Timing of the visit will be determined relative to the ARV ATI at Visit 15. Visits from week 61 to 67 are to be scheduled twice a week at least 2 days apart.

5.1.1. Screening

A qualified study team member will inform each participant of the study, provide him/her with any study details and a copy of the informed consent document to aid him/her in his/her choice for voluntary participation. Study subjects will receive a briefing from the PI or designee during which the study will be explained and participation requirements outlined. The briefing will be followed by an opportunity for questions. Study staff will then review the consent form with potential subjects and answer any additional questions.

After the informed consent has been signed, the following evaluations will be performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Physical examination including vital sign measurement
- Medical history
- Review of concomitant medications
- Review of inclusion/exclusion criteria
- Subject must pass the TOU
- Blood sampling for CBC with differential, CD4, HIV RNA, blood chemistries, troponin, hepatitis B and C serologies, and syphilis serology. Details on hepatitis B and syphilis testing are indicated in Table 4
- ECG with interpretation by cardiologist
- Serum pregnancy testing (women of childbearing potential only)/pregnancy and contraceptive counseling

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 will be provided. Study subjects who qualify for inclusion based on the history, physical, and laboratory results will be contacted and scheduled for enrollment and initial vaccination (Visit 2, Week 0).

Subjects with laboratory values or vital signs not meeting eligibility criteria on the initial screening visit may be re-assessed for eligibility at a repeat screening visit. Laboratory tests may only be repeated if either a laboratory error or a transient condition at screening is suspected. The laboratory tests can only be repeated once. Physiologic parameters, such as vital signs, may be repeated no more than 3 times if in the judgment of the investigator the abnormal result is the result of an acute, short-term rapidly reversible condition. Ineligible subjects will be referred for care as clinically indicated.

5.1.2. Randomization and Vaccination 1/Day 1/Week 0 (Stage 1)

After confirmation of meeting the eligibility criteria, eligible subjects will be randomly assigned as described in Section 3.3.

Day 1 is defined as the day of the first vaccination and the day of study enrollment. If clinical assessment on Day 1 suggests significant changes may have occurred since the Screening Visit, then the physical examination, hematology tests, and blood chemistries will be repeated as needed and the subjects rescheduled for Day 1 assessment. Pregnancy test results for women of reproductive potential must be obtained on each vaccination day prior to the vaccination. Eligible subjects with acute illnesses or who are febrile (temperature $\geq$ 38.0 ^{o}C non-axillary) will be rescheduled for Day 1 vaccination.

Day 1 evaluations, performed prior to the first vaccination, are used as the baseline for subsequent safety assessments. Evaluations to be performed on Day 1, Visit 2 can be found in the SOE (Table 4).

Following each injection, subjects will be observed for reactogenicity in the clinic for a minimum of 30 minutes. Vital signs will be taken before vaccination and at least 30 minutes post-vaccination.

Qualified study personnel will then evaluate the subjects for any signs or symptoms of local or systemic reactions. The injection sites will be examined for local reactions at approximately 30 minutes post-vaccination. If erythema or induration is present, the diameters will be measured and the largest diameter recorded. Findings will be entered on appropriate source documents and eCRF.

For life-threatening allergic reactions that occur immediately post vaccination, the clinic has a protocol for treatment and immediate transfer to a nearby emergency room for stabilization.

Via a memory aid, subjects will be asked to record occurrences of erythema and induration (measured using the ruler supplied), and pain/tenderness, itching, swelling, or warmth at the injection sites on the day of vaccination and then daily for 7 days, for a total of 8 daily records. The investigator or designee should discuss information from the memory aids, document relevant information in the clinic chart (source document) and complete the relevant parts of the eCRF. Subjects will also be asked to record and report presence of the following AEs, in addition to other spontaneously reported AEs:

- fever (from temperature)
- fatigue
- headache
- myalgia

- arthralgia
- chills
- nausea
- vomiting
- rashes
- general itching

5.1.3. Vaccinations 2 – 4 / Weeks 12, 24, 48 (Stage 1)

Subjects will return to the clinic for the assessments as shown in Table 4. The allowable window period for vaccinations 2 – 3 is one week before or after the scheduled dose. For vaccination 4, the window is 2 weeks before or after the scheduled dose.

If after all assessments (history, physical examination, vital signs, and pregnancy testing) have been performed the subject still qualifies (ie, subject does not have an acute illness or temperature ≥38.0ºC (oral or tympanic) and does not meet any vaccination discontinuation criteria (Section 5.2), the next scheduled vaccination will be given.

Following each vaccine administration, subjects will be observed for reactogenicity in the clinic for a minimum of 30 minutes. Vital signs will be taken at least 30 minutes post-vaccination.

Qualified study personnel will then evaluate the subjects for any signs or symptoms of local or systemic reactions. The injection sites will be examined for local reactions at approximately 30 minutes post-vaccination. If erythema or induration is present, the diameters will be measured and the largest diameter recorded. Findings will be entered on appropriate source documents and eCRF.

For life-threatening allergic reactions that occur immediately post vaccination, the clinic has a protocol for treatment and immediate transfer to an emergency room for stabilization.

Subjects will be provided a memory aid, thermometer, and ruler to measure and record local solicited AEs. Subjects will also record unsolicited and solicited systemic AEs in the memory aid 6 hours post vaccination and then daily for the next 7 days. The memory aid will act as a memory tool for the subject but is not considered a source document. For a list of solicited AEs, See Section 5.1.2.

All AEs will be recorded from signing of informed consent form onwards until the end of the study.

5.1.4. Post-Vaccination Follow-Up Visits / After Study Visits Week 0, 12, 24, 48) (Stage 1)

Subjects will be contacted (methods of contact may vary and may include but are not limited to phone calls, clinic visits, home visits, or email communications) 24 – 72 hours after each vaccination. During this time, subjects should report to the clinic staff any concomitant medication and any AEs they may have experienced. Subjects will be reminded to fill out their memory aids provided to them. At the follow-up visit after Week 12, sampling for gene array will also be performed. At the follow-up visit after Week 48, sampling for gene array and PBMC, plasma storage will also be performed.

5.1.5. Safety and Immunogenicity Visits / Weeks 4, 16, 26, 30, 36, 50 (Stage 1)

Subjects will return to the clinic for safety and immunogenicity assessments as detailed in Table 4. At Week 16 only, a 12-lead ECG will be performed.

Subjects will be instructed to contact the investigator immediately should he/she manifest any signs or symptoms that are perceived as serious or if hospitalization of the subject occurs.

All AEs will be recorded from signing of informed consent form onwards until the end of the study.

5.1.6. Preparation for ARV ATI / Week 58 (Stage 1)

All subjects will have a physical examination and laboratory screening at 58 weeks in preparation for ARV ATI. At this visit clinical, immunological, and virological criteria for ARV ATI will be assessed as listed in Section 3.2.5 and 3.2.6. Subjects on ART containing an NNRTI drug will have the NNRTI replaced by a protease inhibitor drug at this visit in order to prevent the possibility of NNRTI drug resistance developing after ARV ATI.

5.1.7. ARV ATI / Week 60 (Stage 1)

At Week 60 criteria for ARV ATI will be reviewed, including all clinical, immunological, and virological criteria listed in Section 3.2.5. Pregnancy is an exclusion criterion for ARV ATI and female subjects of childbearing potential will have a urine pregnancy test at this visit. If the subject continues to meet criteria for ATI, then all ARV drugs will be stopped at this visit.

5.1.8. Monitoring After ARV ATI / Week 61-96 (Stage 2)

Subjects will be followed at least weekly for the first 24 weeks after ARV ATI (Week 61 to 84) and then every 2 weeks for the remainder of the study through Week 96 (exit visit). Each monitoring visit will include a physical examination as well as laboratory testing at outlined in Table 5.

Specific laboratory monitoring includes:

HIV-1 RNA: From Week 61 to 66 HIV RNA testing will be done twice per week and then subsequently once per week from Week 67 to 84 and once every two weeks from Week 86 to 96. Testing is done via quantitative RNA testing on visits where venous blood draw is scheduled or, on all visits where no venous blood draw is scheduled, via qualitative RNA testing from fingerstick. If HIV RNA is detectable in the qualitative RNA test, subjects will be asked to return to clinic immediately for a confirmatory HIV RNA via a venous blood draw. If HIV RNA is confirmed detectable, HIV RNA will be repeated every 3 days by quantitative RNA until the subject restarts ART or until HIV RNA becomes undetectable.

CD4 count will be performed every 4 weeks after ARV ATI. Any result <350 cells/mm^3 or ≤50% compared to baseline at Week 60 will be repeated within 2 weeks.

Other tests: urine pregnancy for female subjects of childbearing potential and routine chemistries (Table 5) will performed every 12 weeks after ARV ATI.

5.1.9. Unscheduled Visits

If a subject is seen for any other visits other than the visits outlined in Table 4 and Table 5 of the protocol, the visit will be captured as an unscheduled visit. The reason for the visit will be documented in the eCRF along with the procedures completed during this visit. All protoco1 related data resulting from this visit will be captured in the clinical database (ie, safety laboratory results).

5.1.10. Neuropsychiatric Examination

Detailed neurological examination, including neuropsychological testing, will be performed at Week 0, 50, and at end of study. Details of the neuropsychological testing can be found in Section 16.5. The tests are used for the continuous monitoring in Study RV254. The results of these tests will be analyzed as part of the RV254 parent protocol. They are not part of this study endpoints and will only be reported if relevant to this study.

The crossed out positions from the questionnaire are to be used at baseline, and will not be included at the future visits.

An abbreviated NPZ-4 assessment will be conducted at Week 72 and will include:

- Abridged Neuropsychological Assessment Test Battery
- SUBSTANCE USE AND SLEEP

5.1.11. Optional Procedures

A subset of subjects may additionally consent for optional procedures, including leukapheresis, genital mucosal secretions, sigmoid biopsy, inguinal lymph node biopsy, lumbar puncture, MRI,

MRS and DTI. Detailed procedures will be outlined in specific site Standard Operational Procedures. Sampling will occur at baseline before vaccination and at Week 50, Week 72 and Week 96. Due to scheduling logistics, optional procedures may be performed up to one week before or after scheduled time points.

Lumbar puncture will be performed by one of the trained research physicians using an atraumatic (Sprotte®) needle to decrease risk of headache using an SOP established at SEARCH.

Sigmoidoscopy will be performed by qualified personnel at PPD
Lymph node biopsy and leukapheresis will be performed by qualified personnel at either PPD

All brain imaging will be performed at PPD. MRI and MRS are non-invasive methods to detect brain pathology (MRI) and to determine the in-vivo concentration of brain metabolites (MRS). Gadolinium will not be used for research purposes. DTI is a sensitive non-invasive magnetic resonance technique to analyze the 3-dimensional diffusion of water within brain tissue. The diffusion of water within the brain is highly dependent on the underlying microarchitecture of the surrounding tissue, which is affected by both normal physiological processes (such as aging) as well as local neuropathological disease processes, such as those seen with HIV infection. Several cell types are distinguishable with commonly measured metabolites, including neurons (N-acetyl-aspartate) and glial or inflammatory cells (myoinositol and choline), often measured as ratios to brain creatine (Talos, 2006). HIV infection is associated with increased myoinositol/creatine and choline/creatine ratios, indicating direct effects on microglial cell concentrations (Chong 1993, Tarasow 2003).

For female subjects of childbearing potential, pregnancy tests will be performed and pregnant women will be excluded from all of the optional procedures.

Brain imaging procedures (MRI, MRS and DTI) and tissue biopsies are part of the procedures in the RV254 cohort. The results of these tests will be analyzed as part of the RV254 parent protocol. They are not part of this study endpoints and will only be reported if relevant to this study.

5.1.12. Visit Windows

The maximum screening period is from Day -45 to Day -3.

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

- Visit 3: Day 29 ± 5 days
- Visit 4: Day 85 ± 7 days (second vaccination)

- Visit 5*: Visit 4 + 3 days (Day 88) ± 2 days (for the gene array testing ideally the visit should take place exactly at +3 days after the vaccination)
- Visit 6*: Visit 4 + 28 days (Day 113) ± 5 days
- Visit 7: Day 169 ± 7 days (third vaccination)
- Visit 8*: Visit 7 + 14 days (Day 183) ± 5 days
- Visit 9*: Visit 7 + 28 days (Day 211) ± 5 days
- Visit 10*: Visit 7 + 84 days (Day 253) ± 5 days
- Visit 11: Day 337 ± 14 days (fourth vaccination)
- Visit 12*: Visit 11 + 3 days (Day 340) ± 2 days (for the gene array testing ideally the visit should take place exactly at +3 days after the vaccination)
- Visit 13*: Visit 11 + 14 days (Day 351) ± 5 days
- Visit 14: Day 407 ± 5 days
- Visit 15: Day 421 ± 7 days (start of ATI)
- Visit 16-21: Days 428-446: visits are to be scheduled twice a week at least 2 days apart; all visits counted relative to start of ATI at Visit 15
- Visit 22: Days 449 ± 2, counted relative to start of ATI at Visit 15
- Visit 23-26, 26a: Days 452-467: visits are to be scheduled twice a week at least 2 days apart; all visits counted relative to start of ATI at Visit 15
- Visit 27: Days 470 ± 2, counted relative to start of ATI at Visit 15
- Visit 28-44: Days 477 - 589 ± 3, all visits counted relative to start of ATI at Visit 15
- Visit 45-50: Days 603-673 ± 5 days, all visits counted relative to start of ATI at Visit 15

*If a subject is not vaccinated on the given day of vaccination, the timings of the post-vaccination visits (see Table 4) will be determined relative to the actual day of vaccination.

If a vaccination visit window is missed due to a study pause (see Section 5.3.2.1), vaccination will be assessed on a case-by-case basis upon discussion between investigator and sponsor.

5.2. Vaccination Discontinuation

Under certain circumstances, a subject will be terminated from participating in further vaccinations. These specific experiences include:

- Investigator's clinical judgment is that it is in the best interest of the subject
- Pregnancy
- Type 1 hypersensitivity associated with vaccination

- Grade 3 or 4 AE that is vaccine related, except for grade 3 solicited local and systemic reactions.
- Serious concomitant illness that is not expected to resolve prior to the next scheduled vaccination (according to the investigator's judgement)
- Treatment with chronic systemic glucocorticoids (e.g. prednisone) or other immunomodulators other than non-steroidal anti-inflammatory drugs. Inhaled, topical, and short course oral steroid use is not exclusionary
- Need for concomitant vaccine that requires discontinuation (see Section 3.2.3)
- Missing any study vaccination by more than 3 weeks from the scheduled vaccination day
- Participant's request

Subjects who are discontinued from additional study vaccinations will continue to be followed according to the schedule to further evaluate safety and monitor adverse experiences through Week 50 (Stage 1), unless consent is withdrawn. The investigator will consider the reason for discontinuation of vaccination and the condition of the subject in determining if the blood collection plan should be altered and, in cases requiring a reduction of blood collection, priority is given to laboratory safety over immunogenicity or other study objectives. Subjects who receive less than 4 study injections will not undergo ARV ATI (Stage 2). All study procedures scheduled for study end (Week 96) will be performed at Week 50, which will be the final study visit for those subjects.

5.3. Study Discontinuation

A subject will be discontinued from the study entirely if:

- Repeated failure to comply with protocol requirements
- Decision by the study sponsor or the PI to stop or cancel the study
- Decision by local regulatory authorities and/or IRBs to stop or cancel the study
- Subject's request

5.3.1. Early Discontinuation or Withdrawal of Subjects

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.

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.

For those subjects who are unable to continue participation in the study, but who do not withdraw consent, an exit visit will be conducted (refer to SOE for list of procedures to be conducted).

The investigator also has the right to withdraw a subject, e.g. because of worsening health status, intercurrent illness, AEs, or pregnancy (for pregnancy follow-up see safety Section 4.1.9). The sponsor reserves the right to request the withdrawal of a subject due to protocol violations, or administrative or other reasons.

Any unnecessary withdrawal should be avoided. Should a subject be withdrawn, all efforts should be made to complete and report the observations as thoroughly as possible. Whenever a subject is withdrawn from the study, independent of the reason, a final evaluation must be completed for that subject and the major reason for which the subject was withdrawn must be stated. All documentation concerning the subject must be as complete as possible.

5.3.2. Premature Termination of the study

The sponsor reserves the right to discontinue the study for safety, ethical, or administrative reasons. Should the study be discontinued, no further vaccinations will be administered but subjects who are ongoing at the time of discontinuation will be followed through the remainder of their follow up visits.

5.3.2.1. Study Pausing 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 6. These study holding rules apply to AEs/SAEs occurring up to 4 weeks after the last vaccination.

Table 6: AE Notification and Safety Pause/AE Review Rules[1]

(S)AE and Relationship[2]	Severity	Site Principal Investigator Action	PSRT/DSMC Action
SAE, related	Any grade	Phone Study Responsible Physician or designee AND fax or email SAE form to Global Medical Safety Office, 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 or email SAE form to Global Medical Safety Office, 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 DSMC 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/DSMC members and coordination of a PSRT/DSMC 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 DSMC 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 DSMC review of a similar AE, the DSMC 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 DSMC 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 6, the PSRT will convene within one business day to review these AEs. The PSRT will review and determine disposition, including whether the DSMC 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 DSMC is complete. Resumption of enrollment and study treatment may be determined by the PSRT or DSMC (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 DSMC to resume or discontinue study activities. The site is responsible for notifying their IRB according to local standards and regulations. The sponsor is responsible for notifying the FDA.

5.4. Laboratory Evaluations

Sample handling will be performed according to site-specific SOPs and MoPH guidelines.

The total number of blood draws and total volume of blood that will be collected from each subject is presented in Table 4 and Table 5. Time points for optional procedures are also presented in the tables. Laboratory testing performed for research purposes will be sent to laboratories in Thailand and abroad following the table in Appendix 16.4. Changes to this appendix will not constitute a protocol amendment but will be adapted through the lab manual.

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.

All biological samples must be collected in the appropriate manner. The investigator will ensure that the personnel and laboratory under his/her supervision comply with these requirements. Further details on shipment, handling, and storage of the samples are provided in the Specimen Handling Guidelines.

Any residual samples will be stored at the sponsor designated laboratories in Thailand (includes PPD) for a maximum of 5 years. Any future analyses conducted on the samples will maintain subject anonymity. Subjects will have to provide their approval for long-term storage of their biological specimens. Subjects will have the right to opt out of having their biological specimens stored once all analyses described in the Informed Consent Form are completed. Opting out of this procedure does not impact the subject's ability to participate in the study.

If it is necessary to store biological samples beyond 5 years, consent will be obtained from the subjects, the appropriate IRBs, and the Thai Ministry of Public Health (MoPH) Ethics Committee. If the investigators are unable to contact subjects, then permission for continued storage may be requested from the IRB without subject consent. This information will be provided to subjects in the consent forms that they sign at study enrollment.

5.5. Potential Risks and Benefits

5.5.1. Risks Related to Vaccines

Subjects may exhibit general signs and symptoms associated with administration of a vaccine or placebo vaccination, 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. To minimize this risk, those with allergies to or have had an allergic reaction to vaccines, vaccine products, neomycin, streptomycin, eggs, or egg products, will not be allowed to participate in this study. Subjects will be observed at the study site for 30 minutes after injection of the study products to monitor the development of any acute reactions. Vital signs will be taken before vaccination and at least 30 minutes post-vaccination. Medications shall be available in the clinic to treat serious allergic reactions.

The effect of this vaccine on a fetus or nursing baby is unknown, so female subjects of child bearing potential will be required to agree to use birth control for sexual intercourse beginning prior to the first vaccination and continuing at least 3 months after the final vaccine/placebo vaccination. Women who are pregnant or nursing will be excluded from the study.

5.5.2. 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 666,712 who received the vaccine). Investigators do not expect these side effects 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 2/3 clinical studies cited in this protocol. Subjects will be actively screened to exclude pre-existing cardiac concerns and monitored for cardiac complications based on clinical symptoms.

5.5.3. Risks Related to Blood Draws

Blood drawing may cause pain, bruising, and, rarely, infection at the site where the blood is taken.

5.5.4. Risk Related to ATI

As this is an exploratory study, all of the risks of ATI may not yet be known. However, the frequent monitoring of clinical, immunological, and virological status is designed to minimize possible risk to subjects from rebound viremia. If rebound viremia occurs, ART will be restarted when HIV viral load rises >1,000 copies/ml, a level and duration of viremia that is expected to have minimal, if any, impact on the subject's CD4+ count and would be expected to have no clinical manifestations or symptoms to the subject. Moreover, the safety of this approach is proven in a recent study of chronically infected adults, many of who had low pre-ART CD4+ count. With twice-weekly viral load monitoring, rapid resumption of ART and viral suppression was demonstrated. No one had clinical adverse events due to ATI and the CD4+ count remained stable (Rothenberger 2015).

If subjects develop viremia, there is a risk of transmitting HIV to sexual partners. All subjects will be notified of this risk and to use condoms for any sexual contact during participation in the study.

There is a risk that subjects could develop HIV resistant virus after ATI. Changing all subjects to a PI-based ART regimen is designed to minimize this risk. If HIV resistance develops it could potentially lead to a higher risk of treatment failure or death during future ART. To detect and address any possible HIV resistance, an HIV genotype test will be done on all patients with rebound viremia before restarting ART. The patient's ART regimen will be adjusted to compensate for any resistance discovered.

5.5.5. Unknown Risks

There may be other serious risks that are not known.

Subjects may believe that this vaccine provides therapeutic benefit for HIV infection. 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 HIV viral rebound after ARV ATI.

5.5.6. Potential Benefits

There is no direct 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 future HIV treatment methods.

As explained in Section 5.5.5, it is not known if the study vaccines increase or decrease the chance of HIV viral rebound after ARV ATI.

6. SAFETY ASSESSMENTS AND REPORTING

6.1. Definitions

6.1.1. Adverse Event Definitions and Classifications

Adverse Events

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 (see Section 6.3.1).

Serious Adverse Events

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.

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 (e.g. 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 according to regulatory and local requirements.

Adverse Reactions

An adverse reaction is an adverse event judged to be related to 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 6.3.4.

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 and MVA-Mosaic, the expectedness of an AE will be determined by whether or not it is listed in the respective IBs.

6.1.2. Rebound in Viral Replication, Study Endpoint not Considered as AE/ADR

Rebound in viral replication post ARV ATI (HIV RNA>50 copies/ml) will not be considered an AE/SAE as it is a study primary efficacy endpoint which is captured in the clinical study database and will be analysed as such.

Rebound in viral replication post ARV ATI (HIV RNA>50 copies/ml) will not be reported as individual expedited safety reports to IRB/ethical committees (ECs) or to Health Authorities during the course of the study. Such occurrences will be analysed according to treatment group allocation and descriptive results made available to IRB/ECs and to Health Authorities with the final analyses of the study results in the clinical study report.

6.1.3. Surveillance, Reporting, and Documentation of Adverse Events

The recording of AEs is an essential part of study documentation. The investigator is responsible for documenting all AEs as follows:

At each visit, all AEs, either observed by the investigator or one of his/her clinical collaborators or reported by the subjects spontaneously or in response to a direct question will be evaluated by the investigator or designee. All AEs will be recorded on eCRFs. Rebound in viral replication

post ARV ATI (HIV RNA>50 copies/ml) will not be considered an AE/SAE (See Section 6.1.2.).

As a consistent method to find out about AEs, the investigator should use a non-leading question, such as:

'Have you felt different since receiving the study vaccine or since the previous visit?'

The subjects will be instructed to contact the investigator immediately should they experience any signs or symptoms they perceive as serious during the period extending from the first study-specific procedure up to and including 6 months after the last administration of the study agent.

6.2. Special Reporting Situations

Safety events of interest of 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, e.g. name confusion)

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

6.2.1. Reporting Requirements to the Local IRB

The site PI will be responsible for providing all Safety Reports and reporting all study pauses, social impact, and major deviations to the local regulatory authority, such as a local IRB, and any country-specific regulatory agencies, in a timely manner according to the institution's guidelines.

6.3. Procedures

6.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported and recorded on the eCRFs by the study site from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (ie, Week 96) and may include additional contact for follow-up of safety. eCRFs will be completed by the research staff as soon as possible after availability of the data.

Rebound in viral replication post ARV ATI (HIV RNA>50 copies/ml) will not be considered an AE/SAE as it is a study endpoint and will be documented in the specific eCRF pages.

All SAEs must be reported to the sponsor during the entire study period using the SAE Form. SUSARs are reported even after the study is over, if the sponsor, DSMC 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 6.3.4.

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 data 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 eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF 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 EC/IRB that approved the protocol unless otherwise required and documented by the EC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IRB will receive a blinded SUSAR summary, unless otherwise specified.

Subjects will be provided with a wallet card referring to 24-hour contact numbers that can be used by subjects and medical site staff.

6.3.1.1. Post-Vaccination Reactions Occurring Immediately After Each Vaccination

As described previously, following each vaccine administration, subjects will be observed for reactogenicity in the clinic for a minimum of 30 minutes. Vital signs will be taken and qualified study personnel will evaluate for any signs or symptoms of local or systemic reactions.

Possible local reactions that should be recorded include erythema and induration (measured using the ruler included with the memory aid that will subsequently be provided to the subject), pain/tenderness, or warmth at the injection site. In addition, systemic symptoms to be noted include fever (≥38.0ºC, non-axillary), fatigue, headache, myalgia, arthralgia, chills, nausea, vomiting, rashes, and itching. For life-threatening allergic reactions that occur immediately post vaccination, site-specific procedures are in place for handling such emergencies.

6.3.1.2. Local Reactions Occurring Within Seven Days After Each Vaccination

Memory Aid Completion

Subjects will be provided with a ruler to measure erythema, induration or other observable reactions.

The subject will be asked to note occurrences of erythema and induration (measured using the ruler included with the memory aid), and pain/tenderness, itching, swelling, or warmth at the injection sites daily for 8 days including the day of vaccination. These occurrences should be recorded on the memory aid provided to serve as a reminder to the subject for the next clinic visit (the memory aids are not considered source documents).

6.3.1.3. Systemic Reactions Occurring Within Seven Days Post-Vaccination

Memory Aid Completion

Subjects will be instructed on how to record daily temperature using a thermometer provided for home use. Subjects should record oral temperature 6 hours post vaccination, and then daily for the next 7 days.

Subjects will also be instructed on how to record and grade daily symptoms on the memory aid for 8 days post-vaccination (including the day of vaccination).

The subject will also be asked to record the following occurrences 6 hours post vaccination and then daily for 7 days on the memory aid:

- temperature (fever ≥38.0°C, non-axillary)
- fatigue
- headache
- myalgia
- arthralgia
- chills
- nausea
- vomiting

- rashes
- itching (general and local)

Post-Vaccination Contact

Between 24 and 72 hours after each vaccination, the investigator or designee will contact the subjects to obtain local and systemic reaction data and to assess clinical status as described in Section 5.1.4.

Instructions to Subjects Regarding Unusual or Severe Signs or Symptoms

Subjects will be instructed to call the specified study personnel immediately (information included on the memory aid and/or appointment and/or emergency card) if any unusual or severe sign or symptom appears after vaccination. Subjects with unusual, moderate, or severe sign and/or symptoms post vaccination will be asked to return to the clinic for evaluation. They will be followed up clinically until resolution of symptoms. Contacts will be arranged as needed. Subjects will be instructed to inform treating medical personnel of their participation in the study and provide them with the contact information on the emergency card provided.

6.3.2. 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 email.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the 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 (e.g. 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 eCRF). 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.

6.3.3. Reporting requirements to the Local IRB

The site PI will be responsible for providing all Safety Reports and reporting all SAEs, study pauses, social impact, and major deviations to the local regulatory authorities, such as a local IRB, and any country-specific IRBs, in a timely manner according to the institution's guidelines and to local regulations.

6.3.4. Causality Assessment of Study Vaccines to Adverse Events

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 (e.g. 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.

Doubtful: An AE for which an alternative explanation is more likely, e.g. concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible: An AE that might be due to the use of study vaccine. An alternative explanation, e.g. concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable: An AE that might be due to the use of study vaccine. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely, e.g. concomitant drug(s), concomitant disease(s).

Very likely: An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

An AE is considered associated with study vaccine if the attribution is possibly, probably, or very likely related.

6.3.5. Severity of Adverse Events

All recorded AEs will be coded for severity using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), **Version 2.0 dated November 2014** found on the website http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf.

For AEs not identified in the grading table the following guidelines will be applied:

Mild	Grade 1	Symptoms causing no or minimal interference with usual social & functional activities
Moderate	Grade 2	Symptoms causing greater than minimal interference with usual social & functional activities
Severe	Grade 3	Symptoms causing inability to perform usual social & 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 or death
Fatal	Grade 5	For any AE where the outcome is death, the severity of the AE is classified as Grade 5

The clinical research team will ascertain accurate recording of all AEs during the study. AE eCRFs will be completed by the research staff as soon as possible after availability of the data. The clinical investigators 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 product.

PIR are solicited AEs and related to study and therefore must be reported as such. The PI or designee must review both PIR and other AE data to insure prompt and complete identification of all events that require expedited reporting as SAEs, study pause rules or other serious and unexpected events.

The clinical research team will follow all recorded AEs to resolution or study completion, whichever occurs first.

6.3.6. Follow-Up of Ongoing Adverse Events and Assessment of Outcome

6.3.6.1. Follow-Up of Non-Serious Adverse Events

Non-serious AEs already documented in the eCRF at a previous assessment and designated as 'ongoing' should be reviewed at subsequent visits. If the event has resolved, the documentation in the eCRF should be completed. If the frequency or severity of a non-serious AE changes significantly, a new record of the AE has to be started. If the AE becomes serious, the procedures for reporting of SAEs have to be followed (Section 6.3.2).

Ongoing non-serious AEs will be monitored until the Week 96 visit.

Outcome will be assessed as:

1 Recovered or Resolved
2 Recovering or Resolving
3 Not Recovered or Not Resolved
4 Recovered or Resolved with Sequelae
5 Fatal
6 Unknown

Abnormal laboratory values will be followed up until they have returned to normal, stabilized, or a satisfactory explanation has been provided.

6.3.7. Treatment of Adverse Events

Treatment of any AE is at the sole discretion of the investigator and according to current available best treatment. The applied measures should be recorded in the eCRF.

6.3.8. 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 (e.g. spontaneous abortion, stillbirth, and congenital anomaly) are considered SAEs and must be reported using the SAE Form.

Any subject who becomes pregnant during the study will complete all procedures scheduled for study end at the time the pregnancy is diagnosed. If the subject was scheduled to receive additional vaccine or placebo, these injections will not be administered after pregnancy has been determined. Pregnant subjects will be offered enrollment in RV412 for continued observation (see Section 4.1.9).

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 consent and notification forms.

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.

6.4. Physical Examination

Physical examinations will be performed by the investigator or designated medically trained clinician. The time points of these examinations are specified in the SOE (Table 4 and Table 5). Any abnormalities or changes in severity noted during the review of body systems should be documented in the source document and recorded on the eCRF.

A new, clinically significant finding (in the opinion of the investigator) not noted at screening must be captured as an AE. In addition, resolution of any abnormal findings during the study will be noted in the source document and in the eCRF.

6.5. Routine Safety Laboratory

Samples for routine safety laboratory parameters will be collected at the time points specified in Table 4 and Table 5.

The following routine safety laboratory parameters will be determined:

- **Serum chemistry**: electrolytes, glucose, BUN, creatinine, total/direct bilirubin, ALT, AST, GGT
- **Hematology safety parameters**: hemoglobin, hematocrit, white blood cells (WBCs), WBC count, WBC differentiation, red blood cell (RBC) count, platelet count

All abnormal laboratory values will be reported as AEs if considered clinically significant. Changes in grade toxicity will be reported in aggregate analysis.

6.6. Vital Signs

Vital signs measurements will be performed at each clinical visit that includes a medical history and physical examination (according to time points provided in the schedule of evaluations).

The following measurements will be performed:

- Heart rate (bpm), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) will be measured (sitting position). A confirmatory vital signs measurement can be performed if inconsistent with a prior measurement.
- Body temperature (oral or tympanic)
- Respiratory rate (breaths per minute)

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

6.7. Electrocardiogram

Supine 12-lead ECGs will be performed at screening and at Week 16, and only repeated if symptoms warrant.

For 30 minutes prior to the ECG, subjects should refrain from meals, hot or cold beverages, 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. All ECG interpretation will be provided by a cardiologist at a referral hospital along with cardiac consultation, if needed. ECGs are to be taken before blood sampling.

7. 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.

7.1. 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. A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

7.2. 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.

8. PROTOCOL SAFETY REVIEW TEAM AND DATA AND SAFETY MONITORING COMMITTEE

8.1. Protocol Safety Review Team

The PSRT will review all AEs on a regular and expedited basis as needed. In addition, the PSRT will review aggregate safety data reports on a regular basis. This team includes the following: Study Chair, Site PI, the Janssen Vaccines & Prevention B.V. Clinical Leader and study responsible physician and global medical safety officer. Additional members could include associate investigators, and senior clinical research nursing staff. A quorum is established with the Study Chair, the site PI, the study responsible physician. The PSRT will decide by consensus whether AEs should also be reviewed by the DSMC.

8.2. Data and Safety Monitoring Committee

An independent DSMC will be set up. The DSMC will evaluate safety, tolerability, and efficacy data from each cohort on an ongoing basis. The DSMC may review an individual SAE or it may choose to review AEs, SAEs, and laboratory and vital sign data. The DSMC may unblind any amount of safety information needed to conduct their assessment. The conclusions of the DSMC will be communicated to the investigators and the IRB/Ethics Committees and the national regulatory authorities in a blinded manner as appropriate. The sponsor agrees to abide by the decision of the DSMC and any directives issued by the national regulatory authorities, the IRBs or Ethics Committees.

The committee will comprise of five members including one infectious diseases specialist, one HIV clinician, one HIV virologist, one biostatistician and one community representative. The committee will review data from the study at the following time points: 1) the first 12 enrolled subjects have completed 2 injections (Week 12) (Stage 1), and 2) the first 12 enrolled subjects complete Week 72 (12 weeks after ARV ATI) (Stage 2). All SAEs will be reviewed by the committee Additional meetings may be called at the discretion of the chair of the DSMC.

In addition, the Community Advisory Board at the PPD will review and follow the progress of this study.

9. DATA EVALUATION AND ANALYSIS

9.1. Analysis Populations

9.1.1. Safety Population

All subjects who received at least 1 injection of Ad26.Mos.HIV or MVA-Mosaic, or placebo, and for whom any post-dose data is available will be included in the safety population.

9.1.2. Immunogenicity Population

The immunogenicity population will consist of all subjects who received at least 1 dose of Ad26.Mos.HIV or MVA-Mosaic and who have at least 1 measured post-dose blood sample collected.

9.1.3. Efficacy Population

The primary efficacy population will consist of all subjects who undergo ARV ATI at Week 60 and interrupt at least one dose of ART (Stage 2), regardless of the time or outcome of treatment interruption. Additionally, as a sensitivity analysis, efficacy will be analyzed in the ITT population consisting of all subjects who received at least one injection (with subjects not undergoing ARV ATI counted as efficacy failures).

9.1.4. Secondary and Exploratory Analyses

These analyses are exploratory and descriptive. The number of subjects included in each analysis will depend on the number of specimens available and the requirements for each specific testing protocol.

9.2. Primary Endpoints

1. Safety: Vaccine related - grade 3 or greater reactogenicity and AE that are product related or probably product related
2. Efficacy: HIV RNA <50 copies/ml at 24 weeks after ARV ATI.

9.3. Secondary and Exploratory Measurements

This is an exploratory study. Therefore, the research assays will be disparate and exploratory in nature. Both cellular and humoral responses will be measured together with biomarkers and transcriptome analysis. These multiple assays will allow correlations that may reveal critical information on therapeutic vaccination and treatment interruption. Assays for the evaluation of immunogenicity will include but are not limited to:

1. Frequency, magnitude and breadth of epitope recognition by ELISPOT, polyfunctinality of T cell responses, binding antibody to Env regions and neutralization of a variety of HIV-1 strains (tier 1, 2).

2. Cell-associated HIV RNA in total CD4+ T cells, and in the memory CD4 subsets
3. Cell-associated HIV DNA (total, integrated and 2 LTR circles) in total CD4+ T cells, and the memory CD4 subsets
4. Viral outgrowth and inducible HIV RNA in total CD4+ T cells, and the memory CD4 subsets
5. Single copy HIV RNA in samples with HIV RNA <50 copies/ml pre and post ARV ATI
6. Frequency, severity and duration of acute retroviral syndrome following ARV ATI
7. HIV specific immune responses in genital mucosal compartments and all immunogenicity assays.
8. Analysis of the expression profiles and transcriptome analysis of sorted and/or unsorted lymphocytes and monocyte/macrophages in the different arms of the study.

9.3.1. Assays That Will be Implemented for Immunogenicity:

Evaluation of immunogenicity is performed as described in the schedule of evaluations. Tissue samples will be evaluated in a similar fashion at Weeks 0, 50, 72 and 96 (or prior to ART resumption) in subjects who are willing to undergo optional invasive procedures.

9.3.1.1. Humoral Immunogenicity

1. Binding antibody to immunogen inserts and a panel of HIV envelope proteins representing the circulating HIV-1 strains.
2. Neutralizing antibody using a representative panel of tier 1 and tier 2 HIV strains with emphasis on the strain infecting the subjects and, if available, the pseudovirus expressing the subjects transmitted founder virus
3. Functional antibody assays (ADCC as an example) using a representative panel of HIV strains with emphasis on the strain infecting the subjects and, if available the pseudovirus expressing the subjects transmitted founder virus.

9.3.1.2. Cellular Immunogenicity

1. IFN-gamma ELISPOT assays of PBMC using peptide pools representing the immunogen inserts and other HIV specific reagents available.
2. Phenotypic and functional characterization of CD4 and CD8 T cells, B cells, monocyte/macrophages by flow cytometry, transcriptome analysis and T-cell receptor analysis.

9.3.1.3. Other Immunological Evaluations

Evaluation of biomarkers and markers for viral expression and reservoir will be performed on stored samples, particularly those from the same time points as the immunogenicity evaluation.

Soluble markers of immune activation will be measured with high throughput immunoassay platforms (Luminex or similar platform).

9.3.1.4. Viral Expression and Reservoir

These evaluations will be done on total CD4+ T cells, and tissue (if available) and sorted populations of interest. The assays that will be used will include but are not limited to:

1. Cell-associated HIV viral RNA
2. Total, integrated HIV DNA and 2 LTR
3. Viral out-growth assay
4. TILDA

9.4. Sample Size Consideration

This is an exploratory analysis of a unique group of early-treated subjects with extremely low HIV reservoir size and preserved immunity. The sample size of 18 in the vaccine arm and 9 in the placebo arm is based on feasibility in regards to number of subjects. The sample size is within the range of subjects recommended in the Code of Federal Regulations (CFR 312.21) for each of the products in this investigation and will allow evaluation of epitope enumeration between arms. It is estimated that the majority of subjects will proceed to ARV ATI. The rate of functional cure is unknown; but we expect that the proportion of subjects achieving drug-free remission of HIV will be similar or higher than the VISCONTI study (15%), because our study subjects have ART initiated earlier and they have exhibited lower HIV DNA. There will not be an adequate statistical power to test differences in post-treatment viremic controllers between arms. Placebo recipients are included for blinding, efficacy and safety purposes and will provide additional control specimens for immunogenicity assays. The study findings will be important in informing the effect of Ad26/MVA on HIV reservoir/immunity and functional cure.

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 18 subjects in the vaccine arm, the observation of 0 such reactions would result in a two-sided exact 95% confidence interval with an upper limit of 18.50%.

9.5. Data Analysis

Subject baseline characteristics will be summarized by study arm. Continuous variables will be expressed as median and IQR. Categorical variables will be presented as number and percentage. Proportion of subjects with AEs and subjects with HIV RNA <50 copies/mL post ARV ATI between study arms will be compared using Fisher's exact test. Differences in the other outcomes

between treatment arms will be assessed using the non-parametric Mann Whitney U test. All hypothesis tests will be two-sided. Statistical significance will be taken at a level of 5 percent.

9.5.1. Primary Objectives and Endpoints

9.5.1.1. Safety

History and physical examination and standard laboratory assessments following each vaccination for safety and tolerability as follows:

1. AEs during the course of the study
2. Vaccine reactogenicity rates for individual and combined symptom subgroups for 1 week after each vaccination using a memory aid
3. Laboratory evaluation will be performed every 12 weeks during the vaccine series, and 2 weeks after the fourth vaccination (CBC only). During ARV ATI, serum chemistry will be performed every 12 weeks and hematology every 4 weeks
    a. Serum chemistry: electrolytes, BUN, creatinine, glucose, total/direct bilirubin, ALT, AST and GGT
    b. Hematology safety parameters: hemoglobin, hematocrit, WBCs, WBC count, WBC differentiation, RBC count, platelet count

9.5.1.2. Efficacy

The proportion of patients with HIV RNA <50 copies/mL at all timepoints after ARV ATI as well as a 95% confidence interval will be reported for each treatment arm.

9.5.1.3. Clinical Outcomes

Clinical outcomes will be described in the two treatment arms, including:

1. Change in CD4 count during ARV ATI.
2. Time to reinitiating ART.
3. Frequency, severity and duration of acute retroviral syndrome.
4. Frequency and characterization of HIV drug resistance in subjects that experience viral rebound during ARV ATI.

9.5.2. Analysis Time Points

The final analysis will be performed once all subjects have completed their final study visit or discontinued earlier. Interim analyses may be performed prior to the final analysis. These analyses would occur in a group-unblinded manner, but no subject-level unblinding would occur.

ICS or ELISPOT will be performed on baseline and Week 26 samples and completed prior to the Week 60 visit to determine whether the study can proceed to Stage 2 (see Section 3.2.5).

10. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- IBs for Ad26.Mos.HIV and MVA-Mosaic.
- Pharmacy manual/site investigational product procedures manual
- Laboratory manual
- Randomization instructions
- eCRF completion guideline
- Master ICF
- Memory aid
- TOU
- Rulers, thermometers
- Subject wallet cards, including:
  - study number;
  - statement, in the local language, 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);
  - subject number;
  - information about who should be contacted in case of emergency.
- Recruitment tools, as applicable

11. ETHICAL AND LEGAL REQUIREMENTS

11.1. General Requirements

The study will be performed according to this Study Protocol and in compliance with the Declaration of Helsinki, the guidelines of the International Conference on Harmonization (ICH) GCP and the respective local legal requirements including the following: US Code of Federal Regulations 45CFR Pt 46; 21CFR Pt 50, 21CFR Pt 56 and 21CFR Pt 312.

11.2. Institutional Review Board/Ethics Committee

Before the start of the study, the investigator will submit the Study Protocol, Subject Information, Informed Consent Form, Information on compensation for study-related injuries, and other study-related documents as required by applicable laws and regulations to the responsible IRBs PPD

PPD

for written approval.

The investigator will inform the IRB according to applicable laws and regulations about Amendments to the Study Protocol including, but not limited to, any new information that require an ethical reconsideration of the Study Protocol.

In addition to the written approval of the IRB the investigator should obtain a statement from the IRB confirming that the institution is composed and organized according to and adheres to GCP and applicable regulations.

Unless otherwise instructed by the IRB(s) or local regulation the investigator must submit to the IRBs defined above:

- All subsequent Amendments to the Study Protocol, changes to the Informed Consent Form or revisions of other documents originally submitted for review
- New or revised subject recruiting materials approved by the sponsor, if applicable
- All subsequent changes of logistical or administrative aspects in submitted protocol documents (for information)
- Serious and/or unexpected AEs occurring during the study, where required
- New information that may affect adversely the safety of the subjects or the conduct of the study
- New edition(s) of the IB and amendments/addenda
- Annual update and/or request for re-approval, where required
- Date of study completion, where required
- Close out Report

11.3. Regulatory Authorities

Before initiating the study, the sponsor will submit any required application to the regulatory authorities and obtain approval according to applicable laws and regulations. The sponsor will also inform the regulatory authorities about Amendments to the Study Protocol including, but not limited to, any new information that require an ethical reconsideration of the Study Protocol.

11.4. Subject Information and Informed Consent

The study informed consent from is included in a separate document file. It describes the IPs to be used and all aspects involved in protocol participation. The investigator will provide a copy of the approved informed consent to the subject and a signed copy will be maintained in the subject's record file. Before a subject's participation in the study, the investigators will obtain written informed consent from the subject, after adequate explanation of the aims, methods,

anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or study medications are administered.

Consent will be obtained in the SEARCH clinic at the PPD . In order to ensure that participation is voluntary and to demonstrate that refusal to participate does not have any effect on subject's clinical care in the main protocol SEARCH010/RV254, consent will be obtained by a research staff who does not provide clinical care to that subject in the main protocol. Subjects will also be informed that the participation is voluntary and that subjects have the right to withdraw at any time without giving the reasons and without any disadvantages for their subsequent care. Subjects will confirm their consent in writing before study start and any study-specific procedure.

As part of the consent procedure, potential subjects will have to pass the TOU that includes 10 questions (Appendix 16.3). The TOU will be given after the study staff have explained the study procedures, the subjects has read the information sheets and consent forms and asked any question, and before the subject signs the consent forms. Seven out of 10 correct responses will be considered a passing score, and questions 1, 2, and 5 must be answered correctly. Subjects may take the test up to 3 times to achieve a passing score.

11.5. Data Access and Protection

Confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The monitors, auditors, the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, or quality assurance reviews and audits without violating the confidentiality of the subject, to the extent permitted by the applicable law and regulations. By signing the written Informed Consent Form, subjects will authorize such access. Subjects should be informed about the purpose of the planned computer data processing and the publication of the data.

Disclosure of the subject's identity will occur only in case of emergency to avoid health risks.

11.6. Data Coding

All subjects consented will be assigned an 8-digit Subject identification. The first four digits represent the study code, followed by a 4-digit number that will be assigned sequentially.

11.7. Future use and Storage of Blood Samples

Each study subject will be asked to voluntarily consent for their blood samples to be stored for other research studies that may be done after this study is completed. In case the subject is 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. 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 up to 5 years 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. In the event that the study team decides that there is scientific merit in additional testing or storage beyond 5 years, then permission for continued storage will be requested from the subjects, the relevant IRBs, and the Thai MoPH Ethics Committee. If subjects are not able to be contacted, then continued storage can occur with sole permission of the IRBs.

11.8. Compensation

Subjects will be compensated for time and inconvenience in accordance with the usual standards and legal obligations for compensation followed at the study site. Compensation amounts for study visits and optional procedures are similar to the main protocol SEARCH010/RV254 and will be paid in cash at the time of the visit or procedure. Applicable guidelines by the local IRB for compensation of research subjects will be followed.

11.9. Compliance with NIH Guidelines for Research Involving Products Containing Recombinant DNA

Because this study is evaluating products containing recombinant DNA, per NIH Guidelines for Research Involving Recombinant DNA Molecules, the study must be submitted to the site Institutional Biosafety Committee (IBC) and must be approved before participants are enrolled at each respective institution. Investigators at each site are responsible for obtaining IBC approval and periodic review of the research per NIH guidelines section IV-B07-b-(6) and section IV-B-2-b. IBC review and approval must be documented by the investigator and submitted as part of protocol registration for this study.

The NIH guidelines also require that human gene transfer studies conducted at or sponsored by institutions that receive NIH funds must be submitted to the NIH Office of Biotechnology Activities (OBA) for review by the Recombinant DNA Advisory Committee (RAC). The NIH guidelines create exceptions to RAC review for vaccines. Although the exception may apply because the study procedure involves electroporation of the DNA, the Protocol team will submit the application with the study concept proposal for RAC review and response.

11.10. Institutional Biosafety Committee (IBC)

The PPD IBC is responsible for reviewing all research studies involving biological agents as described in the Biological Safety Manual. The PPD IBC reviews research, safety procedures, and protocols with the objective of safeguarding the public health and occupational health and providing environmental safeguards for the surrounding community. The PPD IBC reviews, approves, and oversees projects in accordance with the responsibilities defined in the NIH Guidelines for Research Involving Recombinant DNA Molecules. The PI/Laboratory Director is responsible for submitting any procedures that fall under the NIH Guidelines and for completing the IBC Registration Form for Recombinant DNA prior to research initiation and annually thereafter. The form provides Investigators with an efficient means of notifying the PPD IBC regarding NIH compliance and assists investigators when determining their compliance requirements.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Monitoring

The sponsor will monitor this study in accordance with 21 CFR 312. Monitoring visits to the clinic will be made regularly to ensure that the study is carried out according to this Study Protocol and in compliance with GCP and applicable legal requirements.

Source documents will be reviewed for verification of consistency with eCRF data. The investigator guarantees direct access to source documents for monitoring purposes. Source data verification will be performed in accordance with data protection regulations and guidelines. All information reviewed will be handled according to these rules and regulations.

The monitor will review each subject's data as outlined in the study specific Clinical Monitoring Plan.

12.2. Audit and Inspections

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 eCRFs. 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.

12.3. Data Quality Assurance

All eCRF data will be entered into a validated, 21CFR Part 11 compliant, computerized clinical data management system.

The site is required to have a plan in place for assuring the quality of the research being conducted.

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 eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRFs 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.

13. ADMINISTRATIVE REQUIREMENTS

13.1. Protocol Amendments and Protocol Deviations

Protocol Amendments

Protocol amendments are planned changes to a protocol that are documented in a controlled manner through numbered amendments by the sponsor.

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 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 IRB and relevant competent authority. Documentation of amendment approval by the investigator and IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB 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 eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Protocol Deviations

Protocol deviations are unplanned excursions from the protocol that occur during the conduct of the study. Protocol deviations may (major protocol deviations) or may not (minor protocol deviations) affect the safety of the subject or the integrity of clinical study data.

Protocol deviations to inclusion/exclusion criteria may be identified post hoc during routine site monitoring. In such cases, the Study Responsible Physician must decide on a case-by-case basis the appropriate action to take.

Other protocol deviations can include non-clinically significant variations determined by good medical judgment not to affect the integrity of the study or safety of the subject. Also included are occasional insignificant variations to timings of investigational drug/study-related procedures or visit windows (which may be foreseen given the circumstances of an individual subject), or procedures that do not affect the integrity of the study or the safety of the subject, or non-clinically significant test results in the opinion of the investigator which pose no clinical safety concerns. Both the investigator and the sponsor should discuss these deviations prior to or during their occurrence. A record of the outcome (e.g., Note to File) must be retained in the Trial Master File and Trial Center File.

Any protocol deviations identified during routine monitoring are documented in Monitoring Visit Reports in accordance with the appropriate Sponsor procedures. Documentation of protocol deviations on a study basis, reporting of protocol deviations to local health authorities and IRBs, and documentation in the Clinical Study Report must be compliant with the appropriate Sponsor procedures.

13.2. Continuing Review and Close-out Reports

Continuing review reports will be submitted at intervals designated (and at least annually) by the IRB of record in accordance with 32 CFR 219. The continuing review report should be submitted to the PPD IRBs for review and approval on no less than an annual basis. A final study report will be submitted to each IRB for review and approval upon completion of the study.

13.3. Regulatory Documentation

13.3.1. Regulatory Approval/Notification

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

13.3.2. Required Prestudy Documentation

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

- Protocol and amendment(s), if any, signed and dated by the PI
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written 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 IRB, including a current list of the 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 IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the 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
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the PI, 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, where required
- 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

13.4. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. 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.

13.5. Source Documentation

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

Source documents are original documents, data, and records from which the subject's data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, microfiches, radiographs, and correspondence.

The investigator and staff are responsible for ensuring maintenance of a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the sponsor, the DoD, DAIDS, FDA, and/or applicable regulatory authorities.

All eCRF entries have to be verifiable by the source data in the subject file. This does not apply to eCRF entries that are defined as source data.

13.6. 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 eCRFs in English. Study site personnel must complete the eCRF 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 eCRFs are accurate and correct. All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel.

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 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 personnel can make corrections in the eDC tool in response of a query from Study site manager.
- Study site personnel can make corrections in the eDC tool in response of a query from clinical data manager.

13.7. Archiving

The investigator is responsible for the archiving of the investigator's file, the subject's file, and the source data according to national and international legal requirements.

Any records related to the conduct of the study may not be destroyed without written authorization by the sponsor.

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

13.8. Study Completion/Termination

13.8.1. 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.

13.8.2. 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 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

13.9. Volunteer Registry Database

The USAMRMC has a policy to collect information from every volunteer who participates in this study in a "Volunteer Registry Database". There are two objectives of this data collection. First, to answer questions about the volunteers involved in research sponsored by the USAMRMC, and second, to ensure that volunteers are informed of risks or new information.

Such information includes

- Name, Surname
- Identification Number
- Date of Birth
- Contact information
- Study title, date of study participation, and reason for withdrawal if applicable
- Severe adverse reactions including unexpected events that occurred due to vaccination during research participation
- Details of the research product received

This Volunteer Enrollment Database will be kept in Thailand for 75 years under the auspices of the Armed Forces Research Institute of Medical Sciences.

13.10. Use of Information and Publication

All information, including but not limited to information regarding Ad26.Mos.HIV and MVA-Mosaic 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 are considered confidential. 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 and MVA-Mosaic, and thus may be disclosed as required to other clinical investigators or regulatory agencies.

The results of the study will be reported in a Clinical Study Report generated by the sponsor in conjunction with the investigator. Results of analyses performed after the Clinical Study Report

has been issued will be 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.

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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15. SIGNATURES

SPONSOR: Janssen Vaccines & Prevention B.V.; Archimedesweg 4, 2333 CN Leiden, The Netherlands

This Study Protocol was subject to critical review and has been approved.

Medical Lead

[electronic signature appended at the end of the protocol]

Frank Tomaka, MD (Medical Lead)
Janssen Vaccines & Prevention B.V.

Date

PROTOCOL CHAIRS

This Study Protocol has been approved.

Protocol Chair

Jintanat Ananworanich, MD, PhD US Military HIV Research Program (MHRP)	Date

PI

Nittaya Phanuphak, MD, PhD PPD	Date

INVESTIGATORS:

I have reviewed this Study Protocol, including Appendices. I will conduct the clinical study as described and will adhere to ICH/GCP and all the ethical and regulatory requirements stated. I have read and understood the contents of the Investigator's Brochure.

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 vaccine, the conduct of the study, and the obligations of confidentiality.

Principal Investigator

_____ _____

Signature Date

16. APPENDICES

16.1. Definitions of HIV-1 Related Disease

(CDC Classification, 1993: modified for Thailand with addition of Penicilliosis to Category C)

Category B: Symptomatic Conditions in HIV-Infected Patients

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5 °C) or diarrhea lasting >1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

Category C: AIDS-Defining Diagnoses

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month duration)
- Cytomegalovirus disease (other than liver, spleen or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (>1 month duration); or bronchitis, pneumonitis or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- HIV encephalopathy (dementia)
- Isosporiasis, chronic intestinal (>1 month duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or M kansasii, disseminated or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- Penicilliosis (*addition to CDC classification for Thailand*)
- *Pneumocystis carinii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent

- Toxoplasmosis of brain
- Wasting syndrome

16.2. Case Definition for Acute Retroviral Syndrome (ARS)

Case definition must include all of the following:

- Occurs within 30 days after documented rise in plasma HIV-1 RNA of ≥1 log10 or to ≥1,000 copies/mL
- Occurs during ATI or within 7 days of restarting ARV medication after ATI
- Documented fever (temperature >38.5°C)
- At least two major criteria
- At least two minor criteria
- No other cause for signs and symptoms identified

Major criteria (must be present for >7 days):

- Pharyngitis
- Fatigue
- Morbilliform rash
- Myalgia/arthralgia
- Lymphadenopathy
- Subjective fever as reported by subject (may be intermittent)

Minor criteria (must be present for >7 days):

- Headache
- Nausea/vomiting
- Diarrhea
- Mucocutaneous ulceration (oral, genital, and/or anorectal)
- Meningismus/aseptic meningitis
- Night sweats
- Thrombocytopenia (platelets <150,000)
- Leukopenia (WBC <4,000)
- Malaise
- Abdominal pain
- Weight loss (loss of >5% of body weight)

16.3. 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 have been proven to cure HIV.
True ☐	False ☐	2. You will need to come to the clinic for about 50 scheduled visits over the next 2 years.
True ☐	False ☐	3. The vaccines in this study can give you side effects such as redness, bruising, and pain at the injection site..
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 others to HIV infection.
True ☐	False ☐	6. You may take other experimental (test) vaccines 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 donate blood during the study.
True ☐	False ☐	10. During the study staff members may contact you by telephone or email or text message.

16.4. Research Specimen Laboratory Testing[4,5]

Co-Investigating Site	Specimen type	Planned Usage	Specimen Disposition		Overseeing IRB	Sub-project/ Research Questions
			Post-testing plan	Data Usage		
PPD	Blood	Storage	Storage	RV254 study team	PPD	N/A
	CSF	Storage	Storage	RV254 study team		
	Gut tissue	Storage	Storage	RV254 study team		
	Mucosal secretions	Storage	Storage	RV254 study team		
	Lymph node tissue	Storage	Storage	RV254 study team		
PPD	Lymph node tissue	Characterization of virological and immunological events in lymphoid tissue	Storage	Local coinvestigating site and RV254 study team	PPD	Investigation of viral reservoir and immunologic markers and fibrosis
PPD	Blood	HIV-RNA, genotyping/sequencing, immunologic studies of T-cell, B-cell and antibody responses to HIV and host genetic studies to evaluate potential genes associated with HIV infection or diseases progression	Specimen discarded by site	RV254 study team	PPD	Immunologic/virologic characterization
	CSF	HIV-RNA, immune response and immunohistopathology		RV254 study team		Characterize viremia and immunologic responses in the CNS compartment
	Gut tissue	immune response and immunohistopathology		RV254 study team		Characterization of T cell responses in gut tissues
	Mucosal	HIV-RNA, immune response and		RV254 study team		HIV viremia in the

[4] Any changes to this table will not consistute a protocol amendment but will be adapted through the lab manual.

[5] Updated 11 Oct 2017

	secretions	immunohistopathology				genital compartment
	Lymph node tissue	Immunologic and virologic studies		RV254 study team		Investigation of viral reservoir.
PPD	Blood	Performance of novel biomarkers	Specimen discarded by site	Local coinvestigating site and RV254 study team	PPD	Characterization of neuropathology
	CSF	Performance of novel CSF biomarkers	Specimen discarded by site	Local coinvestigating site and RV254 study team		
PP	Blood	Inflammatory and coagulation and tissue fibrosis makers such as CP, sCD14, D-dimer and hyaluronic acid, HIV viral load by high sensitivity assay, immunophenotyping	Specimen discarded by site	Local coinvestigating site and RV254 study team	PP	Characterization of novel biomarkers
	CSF	Inflammatory and immunologic markers	Specimen discarded by site	Local coinvestigating site and RV254 study team		
	Gut tissue	Immunohistochemistry, in situ hybridization, RNA and DNA scope	Specimen discarded by site	Local coinvestigating site and RV254 study team		Characterization of CD4 T cells and associated factors
	Mucosal secretions	Inflammatory and immunologic markers	Specimen discarded by site	Local coinvestigating site and RV254 study team		Investigation of viral burden and immunologic markers
	Lymph node tissue	Immunohistochemistry, markers of immune activation and fibrosis, in situ hybridization, RNA and DNA scope Investigation of systemic inflammation and change to the global T-cell receptor (TCR) and	Specimen discarded by site	Local coinvestigating site and RV254 study team		Investigation of viral reservoir. Characterization of lymphoid immuno(patho)logical events

		B-cell receptor (BCR) repertoires				
PPD	Blood	Investigation of viral reservoir size and immunologic responses	Specimen discarded by site	Local coinvestigating site and RV254 study team	PPD	Investigate reservoir size and immunologic responses in particular, T and B cell function
	CSF	Investigation of cellular response	Specimen discarded by site	Local coinvestigating site and RV254 study team		
	Gut tissue	Investigation of viral reservoir size	Specimen discarded by site	Local coinvestigating site and RV254 study team		
PPD	Blood	Investigation of monocytes, macrophages and innate responses	Specimen discarded by site	Local coinvestigating site and RV254 study team	PPD	Characterization of the inflammatory profile of monocytes
	CSF	Investigation of monocytes, macrophages and innate responses	Specimen discarded by site	Local coinvestigating site and RV254 study team		
	Gut tissue	Investigation of monocytes, macrophages and innate responses	Specimen discarded by site	Local coinvestigating site and RV254 study team		
	Lymph node tissue	Investigation of monocytes, macrophages and innate responses	Specimen discarded by site	Local coinvestigating site and RV254 study team		
PPD	Lymph node tissue	Characterization of virological and immunological events in lymphoid tissue, immunohistochemistry, in situ hybridization, RNA and DNA scope	Specimen discarded by site	Local coinvestigating site and RV254 study team	PPD	Investigation of viral reservoir and immunologic markers and fibrosis
PPD	Blood	Trofile (CCR5 tropism) testing	Specimen discarded by	RV254 study team	N/A	None

PPD			site			
Janssen Vaccines & Prevention B.V.	Blood	Evaluation of immunogenicity	Storage	RV254 study team	N/A	N/A

16.5. Neurological Examination Form, Abridged Neuropsychological Assessment Test Battery, Substance use and Sleep, CDR

SEARCH010 PID: ___ ___ ___ ___ Date: ___ ___/___ ___/___ ___
Visit #: ___ ___ PTT Int. ___ ___ Month / day / year

MACRONEUROLOGICAL EXAM 2.0 (REVISED 1/2016)

☐ **Place an "X" if ALL questions and neurological tests reveal normal results ("0")**
Default to "0" for questions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 17, 18, 19, 20, 22, 23, 24, 25, 28b/c, 29, 30, 31, 32, 35, 36, 37

COGNITIVE FUNCTION

☐ **1. Concentration/Speed of thought**
0 Normal mental ability
1 Notes some diminished capacity for concentration or need for longer time to accomplish normal tasks but able to manage nearly all of daily affairs
2 Definitely loses track of conversation or task, takes more than twice as long to complete some tasks, needs help to manage more difficult tasks of daily life (e.g. financial records) or complex work activities
3 Marked slowing of mental processes, perseveration or loss of train of thought, needs help to manage almost all daily affairs requiring cognition
4 Only rudimentary cognition
5 Cannot evaluate
6 Not elicited

☐ **2. Reading (or TV)**
0 Normal
1 Notes mild increase in effort or occasionally loses place in either reading or TV
2 Reduced reading or TV because of slowness, clearly more laborious, or requires repeated efforts, but can follow news or similar subjects
3 Reading or TV markedly reduced because of difficulty attending or following plot but occasionally reads or watches with reduced attention or comprehension
4 Unable to read or watch TV at all because cannot make sense of subject, etc.
8 Cannot evaluate
9 Not elicited

☐ **3. Memory**
0 Normal
1 Mildly more forgetful than usual, will occasionally miss appointments
2 Definite memory difficulty, needs to keeps lists, forgets events of day or activities in mid task
3 Frankly confused at times about events, places, persons
4 Persistently disoriented to time, frequently to place or person
8 Cannot evaluate
9 Not elicited

☐ **4. Speech**
0 Normal
1 Mild hesitancy, extra deliberation of occasional use of inappropriate words
2 Definite slowness or difficulty finding words of use of wrong or inappropriate words
3 Reduced speech output or frequent speech errors

4 Speech limited to a few phrases at best
8 Cannot evaluate
9 Not elicited

MOTOR FUNCTION

☐ **5. Gait**
0 Normal
1 Mild unsteadiness, imbalance, slowness or weakness, but fully ambulatory without assistance
2 Unsteady or weak, requiring cane or some prop
3 Requires bilateral (e.g. walker or human) prop
4 Unable to walk
8 Cannot evaluate
9 Not elicited

☐ **6. Upper Extremity Coordination**
0 Normal dexterity
1 Mild slowing or clumsiness of hands without functional impairment
2 Moderate clumsiness of hands, altering handwriting or slowing regular hand activities (eating, etc.)
3 Marked clumsiness resulting in difficulty performing ADL (e.g. difficulty feeding without manual help of others)
4 Unable to perform hand-related ADL because of incoordination
8 Cannot evaluate
9 Not elicited

☐ **7. Involuntary Movement (Includes Tremor, Myoclonus & Chorea)**
0 None or normal mild tremor
1 Noticeable new or increase in adventitious movements, but does not interfere with ADL
2 New or increased adventitious movements impair handwriting or other manual tasks, but still can function independently for most ADL
3 Marked adventitious movements interfering with most ADL
4 Severe adventitious movements necessitate nearly full-time care
8 Cannot evaluate
9 Not elicited

BEHAVIOR/MOOD

☐ **8. Mood**
0 Normal spirits, no depression
1 Depressed about illness but does not intrude on function
3 Severe depression, requires suicide precautions
8 Cannot evaluate
9 Not elicited

☐ **9. Social Apathy/Withdrawal**
0 Normal socialization
1 Diminished interest but continues with normal activities
2 Activities reduced because of lack of interest or initiative but maintains most contacts
3 Marked loss of interest in friends and normal social activities, does not seek contact
4 Little or no meaningful socialization
8 Cannot evaluate
9 Not elicited

☐ **10. Emotional Lability/Agitation**

0 Normal
1 Irritable, more easily agitated or excited, but does not alter social ability
2 Clearly labile or hyperactive so that interactions are altered, with occasional inappropriate social interaction
3 Nearly constant hyperactivity or hypomania interfering with social interactions
4 Frank delirium or psychosis

MENTAL STATUS and AFFECT

11. Response slowing
0 Normal or hyperactive
1 Mild slowing of response time
2 Moderate slowing of response time
3 Severely slowed, nearly fully or mute
8 Cannot evaluate
9 Not elicited

SENSATION

12. Neuropathy Symptoms
0 None
1 Mild distal paresthesia or pain not requiring more than occasional non-narcotic analgesics and not interfering with Activities of Daily Living
2 Moderate distal paresthesia/pain requiring daily non-narcotic
3 Severe distal paresthesia or pain requiring daily narcotic analgesic and substantially interfering with Activities of Daily Living
8 Cannot evaluate
9 Not elicited

SEIZURES

13. Seizures
00 None
01 Single partial or generalized seizure
02 Repeated (<3/wk) partial or generalized seizures
03 Frequent (>4/wk) partial or generalized seizures
08 Cannot evaluate
09 Not elicited

OCULAR MOTILITY

14. Smooth Pursuits (Have the participant follow finger a minimum of 2 times horizontally from side to side and 2 times vertically from up to down)

0 Normal
1 Mildly abnormal (mild cogwheeling)
2 Moderately - severely abnormal
8 Cannot evaluate
9 Not elicited

15. Saccades [Place finger in participant's lateral field and ask participant to look at finger (without snapping finger) then your nose, alternating. Repeat for opposite lateral direction, as well as vertically (up and downward)]

00 Normal

01 Mildly abnormal (mild cogwheeling)
02 Moderately - severely abnormal
08 Cannot evaluate
09 Not elicited

STRENGTH
Strength score reflects worst major muscle group or groups. Scores of 0-3 refer to weakness related to ADC only. Test by asking patient to do a deep knee bend, walk on toes and heels, and hop on each foot.

☐ **16. Right Leg**
0 Normal
1 Mild weakness (4/5)
2 Moderate weakness (3/5)
3 Severe weakness (2/5 or worse)
4 Other _____
8 Cannot evaluate
9 Not elicited

☐ **16a. Is weakness related to neuropathy?**
0 No weakness found
1 No, neuropathy not present
2 No, neuropathy present, but not thought to be etiology of weakness
3 Yes, neuropathy somewhat affecting strength or measure of strength
4 Yes, neuropathy responsible for majority of finding.
8 Cannot evaluate
9 Not elicited

☐ **17. Left Leg**
0 Normal
1 Mild weakness (4/5)
2 Moderate weakness (3/5)
3 Severe weakness (2/5 or worse)
4 Other _____
8 Cannot evaluate
9 Not elicited

COORDINATION

☐ **18. Gait Coordination** (Test by asking subject to walk quickly down hall, turn rapidly and return)
0 Normal gait
1 Mild impairment (evident only on rapid turns or tandem)
2 Moderate impairment (clear difficulty of unassisted gait)
3 Severe impairment (walking only with assistance)
4 Non-ambulatory
5 Weakness precludes assessment of gait coordination
8 Cannot evaluate
9 Not elicited

☐ **19. Limb Coordination** (Test by opposition of the first and second fingers, rapid wrist rotation, and rapid foot tapping)
0 Normal
1 Mild slowness or clumsiness (compared to examiner, the movement is slightly slower, fatigues or breaks down earlier)
2 Moderate slowness or clumsiness

3 Weakness precludes assessment of gait coordination
8 Cannot evaluate
9 Not elicited

REFLEXE

☐ **20. Deep Tendon Reflexes**

0 Normal
1 Increased in legs only
2 Generalized increase
3 General decrease (most notably distally)
4 Increased proximally and depressed distally
5 Increased on one side
6 Other _____
7 Depressed or absent ankle jerks only(o/w normal)
8 Cannot evaluate
9 Not tested

21. Jaw Jerk

00 Absent
01 Present
02 Unusually brisk
08 Cannot evaluate
09 Not elicited

NEUROPATHY

☐ **22. Severity of Sensory Loss**

0 Normal
1 Mild impairment (e.g. increased threshold to position, vibration, or light touch in great toes)
2 Moderate impairment (e.g. decrease in position or vibration, pin or cold to ankles)
3 Severe impairment (e.g. decrease or loss of sensation to knees or wrists or comparable level)
8 Cannot evaluate
9 Not elicited

☐ **23. Type of Neuropathy**

0 None
1 Predominantly distal sensory
2 Predominantly motor
3 Mixed distal
4 Mononeuritis or localized radiculopathy
5 Mononeuritis multiplex or polyradicutopathy
8 Cannot assess
9 Not elicited

☐ MOTOR UPDRS EXAMINATION

24. Speech

0 Normal
1 Slight loss of expression, diction and/or volume
2 Monotone, slurred but understandable
3 Marked impairment, difficult to understand
4 Unintelligible
8 Cannot assess
9 Not elicited

☐ **25. Facial Expression**

0 Normal
1 Slight hypomimia, could be normal "Poker Face"
2 Slight but definitely abnormal diminution of facial expression
3 Moderate hypomimia; lips parted some of the time
4 Masked or fixed face with severe or complete loss of facial expression; lips parted 1/4 inch or more
8 Cannot assess
9 Not elicited

~~26a-e.~~ Tremor at Rest (see scoring box)

26a. Face, lips, and chin
26b. Arm, right
26c. Arm, left
26d. Leg, right
26e. Leg left

00	Absent
01	Slight and infrequently present
02	Mild in amplitude and present most of the time
03	Moderate in amplitude and present most of the time
04	Marked in amplitude and present most of the time
08	Cannot assess
09	Not elicited

27a-b. Action or Postural Tremor

a. RIGHT ARM

b. LEFT ARM

00	Absent
01	Slight; present with action
02	Moderate in amplitude present with action only
03	Moderate in amplitude with posture holding as well as action
04	Marked in amplitude; interferes with feeding
08	Cannot assess

28a-e. Rigidity (Judged on passive movement of major joints with subject relaxed in sitting position. Cogwheeling to be ignored. Performed with and without distraction; see scoring box)

☐ ~~28a. Neck,~~
28b. Arm, right

☐ 28c. Arm, left
~~28d. Leg, right~~
~~28e. Leg, left~~

0	Absent
1	Slight and infrequently present
2	Mild and present most of the time
3	Moderate and present most of the time
4	Marked and present most of the time
8	Cannot assess
9	Not elicited

29a-b. Finger Taps (Subject taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately). Please record patient's handedness: ☐ right ☐ left

☐ a. RIGHT FINGERS
☐ b. LEFT FINGERS

0	Normal (15 or more/5 sec)
1	Mild slowing and/or reduction in amplitude (11-14/5 sec)
2	Moderately impaired. Definite and early fatiguing. May have occasional arrest in movement (7-10/5 sec)
3	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movements (3-6/5 sec)
4	Can barely perform the task (0-2/5 sec)
8	Cannot assess
9	Not elicited

30a-b. Hand Movements [Subject opens and closes hands in rapid succession with widest amplitude possible (full digit extension/flexion), each hand separately]

☐ a. RIGHT HAND

☐ b. LEFT HAND

0	Normal
1	Mild slowing and/or reduction in amplitude
2	Moderately impaired. Definite and early fatiguing. May have occasional arrest in movement
3	Severely impaired. Frequent hesitation in initiating movements
4	Can barely perform the task
8	Cannot assess
9	Not elicited

31a-b. Rapid Alternating Movements of Hands/Arms (Pronation-supination of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously)

☐ a. RIGHT ARM

☐ b. LEFT ARM

0	Normal
1	Mild slowing and/or reduction in amplitude
2	Moderately impaired. Definite and early fatiguing. May have occasional arrest in movement
3	Severely impaired. Frequent hesitation in initiating movements
4	Can barely perform the task
8	Cannot assess
9	Not elicited

32a-b. Leg Agility (with knees bent, subject taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3 inches.)

☐ a. RIGHT LEG

☐ b. LEFT LEG

0	Normal
1	Mild slowing and/or reduction in amplitude
2	Moderately impaired. Definite and early fatiguing. May have occasional arrest in movement
3	Severely impaired. Frequent hesitation in initiating movements or arrests
4	Can barely perform the task
8	Cannot assess
9	Not elicited

~~33. Arising from chair (subject attempts to arise from a straight back wood or metal chair, with arms folded across chest)~~

00	Normal
01	Slow; or may need more than one attempt
02	Pushes self up from arms of seat
03	Tends to fall back and may have to try more than one time, but can get up without help
04	Unable to arise without help
08	Cannot assess
09	Not elicited

~~34. Posture~~

00	Normal
01	Not quite erect, slightly stooped posture; could be normal for older person
02	Moderately stooped posture, definitely abnormal; can be leaning slightly to one side
03	Severely stooped posture with kyphosis; can be leaning moderately to one side
04	Marked flexion with extreme abnormality of posture
08	Cannot assess
09	Not elicited

35. Gait

0 Normal
1 Walks slowly, may shuffle with short steps
2 Walks with difficulty, but requires little or no assistance
3 Severe disturbance of gait, requiring assistance
4 Cannot walk at all even with assistance
5 Spastic
6 Circumductive
8 Cannot assess
9 Not elicited

36. Postural Stability (Response to sudden posterior displacement produced by pull on shoulders while subject is erect, with eyes open and feet slightly apart. Subject is prepared.)

0 Normal (2 or less steps)
1 Retropulsion, but recovers unaided
2 Absence of postural response; would fall if not caught by examiner
3 Very unstable, tends to lose balance spontaneously
4 Unable to stand without assistance
8 Cannot assess
9 Not elicited

37. Body Bradykinesias and Hypokinesia

(Combining slowness, hesitance, decreased arm swing, small amplitude and poverty of movement in general)

0 Normal
1 Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude
2 Mild degree of slowness and poverty of movement which is definitely abnormal
3 Moderate slowness, poverty or small amplitude of movement
4 Marked slowness, poverty or small amplitude of movement
8 Cannot assess
9 Not elicited

Examiner Signoff: _____

Abridged Neuropsychological Assessment Test Battery

A.1 COLOR TRAILS I

Time to complete: _____ seconds

A.2 COLOR TRAILS II

Time to complete: _____ seconds

B. GROOVED PEGBOARD TEST

Non-dominant Hand Time _____
Non-dominant Hand Number of Drops _____

C. TRAIL-MAKING TEST A

Time to complete: _____ seconds
Error: _____

D. FLANKER TEST

Completed? ☐ Yes ☐ No

Abridged Neuropsychological Assessment Reporting Form

☐☐ **1. Color Trails 1 and 2**

00 Reliable, standardized test administration
01 Questionable test results (specify reason)
02 Invalid test results (specify reason)
Examiner Comments and
Observations:_____

☐☐ **2. Grooved Pegboard**

00 Reliable, standardized test administration
01 Questionable test results (specify reason)
02 Invalid test results (specify reason)
Examiner Comments and
Observations:_____

☐☐ **3. Trail-making Test A**

00 Reliable, standardized test administration
01 Questionable test results (specify reason)
02 Invalid test results (specify reason)

Examiner Comments and
Observations:_____

SUBSTANCE USE AND SLEEP

☐☐ **1. Do you use recreational drugs? (may include drugs made of local herbs/plants)**

01 NEVER
02 YES, TODAY OR YESTERDAY
03 YES, THIS WEEK BUT NOT TODAY OR YESTERDAY
04 YES, MORE THAN ONE WEEK AGO
05 ONLY IN THE PAST, MORE THAN ONE YEAR AGO
08 REFUSE TO ANSWER
09 DON'T KNOW

☐☐ **2. If you have used recreational drugs today or yesterday, please specify which ones you used (may choose more than one).**

01 MARIJUANA/CANNABIS/BHANG
02 HASHISH
03 CRACK
04 COCAINE
05 METHAMPHETAMINES
06 ECSTASY
07 KHAT
08 HEROIN
09 GLUE/PETROL SNIFFING
10 LSD
11 POPPERS
99 OTHER, SPECIFY: _____

☐☐ **3. Do you drink alcohol?**

01 NEVER
02 YES, TODAY OR YESTERDAY
03 YES, THIS WEEK, BUT NOT TODAY OR YESTERDAY
04 YES, MORE THAN ONE WEEK AGO
05 ONLY IN THE PAST, MORE THAN ONE YEAR AGO
08 REFUSE TO ANSWER
09 DON'T KNOW

☐☐ **4. If you have consumed alcohol today or yesterday, how many drinks have you had in this time period?**

01 1-2 DRINKS
02 3-4 DRINKS
03 5-6 DRINKS
04 7 OR MORE DRINKS
08 REFUSED TO ANSWER
09 DON'T KNOW

☐☐ **5. How many hours sleep did you get in the last 24 hours?**

☐☐ **6. How tired do you feel right now?**
(Rate from 1= Not tired, 5= moderately tired to 10= Very tired)

Clinical Dementia Rating (CDR) Scale

	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented expect for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time & often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems, handles business & financial affairs well: judgment good in relation to past performance	Slight impairment in solving problems, similarities, & differences	Moderate difficulty in handling problems, similarities, &differences;social judgment usually maintained	Severely impaired in handling problems, similarities, & differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer & social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home; appears well enough to be taken to function outside a family home	No pretense of independent function outside home; appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, & intellectual interests well maintained	Life at home, hobbies, & intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies & interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

17. ATTACHMENTS

17.1. Protocol Team Roster[6]

Protocol Chair:
Jintanat Ananworanich MD, PhD
PPD
PPD USA
PPD

Principal Investigator:
Nittaya Phanuphak, MD, PhD
PPD
PPD Thailand
PPD

Sponsor Clinical Leader
Frank Tomaka, MD
Clinical Leader,
Janssen Vaccines & Prevention B.V.
PPD

Project Leader
PPD
PPD Thailand
PPD

Clinical Trials Specialist (Thailand)
PPD

[6] Changes to the roster will not constitute a protocol amendment.

PPD
PPD Thailand
PPD

PPD
Thailand
PPD

Statistical Leader
PPD , MSc
Janssen Pharmaceutica NV
PPD
PPD
BELGIUM
PPD
PPD

Data Manager
PPD PhD
Janssen Pharmaceutica NV
PPD
BELGIUM
PPD
PPD

Clinical Virologist
PPD
BELGIUM
PPD

Head biomarkers viral vaccines

PPD

The Netherlands

PPD

Clinical Immunologist

PPD

The Netherlands

PPD

Global Trial Leader

PPD

Malaysia

PPD

Study Pharmacist

PPD

Thailand

PPD

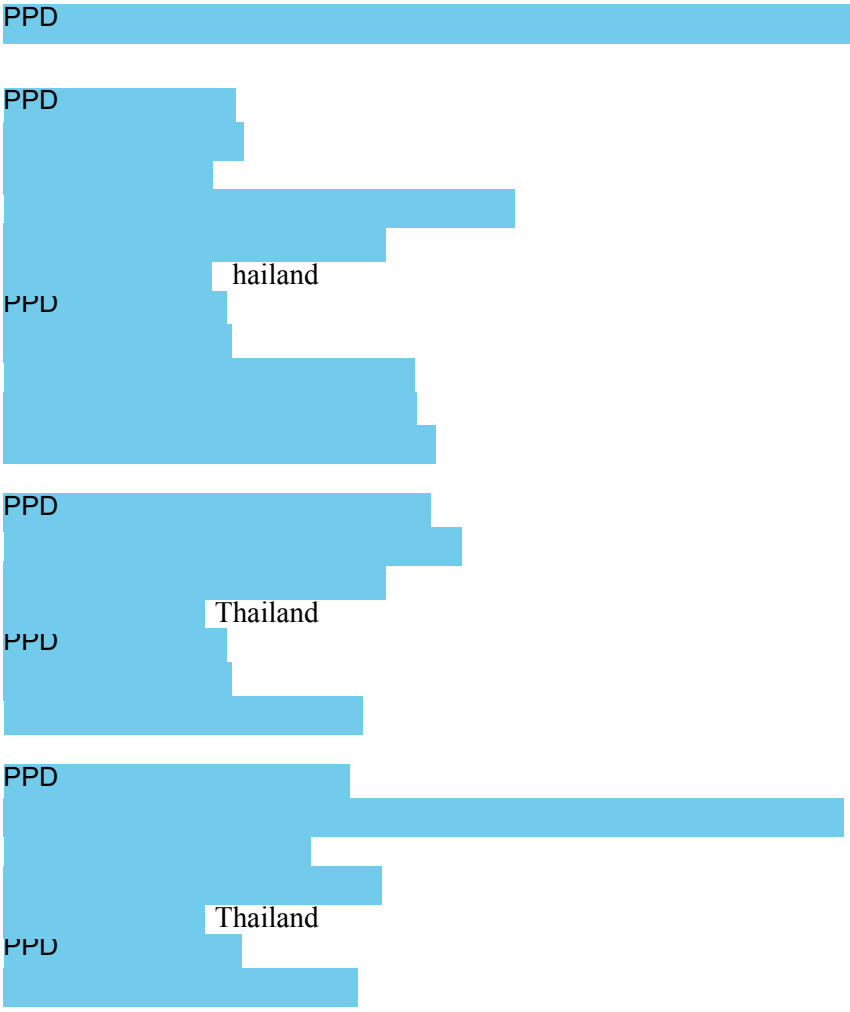
Laboratory coordinator

PPD

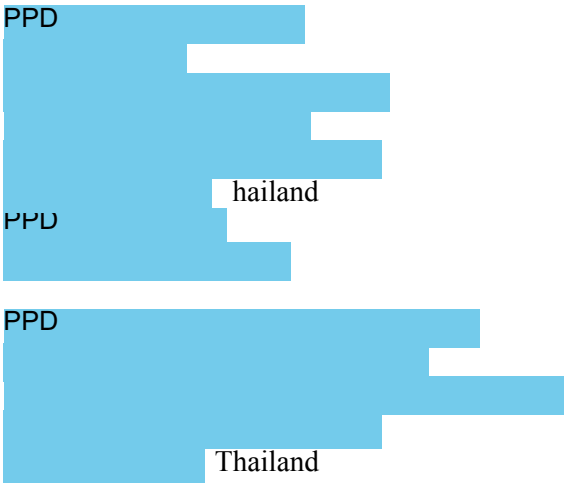
USA

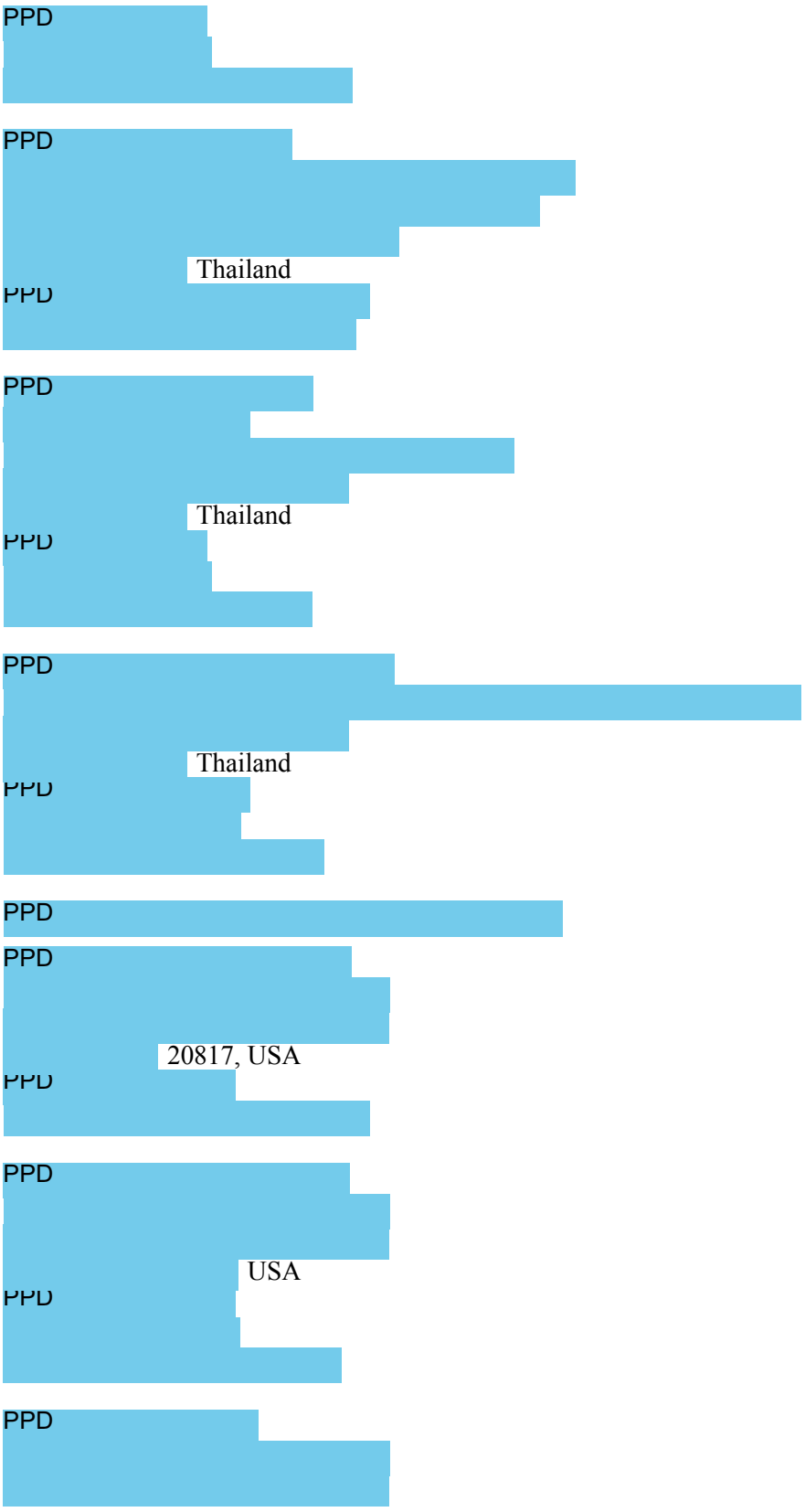
PPD

Investigators



Associate Investigators

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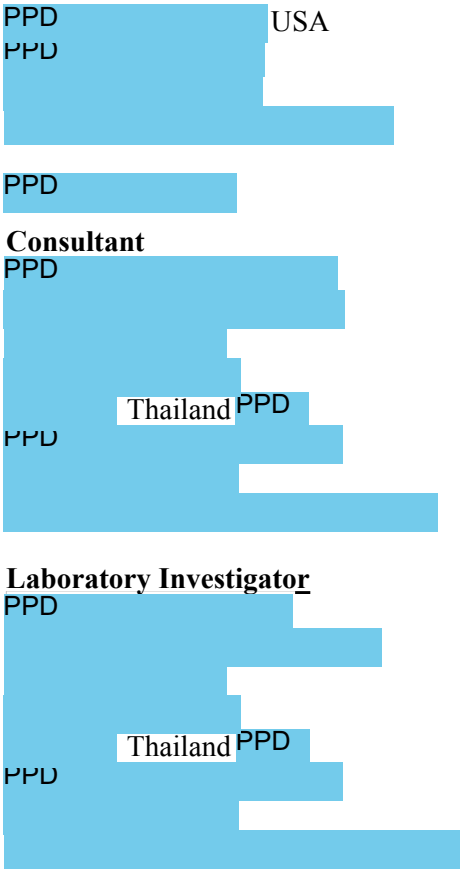


17.2. Study Personnel Roles and Responsibilities

Protocol Chair: Responsible for overall direction and the leadership for the study. The protocol chair acts as liaison between the PI with the vaccine developers, sponsors, and funders, and supports the site PI with clinical study guidance, protocol preparation, protocol review and regulatory approvals.

Principal Investigator: Provides overall project management and the analysis and reporting of the study data. The PI is responsible for local IRB submission and approval, study conduct, and reporting all unanticipated problems and AEs to the protocol team and the IRB. The PI will act as the qualified physician responsible for all study site related medical decisions and will take all necessary precautions to ensure that the study obtains the proper clearance for all publication and abstracts, and maintain a study regulatory file as instructed by the study sponsor.

Sponsor Clinical Leader: Is a qualified research physician who provides technical assistance and supervision on the study design, protocol development and study implementation. The sponsor clinical leader is the main liaison between the sponsor, the PI, and the complementing team.

Project Leader: Coordinates implementation of the study at the Thailand clinic site, ensures that all study procedures are conducted in accordance with the study protocol, provides training and supervision to study clinic staff, and supervises quality assurance activities. The project leader will assist the PI and protocol chair with local and international IRB submissions and reporting requirements, including the reporting of problems and AEs to the protocol team and study sponsors.

Clinical Trials Specialist (Thailand): Is based at the study site in Thailand and under the supervision of the PI coordinates all management and administrative issues for the study, including local IRB submission and other regulatory affairs.

Clinical Operation Group, Clinical Research Division: Is based at Department of Retrovirology, PPD and under the supervision of the protocol chair and PI coordinates all management and administrative issues in the USA for the study, including US DoD submissions and other regulatory affairs.

Statistician: Will receive coded data from the data manager and use those data to perform all investigational data analyses in collaboration with MHRP and the study team.

Data Manager: Responsible for overall data management and providing a final data transfer following final database closure, including, but not limited to, the data dictionary, formats, codes, and any accompanying memorandums. The media format and transfer specifications will be agreed upon with the Sponsor.

Virologist: Is an expert on HIV virology who will provide technical assistance to the project on study design, protocol development, laboratory evaluations, and data analysis and reporting.

Laboratory Coordinator: A qualified laboratory researcher who will lead the development and implementation of all laboratory analyses conducted as part of the protocol. The laboratory coordinator coordinates receiving, storing and distributing of biological specimens from the study. The laboratory coordinator will not have any access to any subjects' identifiers or private information.

Site Investigators: Conduct the participant study visits, and assist with AE assessment and reporting. Site investigators will report any findings and study status directly to the study PI and will also coordinate with the PI in the planning, design, and execution of the study.

Senior Investigators: Are experienced clinical researchers in Thailand who will provide technical assistance to the PI on study design and implementation.

Associate Investigators: Assist the PI and senior investigators in performing specific study tasks and/or procedures under their supervision.

Laboratory Investigators: Laboratory investigators supervise clinical and research laboratory activities for the study. Laboratory investigators will not have contact with study subjects or identifiers.

Study Pharmacist: Qualified pharmacist with responsibility for overseeing the import, preparation, blinding, distribution, inventory, and accountability of vaccine, communication with sponsor / MHRP regarding pharmacy related issues, training and consultation with the study site pharmacy personnel.

Clinical Staff: Can be physicians, nurses, or any specifically trained study personnel to perform clinical duties at the study site, including physical examination, counseling, and vaccine administration.

Department of Defense (DoD) Research Monitor: The role and qualifications of the DoD research monitor are identified as follows:

The DoD research monitor is a member of the PSRT of the study. In the context as a member of the PSRT, the DoD research monitor is required to review all SAEs and unanticipated problems involving risk to volunteers or others, social harms, and all volunteer deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the DoD research monitor should comment on the outcomes of the event or problem, and in the case of a SAE, social harms, or death, comment on the relationship to participation in the study. The DoD research monitor should also indicate whether he/she concurs with the details of the report provided by the site principal investigator.

The medical monitor will also in the context of the PSRT:

1. Discuss research progress, consult on individual cases, or evaluate suspected adverse reaction reports on behalf of the PPD /IRB.

2. May at the direction of the PPD IRB, be involved in oversight functions (e.g., observe recruitment, enrollment procedures, and the consent process for individuals, groups or units; oversee study interventions and interactions; review monitoring plans and UPIRTSO reports; and oversee data matching, data collection, and analysis).

3. Promptly report discrepancies or problems to the PPD IRB.

4. Have the authority, in the context of his PSRT membership, to be involved in all decision making regarding stopping a research study in progress, removingindividual subjects from a study, and taking whatever steps are necessary to protect the safety and well-being of research subjects until the IRB can assess the research monitor's report

Consultants: Protocol consultants are responsible for providing input for the study design, protocol development, and serve as technical advisors and subject matter experts for study execution.

17.3. Collaborating Institutions and Investigators

PPD

PPD

Vaccine Research Center

PPD

AIDS and Cancer Virus Program

PPD

PPD -

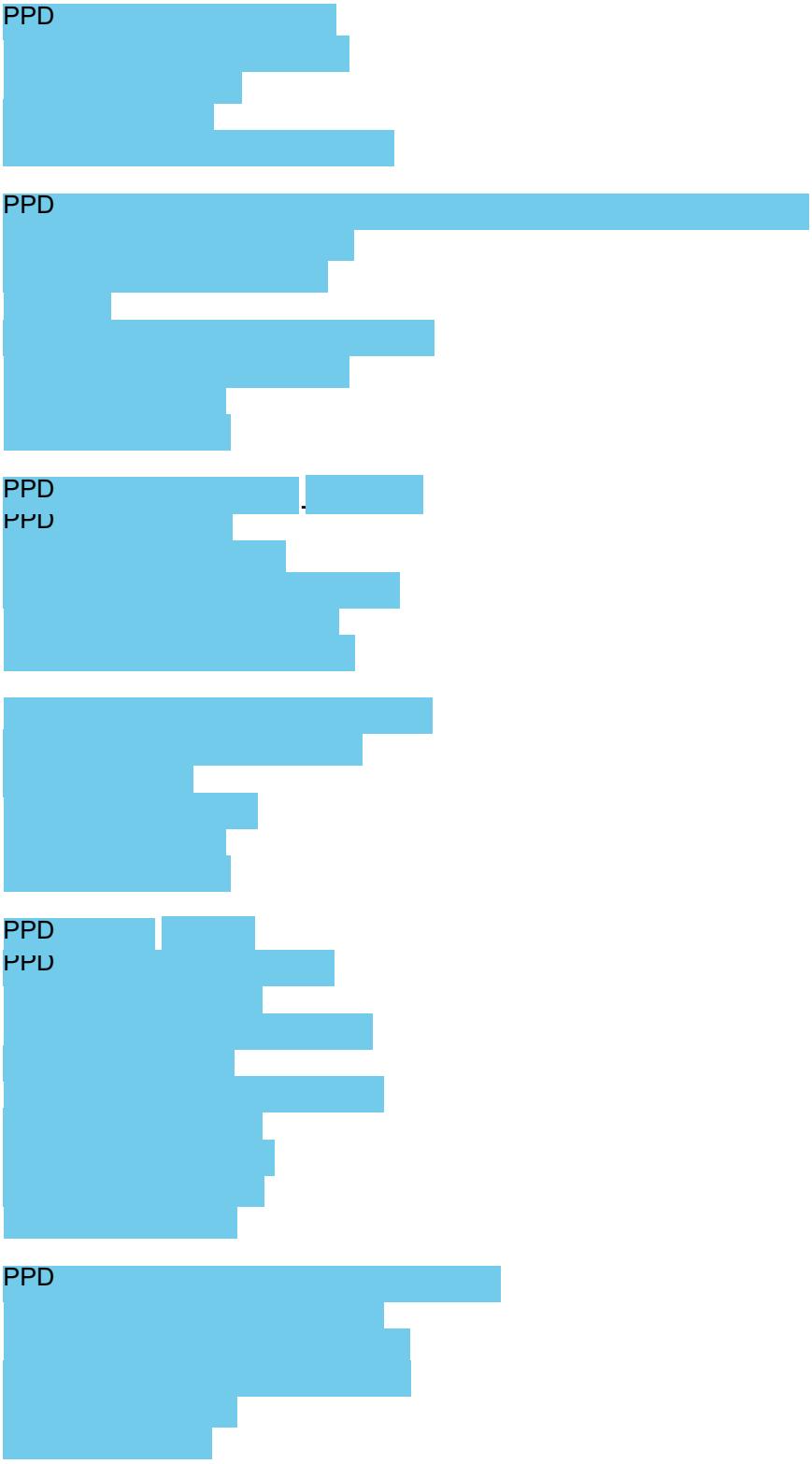
PPD

PPD

PPD -

PPD

[7] These collaborating institutions will receive coded samples and/or data.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SWEDEN

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National Institutes of Health[7]

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SIGNATURES

Signed by	Date	Justification
Frank Tomaka	13Oct2017, 20:39:38 PM, UTC	Document Approval