Janssen Vaccines & Prevention B.V.*

Clinical Protocol

A Randomized, Double-blind, Placebo-controlled First-in-Human, Phase 1/2a Study to Evaluate the Safety, Reactogenicity and Immunogenicity of Monovalent HPV16 and HPV18 Ad26-vectored Vaccine Components and an MVA-vectored HPV16/18 Vaccine Component in Otherwise Healthy Women with HPV16 or 18 Infection of the Cervix

Protocol VAC81623HPV1002; Phase 1/2a

AMENDMENT 3

VAC81623 (JNJ-63682918, JNJ-63682931 and JNJ-65195208)

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

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

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	6 February 2018
Amendment 1	24 May 2018
Amendment 2	11 January 2019
Amendment 3	This document

Amendments below are listed beginning with the most recent amendment.

Amendment 3 (this document)

The overall reason for the amendment: The inclusion/exclusion criteria have been adapted to enroll a broader population of women with any HPV16 or 18 infection of the cervix, not limited to persistent infection. The proposed changes will not impact primary and secondary study objectives. Safety of the different vaccine regimens is not considered to be different between participants with persistent or recently diagnosed HPV16 or 18 infection. Immunogenicity of the different vaccine regimens will be analyzed overall, and the sponsor is interested in exploring responses in recently diagnosed HPV infections for potential development of the therapeutic interventions in countries where the existing screening programs do not consistently identify persistent HPV infections.

Applicable Section(s)	Description of Change(s)
Rationale: The study population has been amended to also include women with recently diagnosed HPV 16 or 18 infections of the cervix.	
Synopsis, Overview of Study Design, Participant Population, Virology and Histology Evaluations, Statistical Methods; Time and Events Schedule; Definitions of terms; 1.2 Overall Rationale for the Study; 3.1 Overview of Study Design; 4.1 Inclusion Criteria; 9.2.3 Virology and Histology; 11.3 Participant Information; 11.5 Immunogenicity Analyses; 11.6 Virology Analyses	Removal of the wording 'persistent' before the wording 'HPV16 or 18 infection'. Update of inclusion criterion 4. Addition of persistent and recently diagnosed infection types. Update of flow chart in Figures 1 and 4.
Rationale: Based on inclusion of women with recently diagnosed HPV 16 or 18 infections of the cervix, additional exploratory objectives/endpoints to assess clearance of recently diagnosed infections are included.	
Synopsis, Objectives, Endpoints, and Hypothesis, Statistical Methods; 2.1 Objectives and Endpoints; 11.6 Virology Analyses	Exploratory objectives/endpoints to assess frequency and kinetics of clearance of HPV16 or 18 infection with/without the concomitant regression of CIN1 have been updated to include persistent and recently diagnosed infection types.
Rationale: Colposcopy examination has been added as study screening procedure for participants who did not have this examination done within the last 12 months.	
Synopsis, Virology and Histology Evaluations; Time and Events Schedule; 4.1 Inclusion Criteria; 9.2.3 Virology and Histology	Implementing colposcopy examination during the screening period in case recent examination results are not available.
Rationale: Change in the visits' and vaccinations' allowed windows to keep these requirements consistent throughout the protocol.	
Time and Events Schedule; 4.2 Exclusion Criteria; 6.2 Criteria for Postponement of Vaccination; 9.1.2 Visit Windows; 9.1.4 Vaccination and Follow-up Period (Day 1 to Day 366)	Wording was updated to keep the flexibility of vaccination rescheduling in case of acute illness.

Applicable Section(s)	Description of Change(s)
Rationale: Exclusion criterion 12 has been updated to include genital herpes infection. As HSV-2 infection might be a co-factor leading to progression of cervical disease, HSV-2 serology testing has been included on the day of the first vaccination and the 12-month follow-up visit (or the early exit visit, if applicable).	
Time and Events Schedule; 4.2 Exclusion Criteria; 9.1.4 Vaccination and Follow-up Period (Day 1 to Day 366); 9.2.1 Safety; 9.2.3 Virology and Histology	The wording 'including genital herpes' has been added to exclusion criterion 12 as well as a note that positive HSV-2 serology is not exclusionary. Exclusion criterion 13 has been removed. HSV-2 serology testing has been included at Visit 2, Visit 14 and the early exit visit.
Rationale: Blinded interim analysis of immune responses has been added prior to the primary analysis as this will allow to identify immunogenicity and overall safety signals and guide further development of the vaccine.	
Synopsis, Statistical Methods; 11.7 Planned Analyses	A paragraph describing the blinded interim immune analysis has been added.
Rationale: The benefit-risk evaluation has been updated to be in line with the Janssen clinical trial protocol template.	
1.2 Benefit-risk Evaluations; 16.1 Study-specific Design Considerations	The benefit-risk wording in Section 16.1 has been moved to a new Section 1.2. Additional benefit-risk wording from the Janssen clinical trial protocol template has been included.
Rationale: In the absence of suitable samples for complete qualification of the cellular assays used for the assessment of the secondary and exploratory endpoints, samples collected at baseline and/or post-vaccination will be used for completion of assay qualification concomitantly to the assessment of immunogenicity.	
Synopsis, Immunogenicity Evaluations; 9.2.2 Immunogenicity	The sentence describing baseline sample use for immunological assay characterization has been updated.
Rationale: Fibrinogen values are highly variable in the target study population. The fibrinogen levels among healthy women may be increased due to oral contraceptives, smoking, or hormone replacement therapy while there is no clinical pathology associated with this abnormality. The sponsor decided to remove this test as it has no added value for the eligibility assessment.	
9.2.1 Safety	The fibrinogen test during screening has been removed.
Rationale: Sponsor's responsible medical officer was updated to reflect current organizational structure.	
Investigator agreement	Sponsor's responsible medical officer was updated.
Rationale: Minor errors and unclarities were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes and clarifications were made.

Amendment 2 (11 January 2019)

The overall reason for the amendment: The dose of the modified vaccinia Ankara (MVA)-vectored HPV16/18 vaccine administered in this study has been changed from $5x10^8$ infectious unit (Inf.U) to a lower dose of $2x10^8$ Inf.U. The use of $2x10^8$ Inf.U MVA.HPV16/18 vaccine is supported by recent data derived from the sponsor's Ebola vaccine program that employed Ad26.ZEBOV, MVA-BN-Filo vaccine regimens and where no differences in the overall dose-dependent immunogenicity responses were observed when comparing MVA doses of $1x10^8$ tissue culture infectious dose of 50% ($TCID_{50}$) with $4.4x10^8$ $TCID_{50}$. Both the number of vaccine responders as well as the magnitude of the responses was similar for both dose levels. This was shown at the peak of the post boost immune response for humoral responses assessed by neutralizing and binding antibody responses, as well as for T cell responses assessed by IFNγ enzyme-linked immunospot (ELISpot) and intracellular cytokine staining (ICS) assay enumerating $CD4^+$ and $CD8^+$ specific T cells. In addition, no immunogenicity response differences were seen after peak responses, as assessed up to one year after vaccination. In addition, in previous non-human primate studies strong cellular immune responses were elicited with MVA-BN-HPV administered at $1.79x10^8$ $TCID_{50}$ (study DS-TEC-117650) which is similar in strength to the proposed dose of $2x10^8$ Inf.U. A diluent will be provided to the sites that will be added to the MVA.HPV16/18 vaccine supplied in vials at a concentration of $5x10^8$ Inf.U/0.5mL.

Further, inclusion criterion 5 (requirement of recent colposcopy result) was updated in line with the current cervical cancer screening guidelines.[30] In addition, minor edits and clarifications were made.

Applicable Section(s)	Description of Change(s)
Rationale: Change of the MVA.HPV16/18 dose from $5x10^8$ Inf.U to $2x10^8$ Inf.U for all subjects.	
Synopsis; 1. Introduction; 3.1 Overview of Study Design; 3.2 Study Design Rationale; 6.1 General Instructions and Procedures; 14.1 Physical Description of Study Vaccine	Reduction of MVA.HPV16/18 dose from $5x10^8$ Inf.U to $2x10^8$ Inf.U for all subjects. The dose will be reduced using a diluent provided to the sites.
Rationale: More information is provided on the preparation of study vaccine using diluents.	
Synopsis; 3.1 Overview of Study Design; 3.2 Study Design Rationale; 6.1 General Instructions and Procedures; 14.1 Physical Description of Study Vaccine	More information is provided on the extractable vial volumes and on the preparation of the study vaccine using diluents. Furthermore, it is clarified that vaccine components will be mixed at the pharmacy or at a designated product preparation area.
Rationale: Inclusion criterion 5 was updated to take into consideration the current United States cervical cancer screening guidelines.[30] A recent colposcopy result will be defined as a colposcopy result with a maximum of 12 months old at screening instead of less than 6 months old at screening.	
4.1 Inclusion Criteria	Update of inclusion criterion 5.
Rationale: Exclusion criterion 12 was changed to clarify that symptomatic vaginal or genital infection should be confirmed by the physician or investigator.	
4.2 Exclusion Criteria	Update of exclusion criterion 12.
Rationale: The procedure for identifying persistent HPV infection is clarified.	
Synopsis; Time and Events Schedule; 4.1 Inclusion Criteria; 9.2.3 Virology and Histology	The text explaining the different possibilities in the identification of persistent HPV infection is replaced by a flow chart.
Rationale: Change in the instructions on the use of the cervico-vaginal brush.	

Applicable Section(s)	Description of Change(s)
9.1.3 Screening Period; 9.2.3 Virology and Histology; Attachment 2	Attachment 2 was removed and replaced in the text by a reference to the Laboratory Manual.
Rationale: Change in the list of manuals.	
15. Study-Specific Materials	The Study Procedure Manual is removed from the study-specific materials list, because this document is not used in this study.
Rationale: Change of the terminology.	
14.1 Physical Description of Study Vaccine	The term solution is replaced by the term suspension for the MVA.HPV16/18 vaccine.
Synopsis; Time and Events Schedule; 2.1 Objectives and Endpoints; 9.1.3 Screening Period; 9.1.4 Vaccination and Follow-up Period; 9.2.3 Virology and Histology; 11.6 Virology Analyses	The term physician is replaced by the term healthcare provider when used in association with the collection of cervical samples.
14.4 Study Vaccine Accountability	The vaccine return form is replaced by the investigational product destruction form.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (24 May 2018)

The overall reason for the amendment: Simplify the design of the study and address FDA feedback received during the IND review (March 2018).

Applicable Section(s)	Description of Change(s)
Rationale: Amending the study design to a non-adaptive Phase 1/2a design.	
Synopsis; 1. Introduction; 3. Study Design and Rationale; 5. Study Vaccine Allocation and Blinding; 6. Dosage and Administration; 9. Study Evaluations; 10. Participant Completion/Discontinuation of Study Vaccine/Withdrawal from the Study; 11. Statistical Methods; 14.3 Storage and Handling; 16.1 Study-Specific Design Considerations	Implementation of a Phase 1/2a study design, with an ascending dose component and a staggered time interval between the vaccination of each participant in Phase 1 and study safety reviews with pauses.
Synopsis; 2. Objectives, Endpoints and, Hypothesis;	Objectives and endpoints adjusted to match the new study design.
11.10 Study Safety Rules	Addition of Study Stopping Rules
Synopsis; Time and Events Schedule; 3.1 Overview of Study Design; 9. Study Evaluations; 11.7 Planned analysis	Deletion of the immunogenicity evaluations at the Visit 2 months post final vaccination and addition of a Visit 6 months post Dose 1.

Applicable Section(s)	Description of Change(s)
Rationale: Safety criteria are provided to determine that it is safe to initiate the Phase 2a component of the study, the pooled assessment of safety will now be reviewed by an external IDMC and study stopping rules are added.	
Synopsis; 3.1 Overview of the Study Design; 5. Study Vaccine Allocation and Blinding; 9.2.1 Safety; 11.7 Planned Analysis; 11.8 Independent Data Monitoring Committee; 11.9 Study Vaccination Pausing and Stopping Rules	Change of DRC to an IDMC.
Synopsis; 11.9 Study Vaccination Pausing and Stopping Rules	Addition of study stopping rules.
Rationale: More information on the vaccine candidates is provided.	
1.1 Background	Addition of more background information on the other vaccine candidates.
Rationale: Providing the FDA toxicity tables in the protocol.	
Attachment 3	Providing the toxicity tables as an attachment to the protocol.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Randomized, Double-blind, Placebo-controlled First-in-Human, Phase 1/2a Study to Evaluate the Safety, Reactogenicity and Immunogenicity of Monovalent HPV16 and HPV18 Ad26-vectored Vaccine Components and an MVA-vectored HPV16/18 Vaccine Component in Otherwise Healthy Women with HPV16 or 18 Infection of the Cervix

The vaccine candidates to be evaluated in this study are:

- Ad26.HPV16 (JNJ-63682918), a recombinant replication-incompetent serotype 26 adenovirus (Ad26) vector encoding genetically modified human papillomavirus (HPV)16 early (E2, E6 and E7) proteins.
- Ad26.HPV18 (JNJ-63682931), a recombinant replication-incompetent Ad26 vector encoding genetically modified HPV18 early (E2, E6 and E7) proteins.
- MVA-mBN411B (JNJ-65195208) (referred to as MVA.HPV16/18 in this document), a live, modified vaccinia Ankara (MVA) – Bavarian Nordic A/S (BN) MVA-BN® vaccine which is non-replicating in human cells and encodes the same genetically modified HPV16 and HPV18 early (E2, E6 and E7) proteins.

In this Phase 1/2a study, there will be 3 heterologous vaccine regimens administered on Day 1 and 57 (Week 8, refer to Table 1):

- Regimen 1 (low dose single, Ad26.HPV16 or Ad26.HPV18 at $5x10^{10}$ viral particles [vp] followed by MVA.HPV16/18 at $2x10^{8}$ infectious units [Inf.U]).
- Regimen 2 (high dose single, Ad26.HPV16 or Ad26.HPV18 at $1x10^{11}$ vp followed by MVA.HPV16/18 at $2x10^{8}$ Inf.U).
- Regimen 3 (mixing of Ad26.HPV16 at $5x10^{10}$ vp + Ad26.HPV18 at $5x10^{10}$ vp, followed by MVA.HPV16/18 at $2x10^{8}$ Inf.U).

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

a) Objectives and endpoints

Primary

Objectives	Endpoints
To assess safety and reactogenicity of the 3 vaccine regimens.	• Solicited local and systemic adverse events (AEs) for 7 days after each vaccination. • Unsolicited AEs from the time of informed consent form (ICF) signature until 28 days after the first vaccination, and thereafter, until 28 days after the second vaccination. • Serious adverse events (SAEs) throughout the study.

Secondary

Objectives	Endpoints
To assess immunogenicity of the 3 vaccine regimens.	T cell responses to the separate or combined protein peptide pools of HPV16 and HPV18 E2, E6 and E7 proteins, including specific $CD4^+$ and $CD8^+$ T cells producing interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα), or IL-2 (combined cytokine expression may also be assessed) will be determined by flow cytometry.

Exploratory

Objectives	Endpoints
To assess the frequency and kinetics of clearance of • persistent or recently diagnosed HPV16 and HPV18 infection (combined[a]) and • persistent or recently diagnosed HPV16 infection and • persistent or recently diagnosed HPV18 infection of the 3 vaccine regimens compared to placebo over the study period.	Healthcare provider- and self-collected cervical samples obtained over the study period will be genotyped by a qualitative HPV genotyping test (Cobas®, Roche) and a quantitative HPV PCR genotyping test to evaluate HPV16 and/or HPV18 viral clearance[b], defined as: • A negative HPV16 genotype over the study period after having a baseline HPV16 infection (persistent or recently diagnosed); OR • A negative HPV18 genotype over the study period after having a baseline HPV18 infection (persistent or recently diagnosed).
To assess regression of CIN1 and concomitant clearance of HPV16 and/or HPV18 infection of the 3 vaccine regimens compared to placebo over the study period.	• Regression of CIN1: A colposcopic impression of normal after having a baseline of CIN1, AND concomitant clearance of baseline (persistent or recently diagnosed) HPV16 and/or HPV18 infection (as defined above).
To further characterize vaccine-elicited immune responses.	These assessments will include, but are not limited to, the assessments described below. Some of the exploratory assessments will only be initiated if indicated by the secondary immunogenicity data. Cell-mediated • Flow cytometry to characterize other cellular immune responses to the separate or combined protein peptide pools of HPV16 and HPV18 E2, E6 and E7 proteins, including, but not limited to, mucosa-homing markers, Th17, Th2, regulatory T cell (Treg), cytolytic markers, activation markers, and exhaustion markers. • Transcriptome analysis to provide phenotypic and functional characterization of peripheral blood mononuclear cells (PBMCs) ex vivo or after stimulation with either HPV16 and/or HPV18 E2, E6, and/or E7 peptide pools. • Enzyme-linked immunospot (ELISpot) assay to

Objectives	Endpoints
	enumerate PBMCs able to produce IFNγ upon stimulation with HPV16 and/or HPV18 E2 (complete, N-terminal, or C-terminal), E6 and/or E7 protein peptide pools. • ChipCytometry analysis of T cell responses to the separate or combined protein peptide pools of HPV16 and/or HPV18 E2, E6, and E7 proteins in PBMCs, including but not limited to $CD4^+$ and $CD8^+$ T cells producing IFNγ, TNFα and/or IL-2. <u>Humoral</u> • Adenovirus neutralization assay to evaluate neutralizing antibody responses against the Ad26 vector. • MVA neutralization assay to evaluate neutralizing antibody responses against the MVA vector. • Antibody responses to the HPV16 and/or HPV18 capsid proteins L1 and/or L2 can be measured to investigate levels of HPV-specific antibodies before vaccination (not induced by vaccination with either Ad26.HPV16 or Ad26.HPV18), as well as induction of L1/L2 antibodies after vaccination as a "bystander" effect due to release of these proteins from infected cells after vaccine-mediated cytolytic T cell responses. L1/L2 antibodies to other HPV genotypes might also be measured. • Antibody responses to E2, E6 and/or E7 of HPV16 and/or HPV18, or to these proteins of other HPV genotypes, can be evaluated.[49]
• To explore potential immune correlates for viral clearance.	• Immunogenicity endpoints of HPV-specific cellular or humoral responses described above, determined at multiple time points after vaccination will be used to explore potential immune correlates of viral clearance of HPV16 and/or HPV18.

[a] The sum of women who clear an HPV16 infection plus women who clear an HPV18 infection.
[b] Women who receive CIN treatment will be considered as not clearing an HPV infection.

b) Hypothesis

No formal statistical hypothesis for safety or immunogenicity will be tested.

OVERVIEW OF STUDY DESIGN

This is a multicenter, randomized, placebo-controlled, double-blind, safety, reactogenicity and immunogenicity Phase 1/2a study of 3 heterologous vaccine regimens with the Ad26.HPV16, Ad26.HPV18 and MVA.HPV16/18 recombinant vectors (Table 1). Vaccination will take place on Day 1 and Day 57. Study participants include approximately 66 women ≥18 to ≤60 years old with HPV types 16 or 18 infection of the cervix.[8]

Vaccination and safety monitoring among the HPV16 infected participants may occur independently from the HPV18 infected participants because the rates of enrollment of women with these 2 HPV types may differ as cervical HPV16 infections are more prevalent than HPV18 infections.

An Independent Data Monitoring committee (IDMC) will be commissioned for this study to evaluate safety data over the course of the study and to review any event that meets a specific study pausing rule, stopping rule, or any other safety issue that may arise.

The IDMC will consist of members independent of the sponsor, including at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The IDMC responsibilities, authorities and procedures will be documented in its charter. The IDMC will review unblinded data (refer to Section 11.8 and Section 11.9 of the protocol for more details).

Randomization, vaccination and safety evaluation

The randomization, vaccination process and safety evaluations described below for HPV16 infected participants will be performed in the same manner and independently among HPV18 infected participants.

HPV16 infected participants (see Table 1)

Dose 1 (Ad26-based)

Phase 1 (Dose Escalation)

- Step 1 [sentinels with low dose or placebo]: The first 2 participants (sentinels) will receive either a low dose Ad26.HPV16 (1 participant) or placebo (1 participant). Dosing of these 2 participants may occur on the same day depending on enrollment rates. Vaccination of additional participants will be halted until a 24-hour and 7-day post vaccination blinded safety review of solicited and unsolicited AEs are performed by the principal investigator (PI) and the sponsor's study responsible physician (SRP).

- Step 2 [completion of Phase 1 with low dose or placebo]: In the absence of clinically significant findings in participants from step 1, 4 additional participants will be dosed: 3 participants will receive low dose Ad26.HPV16 and 1 participant will receive placebo. There will be a staggered interval of 7 days between the vaccination of each of these 4 participants. Vaccination of additional participants will be halted until a 7-day post vaccination safety review of solicited and unsolicited AEs and clinical laboratory results is performed by an Independent Data Monitoring Committee (IDMC) of participants in step 1 and step 2.

- Step 3 [sentinels for dose escalation with high dose or mixed regimen or placebo]: If the IDMC expresses no concerns on the safety data from the HPV16 participants in steps 1 and 2, and the first 2 HPV18 sentinels from step 1[a], then 3 additional sentinel participants will be dosed: 1 participant will receive a high dose Ad26.HPV16, 1 participant will receive the Ad26.HPV16/Ad26.HPV18 mix and 1 participant will receive placebo. Dosing of these 3 participants may occur on the same day depending on enrollment rates. Vaccination of additional participants will be halted until a 24-hour and 7-day post vaccination blinded safety review of solicited and unsolicited AE are performed by the PI and SRP.

[a]No Ad26.HPV16/Ad26.HPV18 mix regimen will be administered until review of 2 sentinels HPV18 data in step 1.

- Step 4 [completion of Phase 1 with high dose or mixed regimen or placebo]: In the absence of clinically significant findings in participants from step 3, 8 additional participants will be dosed: 3 participants will receive high dose Ad26.HPV16, 3 will receive the Ad26.HPV16/Ad26.HPV18 mix and 2 participants will receive placebo. There will be a staggered interval of 7 days between the vaccination of each of these 8 participants. Vaccination of additional participants will be halted until a 7-day post vaccination safety review of solicited and unsolicited AE and clinical laboratory results of participants in step 3 and step 4 and all available safety data of participants in step 1 and 2 is performed by the IDMC.

Phase 2a (Further Vaccination)

- Step 5 [further vaccination with high dose or mixed regimen or placebo]: If the IDMC expresses no safety concerns on the safety data from participants in steps 1-4 and no participant has experienced the criteria that determine it is not safe to initiate the Phase 2a component of the study (see Section 11.8 and 11.9), 16 additional participants will be randomized and dosed: 6 participants will receive high dose Ad26.HPV16, 6 will receive the Ad26.HPV16/Ad26.HPV18 mix and 4 participants will receive placebo. No more than 5 participants per week will be dosed.

Dose 2 (MVA-based)

Phase 1

Completion of IDMC review in step 2 above will also allow the second dose vaccination with MVA.HPV16/18 or placebo of the sentinel participants in step 1[a]. Safety reviews after MVA/placebo vaccinations will follow the same scheme as for the Ad26 vaccinations, ie, a 24-hour and 7-day post vaccination blinded safety review by the PI/SRP will be performed after the MVA/placebo vaccinations of step 1 and 3 sentinel participants and an aggregated 7-day safety review will be performed by the IDMC when the MVA/placebo vaccinations of participants in step 2 and 4 have been completed.

Phase 2a

If the IDMC expresses no safety concerns on the MVA.HPV16/18 / placebo data from participants in Phase 1, the 16 participants from Phase 2 will be dosed with MVA.HPV16/18 or placebo.

The ***HPV18 infected participants*** will follow the same process as described above for the HPV16-infected participants. Vaccination and safety monitoring may occur independently to the HPV16 infected participants (see Table 1).

[a] An ad-hoc IDMC review of all available safety data may take place in case not all participants from step 1 and 2 have been enrolled by the time the first MVA vaccination needs to take place.

Table 1: Study Design

	Vaccine Regimen			Phase 1					Phase 2a	
HPV Type*	**Regimen**	**Day 1**	**Day 57 (Week 8)**	**Step 1 sentinel; low dose**	**Step 2 completion Phase 1; low dose**	**Step 3 sentinel dose escalation high & mixed regimens**	**Step 4 completion Phase 1; high & mixed regimens**	**Subtotal**	**Step 5 further vaccination; high & mixed regimens**	**Total**
16	Regimen 1a (Ad26 low dose)	Ad26.HPV16 ($5x10^{10}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	1	3	-	-	4	-	4
16	Regimen 2a (Ad26 high dose)	Ad26.HPV16 ($1x10^{11}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	-	-	1	3	4	6	10
16	Regimen 3 (mixing of Ad26)	Ad26.HPV16 ($5x10^{10}$ vp) + Ad26.HPV18 ($5x10^{10}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	-	-	1	3	4	6	10
16	Control	Placebo (1.0 mL)	Placebo (0.5 mL)	1	1	1	2	5	4	9
Total HPV16				2	4	3	8	17	16	33
18	Regimen 1b (Ad26 low dose)	Ad26.HPV18 ($5x10^{10}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	1	3	-	-	4	-	4
18	Regimen 2b (Ad26 high dose)	Ad26.HPV18 ($1x10^{11}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	-	-	1	3	4	6	10
18	Regimen 3 (mixing of Ad26)	Ad26.HPV16 ($5x10^{10}$ vp) + Ad26.HPV18 ($5x10^{10}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	-	-	1	3	4	6	10
18	Control	Placebo (1.0 mL)	Placebo (0.5 mL)	1	1	1	2	5	4	9
Total HPV18				2	4	3	8	17	16	33*
Total				4	8	6	16	34	32	66
					PI/SRP	IDMC	PI/SRP	IDMC		

Ad26=adenovirus serotype 26; HPV=human papillomavirus; Inf.U=infectious unit; MVA=modified vaccinia Ankara; vp=viral particles
* If enrollment is slow for HPV18-infected participants, up to 8 HPV18-infected participants can be replaced by HPV16-infected participants, hence a minimum of 25 HPV18 participants is required. The decision will be taken during Step 5.

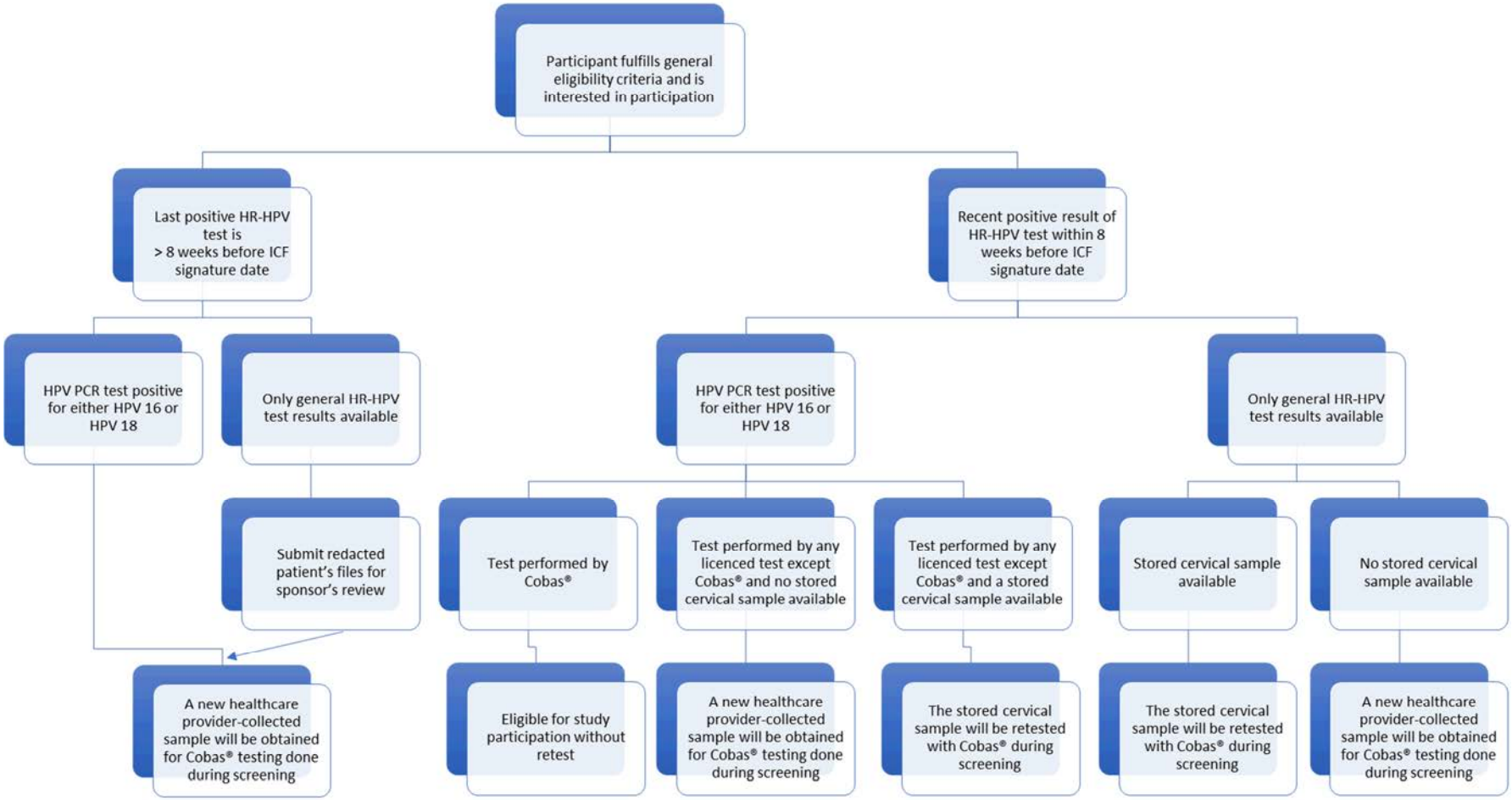
The study duration, from screening until the last follow-up visit, will be approximately 13.5 months per participant. The study consists of a screening period of up to 42 days (6 weeks), followed by vaccinations on Day 1 and Day 57, and follow-up visits up to 12 months after the first vaccination (target visit Day 366±14 days).

PARTICIPANT POPULATION

Study participants must be healthy (on the basis of physical examination, medical history, vital signs measurement, and clinical laboratory tests performed at screening) women, aged ≥18 to ≤60 years on the day of signing the ICF, with HPV type 16 or 18 infection of the cervix determined within 8 weeks prior to screening or at the time of screening.

Women with cytology of HSIL or AIS or a colposcopy result of CIN2+ will be excluded. For the identification of eligible participants see Figure 1.

Figure 1: Flow Chart for Identifying an HPV16 or HPV18 Infection Prior to Vaccination



DOSAGE AND ADMINISTRATION

The following will be used to prepare the study vaccines:

- Ad26.HPV16 (JNJ-63682918): supplied in a single use vial ($1x10^{11}$ vp/mL; 0.5 mL [extractable volume])
- Ad26.HPV18 (JNJ-63682931): supplied in a single use vial ($1x10^{11}$ vp/mL; 0.5 mL [extractable volume])
- MVA.HPV16/18 (JNJ-65195208): supplied in a single use vial ($5x10^{8}$ Inf.U/0.5 mL; 0.5 mL [extractable volume])
- Placebo (0.9% saline): supplied in a single use vial (10 mL [filled volume])
- Diluent (Diluent 5, DS-TEC-79875): supplied in a single use vial (1 mL [extractable volume]) and to be added to the Ad26.HPV16 or Ad26.HPV18 vials for administration of the Ad26.HPV16 or Ad26.HPV18 vaccines at a dose of $5x10^{10}$ vp
- Diluent (tris-buffered saline [TBS] Diluent, DS-TEC-138030): supplied in a single use vial (1.5 mL [extractable volume]), 1.0 mL is to be added to the MVA.HPV16/18 vial for administration of the MVA.HPV16/18 vaccine at a dose of $2x10^{8}$ Inf.U

For each participant, every vaccination with Ad26.HPV16 and/or Ad26.HPV18 will be 1.0 mL in volume. For the low dose of Ad26.HPV16 or Ad26.HPV18 ($5x10^{10}$ vp), 0.5 mL of Ad26.HPV16 or Ad26.HPV18 and 0.5 mL of diluent 5 (DS-TEC-79875) will be mixed and administered as a single injection. For the high dose of Ad26.HPV16 or Ad26.HPV18 ($1x10^{11}$ vp), two vials of 0.5 mL of Ad26.HPV16 or Ad26.HPV18 will be mixed and administered as a single injection. The monovalent Ad26.HPV16 ($5x10^{10}$ vp) and Ad26.HPV18 ($5x10^{10}$ vp), vaccine components will be mixed at the pharmacy or at a designated product preparation area and administered as a single injection; denoted by Ad26.HPV16/Ad26.HPV18 in this document.

Vaccination with MVA.HPV16/18 at a dose of $2x10^{8}$ Inf.U will be 0.5 mL in volume. Therefore, 1.0 mL of the diluent DS-TEC-138030 will be added to the vial of MVA.HPV16/18 (a concentration of $5x10^{8}$ Inf.U per 0.5 mL) and mixed at the pharmacy or at a designated product preparation area, and 0.5 mL of the mix will be administered as a single injection.

To allow blinding, the volume of placebo vaccine will be the same as the volume of the corresponding Ad26.HPV16, Ad26.HPV18 or MVA.HPV16/18 vaccine.

Vaccine regimens are presented in Table 1.

The vaccines will be administered by intramuscular injection into the deltoid muscle of either arm by a blinded study vaccine administrator. Opposite arms should be used for the MVA injection.

SAFETY EVALUATIONS

An IDMC will be established to monitor the safety data over the course of the study and to review any events that meet a specific study pausing rule, study stopping rule, or any other safety issue that may arise (refer to Section 11.8 and Section 11.9 of the protocol for more details).

Adverse events will be reported by the participant. Solicited AEs will be reported for 7 days after each vaccination. Unsolicited AEs will be reported from the time of ICF signature until 28 days after the first vaccination, and thereafter, until 28 days after the second vaccination. Serious adverse events and concomitant medications related to an SAE will be collected from the time of ICF signature until the end of the study.

Other safety assessments include clinical laboratory tests (hematology, biochemistry), vital signs measurements (heart rate, supine systolic and diastolic blood pressure, oral body temperature), and physical examinations at the time points indicated in the Time and Events Schedule.

IMMUNOGENICITY EVALUATIONS

Humoral and cellular immunogenicity assays may include but are not limited to the assays summarized in Table 2 and Table 3. Baseline and post-vaccination samples will be used for the characterization of immunological assays.

Table 2: Summary of Immunogenicity Assays (Cellular)

Assay	Purpose
Secondary endpoint	
ICS	Analysis of T cell responses to the separate or combined protein peptide pools of HPV16 and HPV18 E2, E6 and E7 proteins, including specific $CD4^+$ and $CD8^+$ T cells producing IFNγ, TNFα, or IL-2 (combined cytokine expression may also be assessed)
Exploratory endpoints	
ICS	Analysis of other cellular responses to the separate or combined protein peptide pools of HPV16 and HPV18 E2, E6 and E7 proteins (including, but not limited to, mucosa-homing markers, Th17, Th2, Treg, cytolytic markers, activation markers, exhaustion markers)
Transcriptome analysis	Analysis of gene expression patterns to provide phenotypic and functional characterization of PBMCs ex vivo or after stimulation with HPV16 and/or HPV18 E2, E6, and/or E7 peptide pools.
ELISpot responses	Enumeration of IFNγ-producing HPV16 and/or HPV18 E2 (complete, N-terminal, and/or C-terminal peptide pools), E6 and/or E7-specific T cells
ChipCytometry	Analysis of T cell responses to the separate or combined protein peptide pools of HPV16 and/or HPV18 E2, E6, and E7 proteins in PBMCs, including but not limited to $CD4^+$ and $CD8^+$ T cells producing IFNγ, TNFα and/or IL-2

ELISpot=enzyme-linked immunospot; HPV=human papillomavirus; ICS=intracellular cytokine staining; IFN=interferon; IL=interleukin; NK=natural killer: PBMC=peripheral blood mononuclear cell; Th=T-helper (cell); TNF=tumor necrosis factor; Treg=regulatory T cell

Table 3: Summary of Immunogenicity Assays (Humoral)

Assay	Purpose
Exploratory endpoints	
Adenovirus neutralization assay	Analysis of neutralizing antibodies to adenovirus vector
MVA neutralization assay	Analysis of neutralizing antibodies to MVA vector
L1/L2 ELISA	Analysis of L1 and/or L2 antibodies by ELISA to HPV16 and/or HPV18 or other HPV genotypes
E2, E6 and E7 ELISA	Analysis of E2, E6 and/or E7 antibodies to HPV16 and/or HPV18 or other HR-HPV genotypes

ELISA=enzyme-linked immunosorbent assay; HPV=human papillomavirus; HR-HPV=high-risk human papillomavirus; MVA=modified vaccinia Ankara

VIROLOGY AND HISTOLOGY EVALUATIONS

HPV16 and HPV18 genotyping will be performed with a qualitative PCR test (Cobas®, Roche) on the cervical samples. Prior to vaccination, a participant will have a confirmed diagnosis of an HPV16 or HPV18 infection. More information on the identification of HPV infection is provided in the flow chart (Figure 1).

Cervical samples will be collected by the healthcare provider and by the participant (self-sampling) at the time points indicated in the Time and Events Schedule. Cobas® testing will be performed by a central

sponsor designated laboratory. A quantitative HPV PCR genotyping test that detects HPV16 and HPV18 together with other individual HR-HPV types will be used on all cervical samples (healthcare provider-collected and self-collected).

The healthcare provider will be delegated by the PI and must be qualified by education, training, and experience as per local regulations to perform the delegated task.

Colposcopy examination will occur during screening only for those participants who do not have recent (within the last 12 months) examination results. A mandatory colposcopy examination will occur 12 months after the first dose for all participants. All colposcopy biopsy specimens will be sent to a central laboratory for standardized interpretation.

Management and medical follow-up after the mandatory colposcopy evaluation will be at the discretion of the investigator and local guidelines.

STATISTICAL METHODS

Sample Size Determination

While mild to moderate local and systemic AEs are expected, AEs that preclude further vaccination or more serious ones that would limit product development are not anticipated. With 20 participants in 1 vaccine regimen the observation of 0 such reactions after the first vaccination would be associated with a 95% confidence that the true rate is less than 13.9%. Across regimens (n=48), the observation of 0 such reactions after the first vaccination would be associated with a 95% confidence that the true rate is less than 6.1%.

Planned Analyses

A blinded interim analysis may be performed after all participants from Phase 1 of the study have completed the 21 days post-Dose 2 visit (Week 11) or have discontinued earlier. This analysis, which will include immunogenicity and safety data, will allow to identify immunogenicity and overall safety signals and guide further development of the vaccine.

The primary analysis will occur when all participants have completed the 6 months post-Dose 1 visit (Week 26) or have discontinued earlier. If enrollment is slow for HPV18-infected participants, an interim analysis may first be performed on the HPV16-infected participants. The primary analysis will then be performed on all participants when all HPV18 infected participants have completed the 6 months post-Dose 1 visit (Week 26) or have discontinued earlier. These analyses will include safety and virology data up to the 6 months post-dose 1 visit (Week 26) and immunogenicity data up to the 21 days post-Dose 2 visit (Week 11).

The final analysis will occur when the last participant completes the final visit at 12 months post-Dose 1 (Week 52, Day 366) or discontinued earlier to determine the durability of the immune response and analyze any additional safety, virology and immunological data collected after the primary analysis. If enrollment is slow for HPV18-infected participants, an interim analysis may first be performed on the HPV16-infected participants. The final analysis will then be performed on all participants when all HPV18 infected participants have completed the 12 months post-Dose 1 visit (Week 52) or have discontinued earlier.

The safety and immunogenicity analyses will include the timepoints described in the TIME AND EVENTS SCHEDULE. At the time of the primary analysis, the study will be unblinded for sponsor personnel (including medical personnel, biomarker lead, virologist, statistician, programming and data management). Participants, clinical staff and study-site personnel will remain blinded to the study vaccine allocation until the end of the study.

Safety Analyses

All safety analyses will be performed on the Full Analysis Set (FAS), which includes all participants with at least 1 vaccination. No formal statistical testing of safety data is planned. Safety data will be tabulated by vaccine regimens and pooled placebos and will be analyzed descriptively. The severity of abnormal symptoms, vital signs, AEs and abnormal laboratory values will be graded based on the adapted Food and Drug Administration (FDA) "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007)" (see Attachment 2).

Immunogenicity Analyses

The immunogenicity analyses will be performed on the Per-Protocol Immunogenicity (PPI) set, which will include all randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes. In addition, if participants miss the second dose, but continue the planned visit schedule, samples taken after the planned but missed dose will not be taken into account. An additional analysis will be done for the FAS.

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% CI, or median and quartile range [Q1-Q3], as appropriate) will be calculated for continuous immunological parameters at all time points. Graphical representations of immunological parameters will be made as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunological parameters as applicable.

Virology Analyses

The analyses will be performed on the FAS, including participants for whom virology endpoint measures are available.

Frequency and kinetics of clearance of HPV16 and HPV18 infection will be analyzed either combined or by HPV type (HPV16, HPV18), and by infection type (persistent or recently diagnosed), using both the healthcare provider- and self-collected cervical samples and will be described for the vaccine regimens and placebo during the study duration.

TIME AND EVENTS SCHEDULE

Study Period	***SCRN***	***ACTIVE***

Clinic Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Early Exit** [a]
Study Week #		**0**		**1**	**4**	**8**		**9**	**11**	**12**	**16**	**26**	**34**	**52**	
Target Visit Timing		**DOSE 1**	**Dose 1 + 1 d**	**Dose 1 + 7 d**	**Dose 1 + 28 d**	**DOSE 2**	**Dose 2 + 1 d**	**Dose 2 + 7 d**	**Dose 2 + 21 d**	**Dose 2 + 28 d**	**Dose 2 + 8wks (2 mo)**	**Dose 1 + 6 mo**	**Dose 2 + 6 mo**	**Dose 1 + 12 mo**	
Visit Day [b]	**-42to -2**	**1**	**2**	**8±2**	**29±3**	**57±7** [b]	**58** [b]	**64±2** [b]	**78±3** [b]	**85±3** [b]	**113±5** [b]	**183±14** [b]	**239±14** [b]	**366±14** [b]	
Visit Type	Screening	Randomization and **Dose 1** Safety, Immuno and Virology	Safety (only for sentinels in Step 1 & 3; telephone)	Safety	Safety (telephone)	**Dose 2** Safety, Immuno and Virology	Safety (only for sentinels in Step 1 & 3; telephone)	Safety	Safety, Immuno and Virology	Safety (telephone)	Safety; Virology	Safety, Virology	Safety, Immuno and Virology	Safety, Immuno and Virology	Early Exit
Written informed consent [c]	●														
Inclusion/exclusion criteria	●	❶ [d]													
Demographics	●														
Medical history/pre-study meds	●														
Physical examination [e]	●	❶		●		❶		●	●		●	●	●	●	●
Vital signs [f] incl. oral temperature	●	❸		●		❸		●	●		●	●	●	●	●
Healthcare provider-collected cervical sample for HPV16 and HPV18 PCR [g]	●													●	●
Self-collected cervico-vaginal sample for HPV16 and HPV18 PCR [h]	●	❶				❶			●		●	●	●	●	●
Serum pregnancy test (women of childbearing potential only)	●														
Urine pregnancy test (women of childbearing potential only)		❶				❶									
Prevaccination symptoms check [i]		❶				❶									
Randomization		❶													
Colposcopy[n]	●													●	
HSV-2 serology test		❶												●	●
Safety laboratory blood sample (mL)[j]	❻ 15			● 10				● 10							
Humoral immunity (serum), mL [j]		❶ 10							● 10					● 10	● 10
Cellular immunity (whole blood), mL [j]		❶ 100				❶ 60			● 100				● 60	● 100	● 100
Vaccination		●				●									
30-minute post-vaccination observation [k]		●				●									
Solicited AE recording		- - - - - *Continuous* - - - - -				- - - - - *Continuous* - - - - -									❼
Unsolicited AE recording	- - - - - - - - - - *Continuous* - - - - - - - - - -					- - - - - - - - - - - - *Continuous* - - - - - - - - - - - -									❽
SAE recording		- *Continuous* -													●

Clinic Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Early Exit** [a]
Study Week #		**0**		**1**	**4**	**8**		**9**	**11**	**12**	**16**	**26**	**34**	**52**	
Target Visit Timing		**DOSE 1**	**Dose 1 + 1 d**	**Dose 1 + 7 d**	**Dose 1 + 28 d**	**DOSE 2**	**Dose 2 + 1 d**	**Dose 2 + 7 d**	**Dose 2 + 21 d**	**Dose 2 + 28 d**	**Dose 2 + 8wks (2 mo)**	**Dose 1 + 6 mo**	**Dose 2 + 6 mo**	**Dose 1 + 12 mo**	
Visit Day [b]	**-42to -2**	**1**	**2**	**8±2**	**29±3**	**57±7** [b]	**58** [b]	**64±2** [b]	**78±3** [b]	**85±3** [b]	**113±5** [b]	**183±14** [b]	**239±14** [b]	**366±14** [b]	
Visit Type	Screening	Randomization and **Dose 1** Safety, Immuno and Virology	Safety (only for sentinels in Step 1 & 3; telephone)	Safety	Safety (telephone)	**Dose 2** Safety, Immuno and Virology	Safety (only for sentinels in Step 1 & 3; telephone)	Safety	Safety, Immuno and Virology	Safety (telephone)	Safety; Virology	Safety, Virology	Safety, Immuno and Virology	Safety, Immuno and Virology	Early Exit
Concomitant medications [l]		*Continuous*													
Participant diary, ruler and thermometer distribution		●				●									
Participant diary review [m]			❷	❾			❷	❾							
Approx. daily blood draw (mL)	15	110	–	10	–	60	–	10	110	–	-	-	60	110	110
Approx. cumulative blood draw (mL)	15	125	125	135	135	195	195	205	315	315	315	315	375	**485**	–

❶ pre-dose; ❷ check of diary during the telephone call; ❸ pre- and post-dose; ❻ to include HIV-1/2 and hepatitis B/C serology, laboratory tests at screening are to be done within 42 days of randomization, retesting of laboratory values not meeting eligibility criteria at the screening visit is allowed once using an unscheduled visit during the 42-day screening period, at the discretion of the investigator; ❼ if within 7 days of the previous vaccination; ❽ if within 28 days of the previous vaccination; ❾ diary card collection

a. For those participants who are unable to continue participation in the study up to Week 52, but for whom consent is not withdrawn, an exit visit will be conducted as soon as possible.
b. The timing of the second vaccination and of Visit 12 will be determined relative to the actual day of the first vaccination. The timing of visits 7, 8, 9, 10, 11 and 13 will be determined relative to the actual day of the second vaccination.
c. Signing of the ICF should be done before any study-related activity.
d. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study vaccination is given such that she no longer meets all eligibility criteria, then the screening laboratory tests should be repeated and the Day 1 visit re-scheduled, or the participant should be excluded from participation in the study.
e. A full physical examination, including height and body weight, will be carried out at screening. At other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.
f. Heart rate and blood pressure measurements should be taken in supine position and preceded by at least 5 minutes of rest. Vital signs measurements should be performed before blood sampling. Body temperatures should be measured via the oral route.
g. HPV16 and HPV18 genotyping will be performed with a qualitative PCR test (Cobas®, Roche) on the cervical samples. More information on the identification of HPV16 or HPV18 infection is provided in the flow chart in Section 4.1.
h. Self-sampling for HPV16 and HPV18 PCR will be performed before healthcare provider-sampling of a cervical swab when procedures are indicated on the same day.

i. Investigator must check for acute illness or body temperature ≥38.0°C/100.4°F at the time of vaccination. If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor's medical monitor should be contacted for further guidance.
j. If a situation arises where a study blood draw and vaccination with a licensed vaccine occur on the same day, the blood draw should be made before the vaccination.
k. After vaccination, participants will remain under observation at the study site for at least 30 minutes. Any solicited local (at injection site) and systemic AEs, unsolicited AEs, SAEs, concomitant medications, and vital signs will be documented by study-site personnel following this observation period and participants will be allowed to leave the study site at approximately 45 minutes post-vaccination.
l. Following the 28th day after each vaccination, only concomitant medications associated to SAEs will be recorded.
m. If an event is still ongoing on Day 8 or Day 64 the participant should keep the diary after the review and collect information until resolution. The diary should be reviewed again at the next visit.
n. The screening colposcopy will be performed as study procedure only if a result of colposcopy performed within last 12 months is not available.

AE=adverse event; d=day; FU=follow-up; HIV=human immunodeficiency virus; HR-HPV=high-risk human papillomavirus; ICF=informed consent form; immuno=immunology; mo=month; PBMC=peripheral blood mononuclear cell; PCR=polymerase chain reaction; PI=principal investigator; SAE=serious adverse event; SRCN=screening; SRP=study responsible physician

ABBREVIATIONS

Ad26	adenovirus serotype 26
AE	adverse event
AIS	adenocarcinoma in situ
BN	Bavarian Nordic (A/S)
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CSR	Clinical Study Report
DNA	deoxyribonucleic acid
eCRF	electronic case report form
eDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
ER	emergency room
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First-in-Human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
β-hCG	β-human chorionic gonadotropin
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR	high-risk
HSIL	high-grade squamous intraepithelial lesion
ICF	informed consent form
ICH	International Council on Harmonisation
ICS	intracellular cytokine staining
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFNγ	interferon gamma
IL	interleukin
IRB	Institutional Review Board
Inf.U	infectious unit
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MRK	Merck
MVA	modified vaccinia Ankara
NK	natural killer (cell)
NSAID	non-steroidal anti-inflammatory drug
p53	tumor suppressor protein 53
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	principal investigator

PP	Per-Protocol
PPE	Per-Protocol Efficacy
PPI	Per-Protocol Immunogenicity
PQC	Product Quality Complaint
pRb	retinoblastoma protein
Q	quartile
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SRP	study responsible physician
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBS	tris-buffered saline
$TCID_{50}$	50% tissue culture infectious dose
Th	T-helper (cell)
Treg	regulatory T cell
TNFα	tumor necrosis factor alpha
US	United States
VCR	viral clearance rates
vp	viral particles

DEFINITIONS OF TERMS

HPV type:	HPV16 or HPV18
HPV infection type:	persistent or recently diagnosed

1. INTRODUCTION

The vaccine candidates to be evaluated in this First-In-Human (FIH) study are:

- Ad26.HPV16 (JNJ-63682918), a recombinant replication-incompetent serotype 26 adenovirus (Ad26) vector encoding genetically modified human papillomavirus (HPV) 16 early (E2, E6 and E7) proteins.
- Ad26.HPV18 (JNJ-63682931), a recombinant replication-incompetent Ad26 vector encoding genetically modified HPV18 early (E2, E6 and E7) proteins.
- MVA-mBN411B (JNJ-65195208), a live, modified vaccinia Ankara (MVA) – Bavarian Nordic A/S (BN) MVA-BN® vaccine which is non-replicating in human cells and encodes the same genetically modified HPV16 and HPV18 early (E2, E6 and E7) proteins.

  MVA-mBN411B is referred to as MVA.HPV16/18 in this document.

In this Phase 1/2a study, there will be 3 heterologous vaccine regimens administered in a 2-dose schedule on Day 1 and Day 57 (Week 8, refer to Table 4):

- Regimen 1 (low dose single, Ad26.HPV16 or Ad26.HPV18 at $5x10^{10}$ viral particles [vp] followed by MVA.HPV16/18 at $2x10^{8}$ infectious units [Inf.U])
- Regimen 2 (high dose single, Ad26.HPV16 or Ad26.HPV18 at $1x10^{11}$ vp followed by MVA.HPV16/18 at $2x10^{8}$ Inf.U)
- Regimen 3 (mixing of Ad26.HPV16 at $5x10^{10}$ vp + Ad26.HPV18 at $5x10^{10}$ vp, followed by MVA.HPV16/18 at $2x10^{8}$ Inf.U).

For the most comprehensive nonclinical and clinical information regarding Ad26.HPV16, Ad26.HPV18 and MVA.HPV16/18, refer to the latest version of the Investigator's Brochures for Ad26.HPV16, Ad26.HPV18 and MVA.HPV16/18.

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

1.1. Background

HPV Infection and Disease Burden

Among the more than 150 known HPV types, 40 are sexually transmitted and, of these, about 13 are known to be oncogenic or high-risk (HR)-HPV types.[53] Genital HPV infection is the most common sexually transmitted infection; most sexually active men and women acquire HPV at some point in their lives. In a national health and nutrition survey in the United States (US) covering the period 2011-2014, the prevalence of any HPV infection was 26.1% among females 14-19 years of age, increasing to 59.8% among females 20-24 years of age.[26] HR-HPV types are the cause of almost all cervical cancers[53] and a large proportion of other anogenital cancers. Around 90% of cervical HPV infections are cleared within 5 to 7 years[42]; however, in a minority of infected women (~1%), HPV may ultimately give rise to genital neoplastic lesions. Cervical cancer led to approximately 266,000 deaths worldwide in 2012, with the biggest burden of the disease in low-income countries.[55] Among the HR-HPVs, HPV16 and HPV18 are the most

prevalent types in both low-grade and advanced disease.[24] HR-HPV types 16 and 18 have been established to be the underlying causative agents of more than 50% of cervical pre-cancerous lesions, and more than 70% of cervical cancer cases worldwide.[13,20]

The 3 prophylactic HPV vaccines that are currently on the market, bivalent Cervarix® (directed against HR-HPV16 and 18), tetravalent Gardasil® (directed against HPV6 and 11, and HR-HPV16 and 18) and nonavalent Gardasil® (directed against HPV6 and 11, and HR-HPV16, 18, 31, 33, 45, 52 and 58), prevent infection through the induction of neutralizing antibodies against the major capsid protein L1.[29] However, the prophylactic vaccines suffer from some drawbacks: firstly, they have no therapeutic effect on established HPV-induced genital lesions.[19,21,26,27,28,51] Secondly, the vaccine uptake is well below expectations: in 2013 in the US, only 38% of females 13-17 years of age who were eligible for prophylactic HPV vaccination completed the 3-dose course of therapy, suggesting that many people may be entering their sexually active years without protection against these HR-HPVs.[7] Finally, these vaccines are not indicated for people over the age of 26 years, leaving a large age group unprotected.

Thus, a therapeutic HPV vaccine for the eradication of persistent HR-HPV infections and associated diseases such as cervical intraepithelial neoplasia (CIN) is an urgent unmet medical need.

Progression of HR-HPV-positive CIN into cervical cancer is associated with the failure of the human immune system to induce an adequate HPV-specific T cell response.[17,54] With each CIN stage, the likelihood of progression to cervical cancer increases, underscoring the medical need to stop progression by clearing HPV infection as early as possible. An efficacious therapeutic HPV vaccine most likely needs to elicit strong cellular immune responses, at least against HPV16 and HPV18 and ideally other HR-HPVs. Although the first targets would be clearance of persistent HR-HPV and treatment of CIN stage 1, such a vaccine is likely to have wider applications, because HR-HPV, and particularly HPV16, has been implicated as the causative agent in several other cancers, including vulvar, penile, anal, and oropharyngeal cancers.[44]

HPVs are double-stranded deoxyribonucleic acid (DNA) viruses that encode only a small number of viral proteins. HPV infection targets the cells of the basal epithelial layer. Limited viral replication is accompanied by expression of a number of "early" proteins, such as E2. Viral genomes are maintained as episomes and viral gene expression is tightly controlled as the infected cells move towards the epithelial surface. HPV does not induce cytolysis or cell death, and viral replication and release are not associated with inflammation.[15] Failure to develop an effective cell-mediated immune response to clear or control infection results in persistent infection and, in the case of the oncogenic HPVs, an increased probability of progression to intraepithelial neoplasias and invasive carcinoma.[45] Two "early" proteins, E6 and E7, promote cell proliferation and delay differentiation. During disease progression, the HPV DNA is integrated into the host genome, which coincides with the loss of E2 expression and deregulation of expression of E6 and E7. Increased expression of E7 leads to the degradation of retinoblastoma protein (pRb), which contributes to neoplastic progression, while E6-mediated degradation of the tumor suppressor protein 53 (p53) leads to loss of its functional activities such

as growth-arrest and induction of apoptosis.[18] As a consequence, increased expression of E6 and E7 proteins leads to cell proliferation and eventually immortalization.[15] In summary, cancers usually arise in individuals who fail to resolve their infection and who retain oncogene expression for years or even decades.

Different therapeutic HPV vaccine candidates are currently in clinical development. Most of these target the E6 and E7 proteins of HPV16 and HPV18 and are evaluated in women with high-grade cervical neoplasia (CIN2/3) or cervical cancer.[25] In the Ad26.HPV16/Ad26.HPV18 and MVA-BN-HPV16/18 vaccine vectors the E2 gene is included, in addition to E6 and E7. With this inclusion of E2, the vaccine vectors would treat both early and later stages of disease and the initial focus is on women with normal histology or low-grade cervical neoplasia (not worse than CIN1). Treatment in an early stage of disease is assumed to be less impacted by the immune suppression environment of the infected cells, which increases with disease severity.[41]

In several countries, the screening algorithm for cervical cancer is changing. Detection of HPV DNA instead of detection of abnormal cells in cervical smears is expected to become the primary diagnosis in the triage for HPV-related disease. With DNA-based screening, a large number of HPV16- or HPV18-positive women will be identified who will have normal cytology or low-grade dysplasia upon further testing. The aim of the therapeutic HPV vaccine candidates is to clear HPV persistent infections to reduce the risk of disease progression.

Background Information on the Product

Natural resolution of HPV16-related disease has been shown to be correlated with cellular immune responses against the E2 protein,[11,14,54] and persistence of low-grade lesions or progression of such lesions is associated with an inadequate immune response against the early antigens E6 and E7.[54,12,40] E2 has higher expression levels in early stages of HPV-induced disease (low-grade neoplasia) than in later stages. Upon integration into the host chromosome, E2 expression is lost, resulting in the upregulation of E6 and E7. Given the expression of these 3 proteins in the different disease stages, the sponsor-designed HPV16- and HPV18-specific vaccine antigens contain these 3 proteins, with the intention to treat early stages of HPV-induced disease. Inclusion of E6 and E7 in the vaccine could help to prevent progression to higher grade disease, as E6- and E7-specific T-cell responses have been shown to play a role in the prevention of neoplastic lesions.

Vaccine Candidates

The HPV16- and HPV18-directed therapeutic vaccine candidates Ad26.HPV16 and Ad26.HPV18 were developed based on replication-incompetent recombinant vectors derived from human adenovirus of the serotype 26. Replication-incompetent adenoviral vectors are particularly interesting vaccine candidates in the context of therapeutic vaccination due to their proven ability to induce strong cellular immunity to the transgenes they encode.[1,4,9,38,39]

These strong T cell responses, comprising interferon gamma (IFNγ) secreting $CD8^+$ and $CD4^+$ T cell responses, have been observed in 4 clinical trials using adenoviral vector-based vaccines, targeting human immunodeficiency virus (HIV) (Ad26.ENVA.01)[1], ebola (Ad26.ZEBOV in

combination with MVA.filo)[38], malaria (Ad35.CS.01)[39], and tuberculosis (TB) (Ad35.TB-S).[9] In addition, prime-boost immunizations with Chimpanzee adenovirus 63 and MVA vectors have been shown to induce strong $CD4^+$ and $CD8^+$ response against HCV antigens in humans.[56]

E6 and E7 are viral oncogenes that are responsible for transformation of cells and, therefore, special consideration was given to the safety of these proteins expressed by the vaccine candidates. Thus, the coding regions of E6 and E7 were divided into multiple fragments and subsequently reorganized (shuffled) into a new order, resulting in the expression of a fusion protein (abbreviated as $E6E7^{SH}$) without oncogenic properties, as shown in non-clinical studies. E2 was incorporated as an N-terminal fusion to $E6E7^{SH}$. Three amino acid changes were introduced into the DNA-binding site of E2 to prevent possible effects on viral gene expression, resulting in a fusion protein (abbreviated as $E2E6E7^{SH}$).

Non-Clinical data of Ad26.HPV16/Ad26.HPV18 and MVA.HPV16/18

Strong cellular immune responses after prime-boost immunization with Ad26.HPV16/Ad26.HPV18 and MVA-BN-HPV16/18 vectors were shown in mouse and monkey non-clinical models (Studies DS-TEC-119232 and DS-TEC-117650). In the absence of HPV permissive animal models, the mouse lung tumor cell line TC-1 (derived from primary lung epithelial cells of C57BL/6 mice) was used to show that the vaccine vectors have therapeutic efficacy (Study DS-TEC-109230).

Non-Clinical Safety of Ad26HPV16 or HPV18

Absence of the oncogenic properties of E6 and E7 in the $E2E6E7^{SH}$ fusion proteins was demonstrated in 3 different in vitro models[31] (Study DS-TEC121377). Expression of the $E6E7^{SH}$ proteins of either HPV16 or HPV18 did not lead to degradation of p53 or pRb or to transformation of NIH 3T3 cells, while expression of $E6E7^{SH}$ or $E2E6E7^{SH}$ did not immortalize primary human keratinocytes.

Non-Clinical Toxicity of Ad26HPV16 or HPV18 and MVA.HPV16/18

A Good Laboratory Practice (GLP)-compliant repeated dose toxicity study with the Ad26.HPV16, Ad26.HPV18 and MVA-BN-HPV16/18 vaccine components at the highest feasible dose by intramuscular injections in Sprague-Dawley rats has been performed. The injections were well tolerated, with mild reactions in-life and histopathological effects (injection sites and draining lymph nodes) reflecting a normal response to vaccine administration and none of these reactions were considered adverse. No vaccine-related serious adverse events were found (Study TOX1227).

Biodistribution

Ad26

The biodistribution potential of the Ad26 vector has been evaluated in combination with another (HIV) gene insert (Ad26.ENVA.01) (Bridge GPS, Inc, study 1645-06074). NZW rabbits were

administered placebo or Ad26.ENVA.01 at $5x10^{10}$ vp via a single intramuscular injection on Study Day (SD) 1. Analysis on SD 11 indicated that the Ad26.ENVA.01 vaccine was primarily localized in the injection site muscle and distributed only to the draining (iliac) lymph nodes and spleen. By SD 61, the vaccine was no longer detected in the spleen. By SD 91, detection of the vector was limited to the iliac lymph nodes and injection site muscle in 2 out of 10 treated animals and was below the limit of detection in all of the other examined tissues, confirming clearance of the vector from the animals/tissues. As biodistribution is considered to be dependent on the viral vector and not on the inserted transgene, it can be assumed that Ad26.HPV16 and Ad26.HPV18 will distribute in the same way as the Ad26.ENVA.01 vaccine.

MVA

A definitive biodistribution study (STUDY NO. G216-04) in New Zealand White (NZW) rabbits was established to provide spatial and temporal data regarding the distribution of vaccinia transcripts in rabbits following a single IM or SC immunization of MVA-BN (attenuated vaccine against smallpox virus and used as vector for vaccination against non-pox diseases) at $1x10^8$ $TCID_{50}$. In summary, vaccinia transcripts were detected using RT-PCR methods in several tissues 15 hours following IM and SC administration of MVA-BN®. Skin, muscle, blood, spleen, lung, liver, and pooled lymph nodes were vaccinia positive in some 15-hour samples, while kidney, heart, brain, mesenteric lymph node, ovary, and testes were negative in all 15-hour samples. Many of the positive samples were weakly positive and below the level of quantitation. After 48 hours, fewer samples were vaccinia positive than at the 15-hour time point, and only a single skin and pooled lymph node sample from the SC group were detectable by quantitative PCR. By Day 7, most of the samples and tissues were negative for vaccinia; only injection site skin or injection site muscle tissues were weakly positive in a few rabbits at levels too low to quantify.

Ad26.HPV16 or 18 Clinical Data

No clinical data with the Ad26HPV16 or 18 vaccine are currently available since this will be the FIH study.

Clinical Experience With Ad26-based Vaccines

The Janssen adenoviral vaccine safety database report[2] describes safety data from completed clinical studies using 4 Ad26-based vaccine candidates: Ad26.CS.01 (malaria), Ad26.RSV.FA2 (RSV), Ad26.ENVA.01 (HIV), and Ad26.ZEBOV (Ebolavirus) up to a cut-off date of 31 August 2017[2].[2] In these studies, 962 participants received at least 1 vaccination with an Ad26-based vaccine. Most participants (93.2%) received Ad26 at a dose level of $5x10^{10}$ vp and 2.6% participants were vaccinated with Ad26 at the highest dose level tested ($1x10^{11}$ vp).

The majority of solicited local and systemic AEs were of mild or moderate and usually started within 1 to 2 days after vaccination. Most of the events were transient and resolved within 1 to 3 days. The most frequently solicited AEs include injection site pain and warmth, malaise, fatigue and headache. The most commonly experienced unsolicited AE was upper respiratory tract infection – 8.3% of Ad26 participants *vs.* 13.7% of placebo participants. The most commonly

reported unsolicited AEs considered related to the vaccine were neutropenia/neutrophil count decreased (4.9% of Ad26 participants *vs.* 4.4% of placebo participants). SAE were reported in 17 Ad26 participants (2 participants acquired an HIV infection; 2 spontaneous abortions among others). Severe allergic reactions have not been reported to date and there have been no deaths.

There was no evidence of a higher frequency of local AEs with increasing Ad26 dose. There was a trend towards a slight increase in the incidence of chills, pyrexia, and malaise with increasing Ad26 dose.

Two suspected unexpected serious adverse reactions (SUSARs) have been reported to date following Ad26 vaccination in the HIV and Ebola vaccine programs.

One serious adverse event (SAE) of severe allergic reaction/hypersensitivity starting 12 hours after first study product administration was reported in a 50-year-old male study participant following administration of the Ad26.Mos.HIV that was assessed by the investigator and the sponsor as related to study vaccine. Clinical observations by the emergency room physician noted no clinical signs of allergic reaction (no rash, no lip/tongue/oropharyngeal/uvular swelling, normal findings of cardiovascular and respiratory system). Diphenhydramine was administered; no hospitalization or administration of corticosteroids occurred. The reaction was resolved within 1 day of onset. Concurrent medical conditions included drug abuse, bipolar disorder (not disclosed by the participant to the investigator) with hallucinatory decompensation and chest pain 1 week after the severe allergic reaction. The participant was withdrawn from the study due to non-compliance (history of drug abuse and non-reported psychiatric issues).

In the Ebola vaccine development program (Ad26.ZEBOV), 1 SAE of "small fibre neuropathy" in a 38-year-old male participant with onset of paresthesia 2 weeks after vaccination with Ad26.ZEBOV was considered to be possibly related to the study product by the investigator and the sponsor. Although this AE is possibly related to study product, the neurologist experts consulted have concluded that the evolution of this event is atypical for a possible vaccine-related neuropathy.

In conclusion, the Ad26- based vaccines were safe and well-tolerated. No significant safety issues have been identified from the data available in the current adenoviral vaccine safety database. Importantly at a given dose level, no significant differences in the safety profiles of Ad26-based vaccines have been observed irrespective of the transgene insert used.

More detail on these studies can be found in the Janssen adenoviral vaccine safety database report and the Ad26.HPV16 and Ad26.HPV18 IBs.[2]

MVA.HPV16/18 Clinical Data

No clinical data with the MVA.HPV16/18 vaccine are currently available since this will be the FIH study.

Clinical Experience With MVA-based Vaccines

The safety profile of recombinant MVA-BN-based vaccines is similar to that of MVA-BN®, which has been used in various clinical trials in approximately 7,500 participants. Recombinant MVA-BN-based vaccines, eg, MVA-BN-HIV and MVA-BN-HER2, have been tested in varying schedules of repeated vaccinations with doses up to $5x10^8$ Inf.U in Phase 1 and Phase 2 studies. The main risks associated with the administration of the MVA-BN vector is the development of local reactions at the vaccination site (eg, pain, erythema, induration, swelling, and pruritus), as well as of generalized symptoms like fatigue, headache, myalgia, and nausea which were mostly mild and transient. For further details on the safety profiles of other MVA-vectored vaccine candidates, see the MVA.HPV16/18 IB.

Clinical Experience With Heterologous Vaccine Regimen Containing Ad26-based vaccine and MVA-based vaccine

Four completed studies of different 2-dose regimens containing an Ad26 vector vaccine encoding Ebola virus glycoprotein (Ad26.ZEBOV) and the MVA vector vaccine encoding glycoproteins from filoviruses (MVA-BN-Filo) among 325 healthy adults in the UK, US, Kenya, Tanzania and Uganda have demonstrated no significant safety issues. An ongoing Phase 1/2a study (HIV-V-A004) consisting of distinct 4-dose heterologous regimens which include combinations of Ad26.Mos.HIV with MVA.Mos have also not shown any significant safety concerns.

1.2. Benefit-risk Evaluations

1.2.1. Known Benefits

The clinical benefits of Ad26.HPV16, Ad26.HPV18, and MVA.HPV16/18 have yet to be established.

1.2.2. Potential Benefits

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

1.2.3. Potential Risks

The following potential risks for Ad26.HPV16, Ad26.HPV18, and MVA.HPV16/18 will be monitored during the study and are specified in the protocol:

Risks Related to Adenoviral-vectored Vaccines

There is no clinical experience with Ad26.HPV16 and Ad26.HPV18 and the safety profile has not yet been established.

Safety data available from 11 completed clinical studies among approximately 1000 participants that received at least 1 dose of other Ad26-vectored vaccine candidates, in which Ad26 with different inserts has been evaluated at dose levels ranging from $1x10^9$ vp to $1x10^{11}$ vp, indicate

that no significant safety concerns would be anticipated from vaccination with Ad26.HPV at doses of $5x10^{10}$ vp and $1x10^{11}$ vp.

For further details on the safety profiles of other Ad26-vectored vaccine candidates, read Section 1.1 (Clinical Experience With Ad26-based Vaccines) in this protocol and the Ad26.HPV IB.

Risks Related to MVA-vectored Vaccines

There is no clinical experience with MVA. HPV16/18 and the safety profile has not yet been established.

The safety profile of recombinant MVA-BN-based vaccines is similar to that of MVA-BN®, which has been used in various clinical trials in approximately 7,800 participants. Recombinant MVA-BN-based vaccines, eg, MVA-BN-HIV and MVA-BN-HER2, have been tested in varying schedules of repeated vaccinations with doses up to $5x10^8$ Inf.U in Phase 1 and Phase 2 studies providing a safety profile that does not raise significant concerns. For further details on the safety profiles of other MVA-vectored vaccine candidates read section 1.1 (Clinical Experience With MVA-based Vaccines) in this protocol and the MVA.HPV16/18 IB.

Risks Related to Vaccination

In general, IM injection may cause stinging, local itching, arm discomfort, bruising, swelling, or redness of the skin at vaccine injection sites. Participants may exhibit general signs and symptoms associated with the administration of a vaccine injection, including fever, chills, rash, aches and pains, nausea, headache, dizziness, and fatigue. These side effects should be monitored, but are generally short-term and do not require treatment. Participants may self-administer medications such as acetaminophen, non-steroidal anti-inflammatory drugs or antihistamines, as required.

Allergic reactions, possibly severe reactions (eg, hypersensitivity reactions), are known to occur with any injected vaccine, although rarely. Therefore, study site personnel should monitor the participant for 30 minutes after injection of the candidate vaccine as described in the study protocol. Appropriate drugs and medical equipment should be readily available.

Carcinogenicity, Mutagenicity, and Impairment of Fertility

Nonclinical carcinogenicity, mutagenicity, or fertility studies have not been conducted with Ad26.HPV16, Ad26.HPV18, and MVA.HPV16/18.

E6 and E7 are viral oncoproteins that are responsible for transformation of cells. In the vaccine component, the coding regions of E6 and E7 are divided into multiple fragments and then the fragments are re-ordered (shuffled), resulting in the expression of a fusion protein (abbreviated as $E6E7^{SH}$ [ie, E6E7 shuffled]). Nonclinical studies using the vaccine insert $E6E7^{SH}$ were conducted to show that the oncogenic properties of E6 and E7 were not present after expression of the shuffled insert. The main function of HPV E2 is the regulation of viral replication, and expression of E2 has been shown to inhibit growth of both HPV-positive and HPV-negative

cells. We have assessed any potential risks associated with the E2E6E7^{SH} vaccine insert as negligible.

Pregnancy

No preclinical developmental or reprotoxicity studies have yet been performed with Ad26.HPV16, Ad26.HPV18, or MVA.HPV16/18. However, a GLP-compliant combined embryo-fetal and pre- and postnatal development study has been conducted in rabbits with Ad26/MVA-BN vectors in combination with other inserts (Ad26.ZEBOV/MVA-BN-Filo). In this study, there was no maternal or developmental toxicity observed following maternal exposure during the premating and gestation period.

The effect of this vaccine on a fetus or nursing baby is unknown, so participants of childbearing potential having sexual intercourse with males will be required to agree to use birth control for sexual intercourse, as specified in the clinical study protocol. Participants who become pregnant while enrolled in a study must not receive any additional dose of study vaccine, but remaining visits and study procedures should be completed unless medically contraindicated or applicable regulations require termination from the study. All pregnancies and pregnancy outcomes will be recorded.

Adverse Drug Reactions

No clinical studies with Ad26.HPV16, Ad26.HPV18, or MVA.HPV16/18 have been performed to date. Therefore, adverse reactions have not been identified.

Additional Information

An increased risk of HIV acquisition was reported in 2007 in 2 studies in which Merck's (MRK) Ad5-vectored prophylactic HIV-1 *gag/pol/nef* vaccine was administered. The randomized double-blind placebo-controlled Phase 2b STEP study performed in North America revealed a statistically significant increase in HIV-1 acquisition at 18 months of follow-up in both a subgroup of Ad5 seropositive male participants who received the MRK vaccine and in a subgroup of uncircumcised male participants who received the MRK vaccine, compared with placebo.[6,16] The Phase 2b Phambili study performed in Africa and using the same vaccine, revealed a statistically significant increase in HIV-1 infection for participants who received the vaccine compared with placebo at long-term follow-up (median of 42 months).[23] An increased risk of HIV acquisition was however not reported in a prematurely unblinded study of DNA priming followed by a booster dose of rAd5 HIV-1 *env/gag/pol* vaccine (HIV Vaccine Trial Network study 505 in 2013). In this study, Ad5-seropositive participants and uncircumcised males were specifically excluded on the basis of the STEP data.[24] It must be emphasized that vaccination in itself does not cause HIV; only exposure to infected fluids transmits HIV.

The mechanism for the possible increase in HIV-1 susceptibility following vaccination with the MRK Ad5-vectored HIV vaccine remains unclear. The leading hypothesis is that the MRK Ad5-vectored HIV vaccine may have activated pre-existing Ad5-reactive CD4^{+} T cells that travel to mucosal surfaces and express HIV-coreceptors that may facilitate infection upon

HIV exposure.[37] The currently available data are however considered insufficient to allow this hypothesis to be confirmed or refuted.

While the results from the STEP and Phambili studies have been considered to be specifically associated with the particular MRK Ad5-vectored HIV vaccine used and the specific populations in whom the vaccine was tested, potential implications of the findings for studies using different adenovirus vectors and antigen inserts were raised in 2015 in 2 letters to the British Medical Journal[5,34] and in a subsequent review.[37] The authors particularly raised their concerns in view of the fast track evaluation of the candidate Ebola virus vaccines in regions with concentrated HIV epidemics, and recommended long-term follow-up of study participants, including voluntary HIV counselling and testing in adenovector-based Ebola vaccine studies.

To date, no evidence of a potential association between the administration of vaccines other than the MRK Ad5-vectored HIV vaccine and increased risk of HIV acquisition exists. However, following the publication of these 2 letters in the British Medical Journal, an internal Working Group co-led by representatives from Clinical Development and Global Medical Safety, and with input from scientists working on viral vaccines, was established by the sponsor to critically evaluate the potential implications of the findings from the STEP and Phambili studies for studies using different adenovirus vectors and antigen inserts for HIV and other indications.

Adenoviruses such as Ad26 and Ad35 are biologically different from Ad5 in terms of receptor usage, endosomal escape, interaction with pattern recognition molecules, and in their inflammatory profiles.[3,35,41,47,48,56] A clinical study with the Ad26-vectored HIV vaccine expressing the ENVA protein showed no increased general or adenovirus-reactive $CD4^+$ T cells in the gut mucosa, regardless of baseline Ad26 seropositivity.[3] Evidence from preclinical non-human primate studies, clinical vaccine studies, and in vitro experiments on Ad5 and other adenovirus serotypes is not conclusive in terms of a causative association between vaccine-induced cellular immune responses, immune activation and viral acquisition, whether specific for HIV/simian immunodeficiency virus vaccine insert or the vector backbone. Furthermore, analysis of historical clinical study data from 1,695 participants in 27 studies with the Sponsor's Ad26/Ad35 vectored vaccine candidates showed no evidence of increased rates of HIV infection.[2]

The conclusion of the Working Group, in collaboration with an external expert Advisory Board, is that the possibility of an increased risk of HIV acquisition after vaccination with Ad26-vecored vaccines is theoretical.

Monitoring of incident HIV infections during the clinical studies with the sponsor's adenovector-based candidate vaccines will be done through its routine pharmacovigilance and signal detection activities and consolidated at the time of the adenoviral vaccine safety database updates.

Risks from Blood Draws

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

Unknown Risks

There may be other serious risks that are not known.

1.2.4. Overall Benefit-Risk Assessment

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

- Currently, there is no approved therapy to eradicate HPV infection of the cervix and standard of care includes monitoring of early infection and treatment upon progression to high-grade genital lesions.
- No significant safety issues have been identified from the data available for clinical experience with Ad26-based and MVA-BN-based vaccines. Importantly, no significant differences in the safety profiles of Ad26-based and MVA-BN-based vaccines have been observed irrespective of the transgene insert used.
- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 4) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study:
  - In general, safety evaluations will be performed at scheduled visits during the study, as indicated in the Time and Events Schedule.
  - After vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events and will be allowed to leave the vaccination site at approximately 45 minutes post-vaccination. Any unsolicited, solicited local or systemic AEs and vital signs will be documented during this observation period. Participants will use a diary to document solicited local and systemic symptoms for 7 days post-vaccination. Details are provided in Section 9.1.4.
  - Participants in Step 1 and Step 3 of Phase I of the study will undergo safety follow-up by study staff 24 hours after each vaccination by telephone and all participants will have follow-up visits 7 days after each vaccination, as indicated in the Time and Events Schedule.
  - The investigator or the designee will document unsolicited adverse events as indicated in Section 12.3.1.
  - Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

- Several safety measures are included in this protocol to minimize the potential risk to participants, including the following:
  - Post-vaccination safety review in sentinel cohorts by principal investigator (PI) and study responsible physician (SRP), and Independent Data Monitoring Committee (IDMC) is described in Section 3.1.
  - For all participants, there are pre-specified rules that would result in pausing of further vaccinations if predefined conditions occur, preventing exposure of new participants to study vaccine until the IDMC reviews all safety data (see Section 11.9).
  - Participants will discontinue study vaccine for the reasons included in Section 10.2.
  - Contraindications to vaccination are included in Section 10.3.

1.3. Overall Rationale for the Study

This FIH study is part of a vaccine program which aims to generate a therapeutic vaccine for women persistently infected with HPV types 16 or 18, with a focus on early disease interception. In this study, women with HPV types 16 or 18 infection of cervix will be enrolled. For the purpose of early safety and immunogenicity evaluation, women with either persistent or recently diagnosed HPV infections will be included. Women with cytology of high-grade squamous intraepithelial lesion (HSIL) or adenocarcinoma in situ (AIS) or a colposcopy result of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) will be excluded.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Primary

Objectives	Endpoints
Primary	
To assess safety and reactogenicity of the 3 vaccine regimens.	• Solicited local and systemic adverse events (AEs) for 7 days after each vaccination. • Unsolicited AEs from the time of informed consent form (ICF) signature until 28 days after the first vaccination, and thereafter, until 28 days after the second vaccination. • Serious adverse events (SAEs) throughout the study.

Secondary

Objectives	Endpoints
To assess immunogenicity of the 3 vaccine regimens.	T cell responses to the separate or combined protein peptide pools of HPV16 and HPV18 E2, E6 and E7 proteins, including specific $CD4^+$ and $CD8^+$ T cells producing IFNγ, tumor necrosis factor alpha (TNFα), or interleukin 2 (IL-2) (combined cytokine expression may also be assessed) will be determined by flow cytometry.

Exploratory

Objectives	Endpoints
To assess the frequency and kinetics of clearance of • persistent or recently diagnosed HPV16 and HPV18 infection (combined[a]) and • persistent or recently diagnosed HPV16 infection and • persistent or recently diagnosed HPV18 infection of the 3 vaccine regimens compared to placebo over the study period.	Healthcare provider- and self-collected cervical samples obtained over the study period will be genotyped by a qualitative HPV genotyping test (Cobas®, Roche) and a quantitative HPV PRC genotyping test to evaluate HPV16 and/or HPV18 viral clearance[b], defined as: • A negative HPV16 genotype over the study period after having a baseline HPV16 infection (persistent or recently diagnosed); OR • A negative HPV18 genotype over the study period after having a baseline HPV18 infection (persistent or recently diagnosed).
To assess regression of CIN1 and concomitant clearance of HPV16 and/or HPV18 infection of the 3 vaccine regimens compared to placebo over the study period.	• Regression of CIN1: A colposcopic impression of normal after having a baseline of CIN1, AND concomitant clearance of baseline (persistent or recently diagnosed) HPV16 and/or HPV18 infection (as defined above).
To further characterize vaccine-elicited immune responses.	These assessments will include, but are not limited to, the assessments described below. Some of the exploratory assessments will only be initiated if indicated by the secondary immunogenicity data. Cell-mediated • Flow cytometry to characterize other cellular immune responses to the separate or combined protein peptide pools of HPV16 and HPV18 E2, E6 and E7 proteins, including, but not limited to, mucosa-homing markers, Th17, Th2, regulatory T cell (Treg), cytolytic markers, activation markers, and

Objectives	Endpoints
	exhaustion markers. • Transcriptome analysis to provide phenotypic and functional characterization of peripheral blood mononuclear cells (PBMCs) ex vivo or after stimulation with either HPV16 and/or HPV18 E2, E6, and/or E7 peptide pools. • Enzyme-linked immunospot (ELISpot) assay to enumerate PBMCs able to produce IFNγ upon stimulation with HPV16 and/or HPV18 E2 (complete, N-terminal, or C-terminal), E6 and/or E7 protein peptide pools. • ChipCytometry analysis of T cell responses to the separate or combined protein peptide pools of HPV16 and/or HPV18 E2, E6, and E7 proteins in PBMCs, including but not limited to $CD4^+$ and $CD8^+$ T cells producing IFNγ, TNFα and/or IL-2. <u>Humoral</u> • Adenovirus neutralization assay to evaluate neutralizing antibody responses against the Ad26 vector. • MVA neutralization assay to evaluate neutralizing antibody responses against the MVA vector. • Antibody responses to the HPV16 and/or HPV18 capsid proteins L1 and/or L2 can be measured to investigate levels of HPV-specific antibodies before vaccination (not induced by vaccination with either Ad26.HPV16 or Ad26.HPV18), as well as induction of L1/L2 antibodies after vaccination as a "bystander" effect due to release of these proteins from infected cells after vaccine-mediated cytolytic T cell responses. L1/L2 antibodies to other HPV genotypes might also be measured. • Antibody responses to E2, E6 and/or E7 of HPV16 and/or HPV18, or to these proteins of other HPV genotypes, can be evaluated.

Objectives	Endpoints
• To explore potential immune correlates for viral clearance.	• Immunogenicity endpoints of HPV-specific cellular or humoral responses described above, determined at multiple time points after vaccination will be used to explore potential immune correlates of viral clearance of HPV16 and/or HPV18.

[a] The sum of women who clear an HPV16 infection plus women who clear an HPV18 infection
[b] Women who receive CIN treatment will be considered as not clearing an HPV infection.

Refer to Section 9 for evaluations related to endpoints.

2.2. Hypothesis

No formal statistical hypothesis for safety or immunogenicity will be tested.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter, randomized, placebo-controlled, double-blind, safety, reactogenicity and immunogenicity Phase 1/2a study of 3 heterologous vaccine regimens with the Ad26.HPV16, Ad26.HPV18, and MVA.HPV16/18 recombinant vectors (Refer to Table 4). Vaccination will take place on Day 1 and Day 57. Study participants include approximately 66 women ≥18 to ≤60 years old with HPV types 16 or 18 infection of the cervix. This can be either persistent or recently diagnosed HPV infection, see Section 11.3 for definitions. Vaccination and safety monitoring among the HPV16 infected participants may occur independently from the HPV18 infected participants because the rate of enrollment of women with these 2 HPV types may differ as cervical HPV16 infections are more prevalent than HPV18 infections.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to evaluate safety data over the course of the study and to review any event that meets a specific study pausing rule, stopping rule, or any other safety issue that may arise.

The IDMC will consist of members independent of the sponsor, including at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The IDMC responsibilities, authorities and procedures will be documented in its charter. The IDMC will review unblinded data (see Sections 11.8 and 11.9).

Randomization, vaccination and safety evaluations

The randomization, vaccination process and safety evaluations described below for HPV16 infected participants will be performed in the same manner and independently among HPV18 infected participants.

HPV16 infected participants (Table 4 and Figure 2).

Dose 1 (Ad26-based)

Phase 1 (Dose Escalation)

- Step 1 [sentinels with low dose or placebo]: The first 2 participants (sentinels) will receive either a low dose Ad26.HPV16 (1 participant) or placebo (1 participant). Dosing of these 2 participants may occur on the same day depending on enrollment rates. Vaccination of additional participants will be halted until a 24-hour and 7-day post vaccination blinded safety review of solicited and unsolicited AEs are performed by the principal investigator (PI) and the sponsor's study responsible physician (SRP).
- Step 2 [completion of Phase 1 with low dose or placebo]: In the absence of clinically significant findings in participants from step 1, 4 additional participants will be dosed: 3 participants will receive low dose Ad26.HPV16 and 1 participant will receive placebo. There will be a staggered interval of 7 days between the vaccination of each of these 4 participants. Vaccination of additional participants will be halted until a 7-day post vaccination safety review of solicited and unsolicited AEs and clinical laboratory results is performed by an IDMC of participants in step 1 and step 2.
- Step 3 [sentinels for dose escalation with high dose or mixed regimen or placebo]: If the IDMC expresses no concerns on the safety data from the HPV16 participants in steps 1 and 2, and the first 2 HPV18 sentinels from step 1[a], then 3 additional sentinel participants will be dosed: 1 participant will receive a high dose Ad26.HPV16, 1 participant will receive the Ad26.HPV16/Ad26.HPV18 mix and 1 participant will receive placebo. Dosing of these 3 participants may occur on the same day depending on enrollment rates. Vaccination of additional participants will be halted until a 24-hour and 7-day post vaccination blinded safety review of solicited and unsolicited AE are performed by the PI and SRP.
- Step 4 [completion of Phase 1 with high dose or mixed regimen or placebo]: In the absence of clinically significant findings in participants from step 3, 8 additional participants will be dosed: 3 participants will receive high dose Ad26.HPV16, 3 will receive the Ad26.HPV16/Ad26.HPV18 mix and 2 participants will receive placebo. There will be a staggered interval of 7 days between the vaccination of each of these 8 participants. Vaccination of additional participants will be halted until a 7-day post

[a]No Ad26.HPV16/Ad26.HPV18 mix regimen will be administered until review of 2 sentinels HPV18 data in step 1.

vaccination safety review of solicited and unsolicited AE and clinical laboratory results of participants in step 3 and step 4 and all available safety data of participants in Step 1 and 2 is performed by the IDMC.

Phase 2a (Further Vaccination)

- Step 5 [further vaccination with high dose or mixed regimen or placebo]: If the IDMC expresses no safety concerns on the safety data from participants in steps 1-4 and no participant has experienced the criteria that determine it is not safe to initiate the Phase 2a component of the study, 16 additional participants will be randomized and dosed: 6 participants will receive high dose Ad26.HPV16, 6 will receive the Ad26.HPV16/Ad26.HPV18 mix and 4 participants will receive placebo. No more than 5 participants per week will be dosed.

Note: the criteria to move to Phase 2a is that no participant in Phase 1 of the study experiences any of the events encompassed in the study vaccination pausing rules serious enough to not proceed with study as per IDMC.

Dose 2 (MVA-based)

Phase 1

Completion of IDMC review in step 2 above will also allow the second dose vaccination with MVA.HPV16/18 or placebo of the sentinel participants in step 1[a]. Safety reviews after MVA/placebo vaccinations will follow the same scheme as for the Ad26 vaccinations, ie, a 24-hour and 7-day post vaccination blinded safety review by the PI/SRP will be performed after the MVA/placebo vaccinations of step 1 and 3 sentinel participants and an aggregated 7-day safety review will be performed by the IDMC when the MVA/placebo vaccinations of participants in step 2 and 4 have been completed.

Phase 2a

If the IDMC expresses no safety concerns on the MVA.HPV16/18 / placebo data from participants in Phase 1, the 16 participants from Phase 2 will be dosed with MVA.HPV16/18 or placebo.

The **HPV18 infected participants** will follow the same process as described above for the HPV16-infected participants (Table 4 and Figure 3). Vaccination and safety monitoring may occur independently to the HPV16 infected participants (see Table 4).

The study duration, from screening until the last follow-up visit, will be approximately 13.5 months per participant. The study consists of a screening period of up to 42 days (6 weeks), followed by vaccinations on Day 1 and Day 57, and follow-up visits up to 12 months after the

[a] An ad-hoc IDMC review of all available safety data may take place in case not all participants from step 1 and 2 have been enrolled by the time the first MVA vaccination needs to take place.

first vaccination (target visit Day 366±14 days). If a participant is unable to complete the study, but has not withdrawn consent, an early exit visit will be conducted.

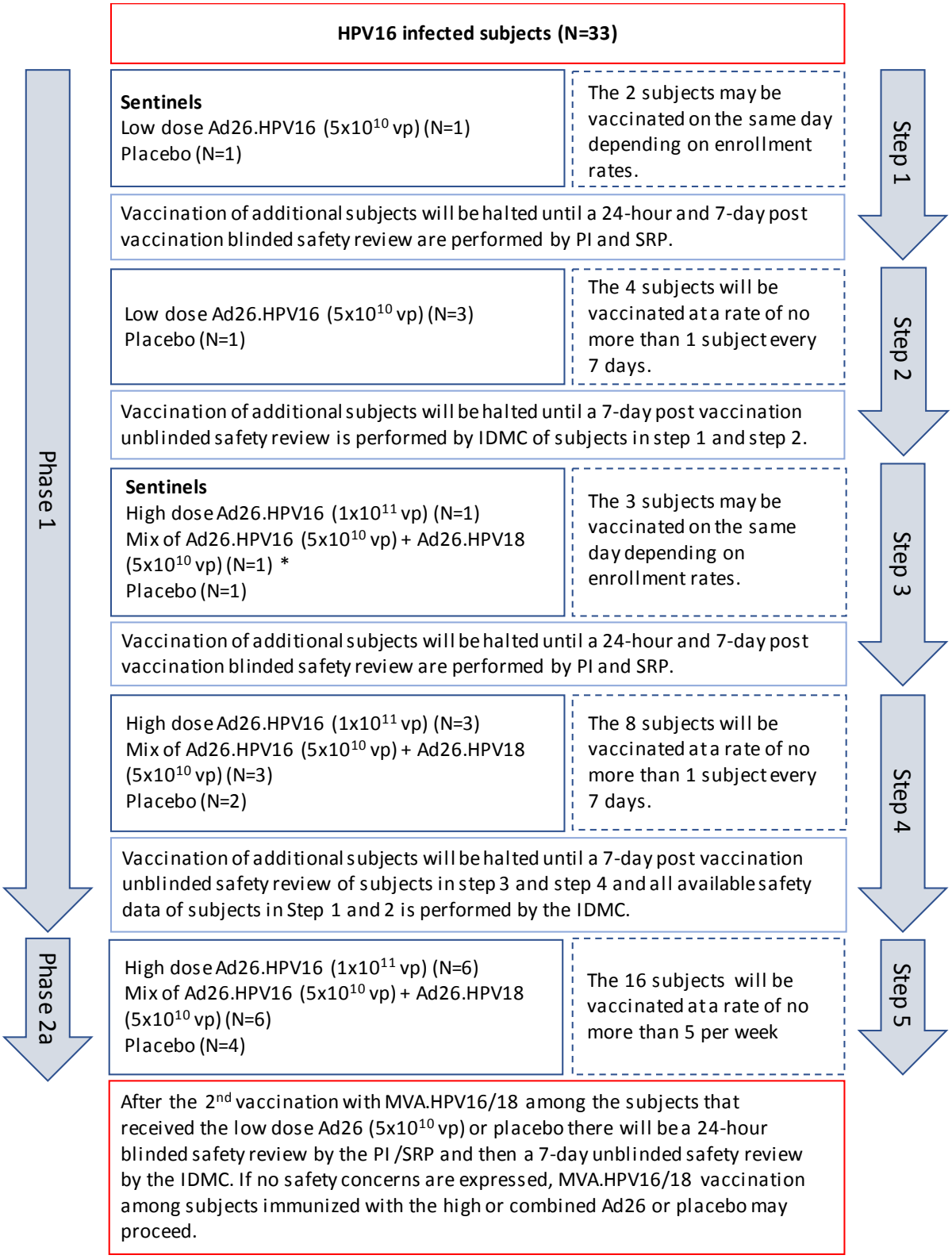
A diagram of the study design is provided in Figure 2 and Figure 3.

Table 4: Study Design

	Vaccine Regimen			Phase 1					Phase 2a	
HPV Type*	**Regimen**	**Day 1**	**Day 57 (Week 8)**	**Step 1 sentinel; low dose**	**Step 2 completion Phase 1; low dose**	**Step 3 Sentinel dose escalation high & mixed regimens**	**Step 4 completion Phase 1; high & mixed regimens**	**Subtotal**	**Step 5 further vaccination; high & mixed regimens**	**Total**
16	Regimen 1a (Ad26 low dose)	Ad26.HPV16 ($5x10^{10}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	1	3	-	-	4	-	4
16	Regimen 2a (Ad26 high dose)	Ad26.HPV16 ($1x10^{11}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	-	-	1	3	4	6	10
16	Regimen 3 (mixing of Ad26)	Ad26.HPV16 ($5x10^{10}$ vp) + Ad26.HPV18 ($5x10^{10}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	-	-	1	3	4	6	10
16	Control	Placebo (1.0 mL)	Placebo (0.5 mL)	1	1	1	2	5	4	9
Total HPV16				2	4	3	8	17	16	33
18	Regimen 1b (Ad26 low dose)	Ad26.HPV18 ($5x10^{10}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	1	3	-	-	4	-	4
18	Regimen 2b (Ad26 high dose)	Ad26.HPV18 ($1x10^{11}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	-	-	1	3	4	6	10
18	Regimen 3 (mixing of Ad26)	Ad26.HPV16 ($5x10^{10}$ vp) + Ad26.HPV18 ($5x10^{10}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	-	-	1	3	4	6	10
18	Control	Placebo (1.0 mL)	Placebo (0.5 mL)	1	1	1	2	5	4	9
Total HPV18				2	4	3	8	17	16	33*
Total				4	8	6	16	34	32	66
					PI/SRP	IDMC	PI/SRP	IDMC		

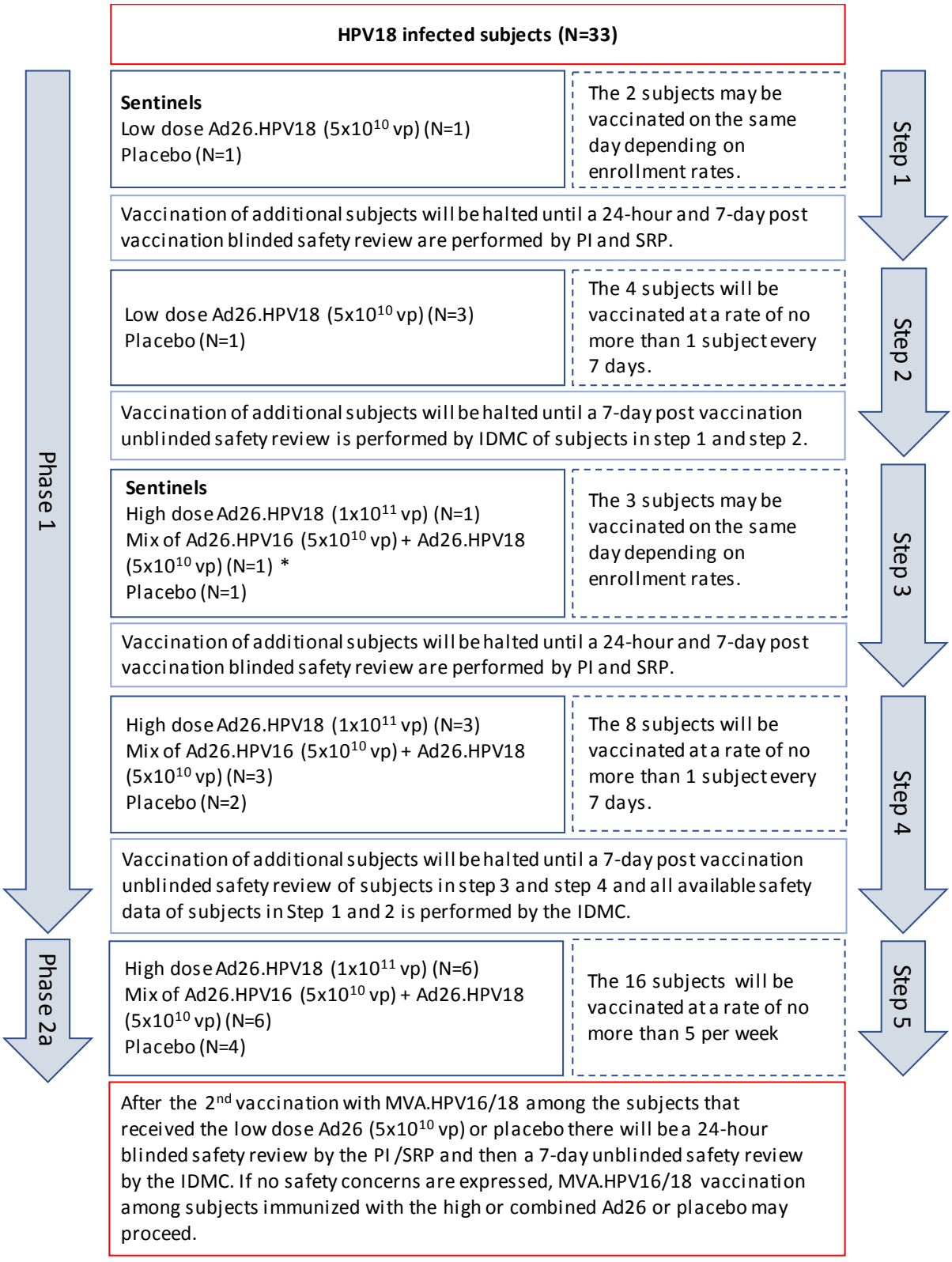
Ad26=adenovirus serotype 26; HPV=human papillomavirus; Inf.U=infectious unit; MVA=modified vaccinia Ankara; vp=viral particles
* If enrollment is slow for HPV18-infected participants, up to 8 HPV18-infected participants can be replaced by HPV16-infected participants, hence a minimum of 25 HPV18 participants will be allowed. The decision will be taken during Step 5.

Figure 2: Schematic Overview of the Study - HPV16 Infected Participants



* Two sentinel participants from the HPV18 group are required for IDMC review in step 2 before starting step 3.

Figure 3: Schematic Overview of the Study - HPV18 Infected Participants



* Two sentinel participants from the HPV16 group are required for IDMC review in step 2 before starting step 3.

3.2. Study Design Rationale

Rationale for Heterologous Immunizations

The study will use heterologous immunizations with replication-incompetent adenovirus- and MVA-vectored vaccine components that express HPV16 and HPV18 proteins. So far, in other programs conducted by the sponsor, such heterologous regimens have shown successful induction of strong, long-lived antigen-specific T cell responses. Strong T cell responses were seen in clinical studies with vectors expressing antigens from HIV-1, and Ebola.[10,38] In the latter, heterologous regimens using an Ad26-based immunization, followed by immunization with MVA-based vectors within a timeframe of 8 weeks induced strong and durable T cell responses to Ebola antigens.

Supporting the Ad/MVA approach, strong HPV-specific T cell responses were observed in non-human primate studies conducted by the sponsor, using regimens that consisted of Ad26.HPV16 and Ad26.HPV18, each at $1x10^{11}$ vp followed with MVA.HPV16/18 at $1.79x10^{8}$ Inf.U with an 8-week interval between immunizations. (see Section 1.1)

Rationale for Dose Selection

Safety data from clinical studies with other Ad26-vectored vaccines expressing different antigens are supportive of dosing the Ad26-based HPV vaccine components in this study at $5x10^{10}$ vp and $1x10^{11}$ vp. Both doses have been used in other Ad26 vaccine programs to successfully induce cellular immunity against the transgene, and results from the studies in non-human primates using $1x10^{11}$ vp of Ad26.HPV16 and $1x10^{11}$ vp of Ad26.HPV18 indicate that strong cellular immune responses were elicited at this dose.

The current study will use MVA.HPV16/18 at a dose of $2x10^{8}$ Inf.U per immunization. In recombinant MVA-BN vaccine studies (HIV and therapeutic breast cancer vaccine [MVA-BN-HER2]), doses up to $5x10^{8}$ $TCID_{50}$ were administered in varying schedules (refer to the IB for MVA.HPV16/18). In addition, an adequate safety profile has been established for the heterologous regimen of Ad26.ZEBOV and MVA-BN-Filo with doses up to $4x10^{8}$ $TCID_{50}$.[2]

Rationale for Choice of Regimens

Regimen 1: Separate administration of low dose Ad26.HPV16 or Ad26.HPV18 (matching the participant's underlying HPV infection) at Day 1, followed by MVA.HPV16/18 at Day 57 will be part of the ascending dose design. We will assess safety initially among a small group of participants immunized with this low dose Ad26.HPV16 or 18 regimen. After satisfactory completion of the safety review the next participants enrolled may receive the higher dose regimens (2 and 3).

Regimen 2: Separate administration of $1x10^{11}$ vp of Ad26.HPV16 or $1x10^{11}$ vp of Ad26.HPV18 (matching the participant's underlying HPV infection) at Day 1, followed by MVA.HPV16/18 at Day 57 will be used to assess safety and immunogenicity.

Regimen 3: Mixing of a single-syringe administration of $5x10^{10}$ vp of Ad26.HPV16 and $5x10^{10}$ vp of Ad26.HPV18 (ie, Ad26.HPV16/Ad26.HPV18) at Day 1, followed by MVA.HPV16/18 at Day 57 will be used to assess safety and immunogenicity and data will be compared to regimen 2.

4. PARTICIPANT POPULATION

Screening for eligible participants will be performed within 42 days before administration of the first dose of study vaccine.

The inclusion and exclusion criteria for enrolling participants in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

4.1. Inclusion Criteria

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

1. must sign an ICF indicating that she understands the purpose, procedures and potential risks and benefits of the study, and is willing to participate in the study.

2. willing and able to adhere to the prohibitions and restrictions specified in this protocol.

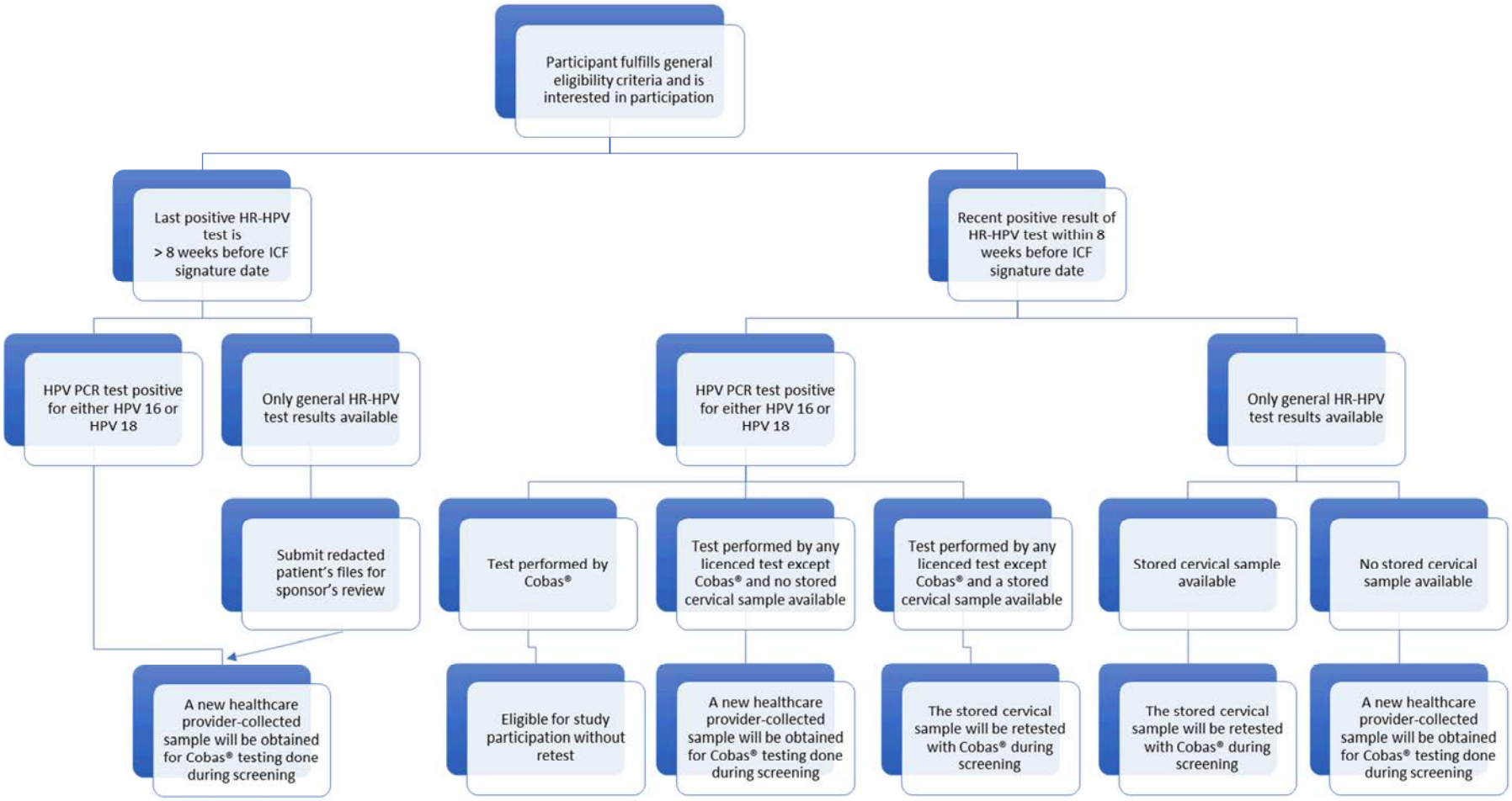
3. female, ≥18 and ≤60 years of age, inclusive, on the day of signing the ICF.

4. Criterion modified per Amendment 3:

   4.1 must have an HPV type 16 or 18 infection of the cervix as determined by a qualitative PCR test (Cobas®, Roche) within 8 weeks prior to screening or at the time of screening. Available history of HR-HPV positivity and HPV16 or HPV18 positivity will be recorded in the CRF (Figure 4).

   Note: To be eligible for screening, all participants must have at least 1 historical positive cervical HR-HPV PCR test result. If the genotype of the previous test is unknown, the participant will be screened after consultation with the sponsor.

Figure 4: Flow Chart for Identifying an HPV16 or HPV18 Infection Prior to Vaccination



5. Criterion modified per Amendment 3:

   5.1 Criterion modified per Amendment 2

   5.2 must have a recent colposcopy result (with a maximum of 12 months old at screening); in case a colposcopy has not been performed before, it will be done as screening procedure.

6. contraceptive (birth control) use by participants should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

   Before randomization, participants must be either (as defined in Attachment 1):

   a. Not of childbearing potential
   b. Of childbearing potential and practicing an acceptable effective method of contraception and agree to remain on such a method of contraception from signing the ICF until 3 months after the last dose of study vaccine. Use of hormonal contraception should start at least 28 days before the first administration of study vaccine. Acceptable methods for this study include:
      - Hormonal contraception;
      - Intrauterine device;
      - Intrauterine hormone-releasing system;
      - Male or female condom with or without spermicide;
      - Cap, diaphragm or sponge with a vaginal spermicide;
      - Vasectomized partner (the vasectomized partner should be the sole partner for that participant);
      - Sexual abstinence*

   Sexual abstinence is considered an effective method **only if defined as refraining from heterosexual intercourse from signing the ICF until 3 months after the last dose of study vaccine. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

7. all participants of childbearing potential must:

   a. Have a negative highly sensitive serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening
   b. Have a negative urine β-hCG pregnancy test immediately prior to each study vaccine administration

8. must be healthy as confirmed by medical history, physical examination, vital signs, and clinical laboratory tests performed at screening.

If laboratory screening tests are outside the normal reference ranges, repeat of screening tests is permitted once during screening to assess eligibility, provided there is no clear explanation for the out-of-range value. If the repeated tests are again outside the normal reference ranges, but within the limits representing Food and Drug Administration (FDA) toxicity grade 1 (see Attachment 2: Toxicity Tables), the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant. This determination must be recorded in the participant's source documents by the investigator. For repeated tests that show abnormalities of toxicity grade 2 or above, the investigator's judgment needs to be confirmed by the sponsor's medical monitor.

9. agrees not to donate blood until 3 months after receiving the last dose of study vaccine.

4.2. Exclusion Criteria

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

1. in case cytology results are available, participant has current or history of HSIL, AIS or any high-grade vulvar, vaginal or anal intraepithelial neoplasia.

2. current or history of CIN2+ or cervical cancer.

3. confirmed co-infection with both HPV16 and HPV18.

4. Criterion modified per Amendment 3:

   4.1 acute illness (this does not include minor illnesses such as diarrhea or mild upper respiratory tract infection) or temperature ≥38.0 ºC within 24 hours prior to the first dose of study vaccine; enrollment at a later date is permitted.

   Note: Before vaccination, the investigator must check for any symptoms of an acute illness or oral temperature ≥38.0 °C. If the randomization visit cannot be rescheduled within the allowed screening window or the contraindications to vaccination persist, the sponsor should be contacted for further guidance.

5. history of an underlying clinically significant acute or chronic medical condition, other than infection with HPV, or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

6. had major surgery (per the investigator's judgment), within 12 weeks before first vaccination, or will not have fully recovered from surgery, or has surgery planned within 6 months after the last dose of study vaccine.

Note: Participants with planned surgical procedures to be conducted under local or locoregional anesthesia and not judged as major by the investigator may participate.

7. tests positive for HIV at screening.

8. chronic active hepatitis B or hepatitis C infection, verified at screening by hepatitis B surface antigen or anti-hepatitis C virus antibody, respectively.

9. vaginal atrophy with or without topical hormonal therapies or systemic selective estrogen receptor modulators.

10. exposed to at least 1 dose of an HPV prophylactic vaccine or participant has participated in the past in another preventive or therapeutic HPV vaccine study.

11. clinically significant gynecological abnormalities that could, in the judgment of the investigator, interfere with study evaluation (eg, prolapse, myoma, fibroid, hysterectomy).

12. Criterion modified per Amendment 3:

    12.1 Criterion modified per Amendment 2

    12.2 symptomatic vaginal or genital infection (including genital herpes) as confirmed by physician or investigator. Note: positive HSV-2 serology is not exclusionary.

13. Criterion removed per Amendment 3.

14. has had major psychiatric illness or drug or alcohol abuse which in the investigator's opinion would compromise the participant's safety or compliance with the study procedures.

15. received or plans to receive:
    a. licensed live attenuated vaccines - within 28 days before or after planned administration of the first or subsequent study vaccinations
    b. other licensed (not live) vaccines - within 14 days before or after planned administration of the first or subsequent study vaccinations.

16. received an investigational drug or used an invasive investigational medical device within 30 days or received an investigational vaccine within 6 months before the planned administration of the first dose of study vaccine or is currently enrolled or plans to participate in another investigational study during the course of this study.

    Note: participation in an observational clinical study is allowed with prior approval of the sponsor.

17. received treatment with immunoglobulins in the 2 months, or blood products in the

4 months before the planned administration of the first dose of study vaccine or has any plans to receive such treatment up to 12 months after the first dose of study vaccine.

18. known allergy or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine products (including any of the constituents of the study vaccine(s)) (refer to Investigator's Brochures).

19. history of chronic urticaria (recurrent hives), eczema and/or atopic dermatitis.

20. history of acute polyneuropathy (eg, Guillain-Barré syndrome).

21. abnormal function of the immune system resulting from:

    a. Clinical conditions (eg, autoimmune disease or immunodeficiency);
    b. Chronic (longer than 10 days) or recurrent use of systemic corticosteroids during the study and within 6 months before first administration of study vaccine (*Note*: ocular, topical or inhaled steroids are allowed);
    c. Administration of antineoplastic and immunomodulating agents, including herbal products, or radiotherapy during the study and within 6 months before first administration of study vaccine.

22. history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin or malignancy which is considered cured with minimal risk of recurrence).

23. contraindication to intramuscular injections and blood draws, eg, bleeding disorders.

24. pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study vaccine.

25. employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator, or an employee of the sponsor.

26. cannot communicate reliably with the investigator.

27. who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study, or is unlikely to complete the full course of vaccination and observation.

NOTE: Investigators should ensure that all study enrollment criteria have been met prior to the first vaccination. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study vaccination is given such that she no longer meets all eligibility criteria, then the screening laboratory tests should be repeated and the Day 1 visit re-scheduled, or the participant should be excluded from participation in the study. Section 9.1.3, Screening Period, describes options for

retesting. Section 17.4 Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

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

1. Refer to Section 8, Pre-study and Concomitant Therapy for details regarding prohibited and restricted therapy during the study.
2. Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (Section 4.1 and Section 4.2, respectively).

5. STUDY VACCINE ALLOCATION AND BLINDING

Study Vaccine Allocation

Randomization will be stratified by HPV type (16 and 18) and within each HPV type, randomization will be performed in different steps (see Table 1). Between the steps, randomization will be halted until a 24-hour and 7-day review by the PI and SRP or an IDMC review have been performed. For HPV16 infected participants the following randomization steps will take place:

- Step 1: 2 participants will be randomly assigned to receive low dose Ad26.HPV16 or placebo. These participants may be randomized on the same day.
- Step 2: 4 participants will be randomly assigned to receive low dose Ad26.HPV16 (3 participants) or placebo (1 participant). There will be a staggered interval of 7 days between the vaccination of each of these 4 participants.
- Step 3: 3 participants will be randomly assigned to receive high dose Ad26.HPV16 or the Ad26.HPV16/Ad26.HPV18 mix or placebo. These participants may be randomized on the same day.
- Step 4: 8 participants will be randomly assigned to receive high dose Ad26.HPV16 (3 participants) or the Ad26.HPV16/Ad26.HPV18 mix (3 participants) or placebo (2 participants). There will be a staggered interval of 7 days between the vaccination of each of these 8 participants.
- Step 5: 16 participants will be randomly assigned to receive high dose Ad26.HPV16 (6 participants), Ad26.HPV16/Ad26.HPV18 mix (6 participants) or placebo (4 participants). No more than 5 participants will be vaccinated per week.

  The same randomization process will be used for the HPV18-infected participants.

If enrollment is slow for HPV18-infected participants, up to 8 HPV18-infected participants can be replaced by HPV16-infected participants, hence a minimum of 25 HPV18 participants will be allowed; the decision will be taken during Step 5.

Blinding

The participants, study-site personnel (including vaccine administrator) and investigator will be blinded to study vaccine allocation throughout the study, except for the pharmacist or qualified staff member with primary responsibility for study vaccine preparation and dispensing.

At the time of the primary analysis, the study will be unblinded for sponsor personnel (including medical personnel, biomarker lead, virologist, statistician, programming and data management). Participants, clinical staff and study-site personnel will remain blinded to the study vaccine allocation until the end of the study.

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

The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the appropriate section of the electronic case report form (eCRF), and in the source document.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed.

6. DOSAGE AND ADMINISTRATION

6.1. General Instructions and Procedures

The following will be used to prepare the vaccines:

- Ad26.HPV16: supplied in a single use vial ($1x10^{11}$ vp/mL; 0.5 mL [extractable volume])
- Ad26.HPV18: supplied in a single use vial ($1x10^{11}$ vp/mL; 0.5 mL [extractable volume])
- MVA.HPV16/18: supplied in a single use vial ($5x10^{8}$ Inf.U/0.5 mL; 0.5 mL [extractable volume])
- Placebo (0.9% saline): supplied in a single use vial (10 mL [filled volume])
- Diluent (Diluent 5, DS-TEC-79875): supplied in a single use vial (1 mL [extractable volume]) and to be added to the Ad26.HPV16 or Ad26.HPV18 vials for administration of the Ad26.HPV16 or Ad26.HPV18 vaccines at a dose of $5x10^{10}$ vp
- Diluent (tris-buffered saline [TBS] Diluent, DS-TEC-138030): supplied in a single use vial (1.5 mL [extractable volume]), 1.0 mL is to be added to the MVA.HPV16/18 vial for administration of the MVA.HPV16/18 vaccine at a dose of $2x10^{8}$ Inf.U

For each participant, every vaccination with Ad26.HPV16 and/or Ad26.HPV18 will be 1.0 mL in volume. For the low dose of Ad26.HPV16 or Ad26.HPV18 ($5x10^{10}$ vp), 0.5 mL of Ad26.HPV16 or Ad26.HPV18 and 0.5 mL of diluent 5 (DS-TEC-79875) will be mixed and administered as a single injection. For the high dose of Ad26.HPV16 or Ad26.HPV18 ($1x10^{11}$ vp), two vials of 0.5 mL of Ad26.HPV16 or Ad26.HPV18 will be mixed and administered as a single injection.

The monovalent Ad26.HPV16 ($5x10^{10}$ vp) and Ad26.HPV18 ($5x10^{10}$ vp), vaccine components will be mixed at the pharmacy or at a designated product preparation area and administered as a single injection.

Vaccination with MVA.HPV16/18 at a dose of $2x10^{8}$ Inf.U will be 0.5 mL in volume. Therefore, 1.0 mL of the diluent DS-TEC-138030 will be added to the vial of MVA.HPV16/18 (a concentration of $5x10^{8}$ Inf.U per 0.5 mL) and mixed at the pharmacy or at a designated product preparation area, and 0.5 mL of the mix will be administered as a single injection.

To allow blinding, the volume of placebo vaccine will be the same as the volume of the corresponding Ad26.HPV16, Ad26.HPV18 or MVA.HPV16/18 vaccine.

The vaccines will be administered by intramuscular injection into the deltoid muscle of either arm by a blinded study vaccine administrator. Opposite arms should be used for the MVA injection unless local site reaction cannot be assessed reliably in the opposite arm. The arm in which the vaccine has been administered should be recorded in the eCRF. The injection site should be free from any injury, local skin problem, significant tattoo or other issue that might interfere with evaluating the arm after injection (eg, participants with a history of skin cancer must not be vaccinated at the previous tumor site). No local or topical anesthetic will be used prior to injection.

Blinding will be achieved by preparation of study vaccine by an unblinded pharmacist or other qualified study-site personnel with primary responsibility for study vaccine preparation and dispensing, and by the administration of vaccine in a masked syringe by a blinded study vaccine administrator. Full details of the study vaccine preparation will be provided in the Site Investigational Product and Procedures Manual.

6.2. Criteria for Postponement of Vaccination

A participant will not be given the first or second vaccination if she experiences any of the following events at the scheduled time for vaccination:

- Severe acute illness at the time of vaccination (this does not include minor illnesses such as diarrhea)
- Fever (body temperature ≥38.0°C/100.4°F) at the time of vaccination.

If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor should be contacted for further guidance.

For contraindications to vaccination that result in discontinuation of study vaccine, refer to Section 10.2.

7. STUDY VACCINE COMPLIANCE

Study vaccine will be administered intramuscularly by a blinded study vaccine administrator. The vaccine administrator will be a trained and qualified study nurse, medical doctor, or otherwise qualified health care professional. The date and time of each study vaccine administration will be recorded in the eCRF.

8. PRE-STUDY AND CONCOMITANT THERAPY

Pre-study specific therapies such as analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs (NSAIDs), administered up to 30 days before first vaccination must be recorded at screening.

Concomitant therapies must be recorded from the time of ICF signature through 28 days after each vaccination, and additionally outside of these periods when associated with an SAE meeting the criteria outlined in Section 12.3.2. Information on concomitant use of herbal supplements or vitamins will not be collected.

Use of any experimental medication (including experimental vaccines other than the study vaccine) during the study is not allowed. Participants may not receive an investigational drug or use an investigation medical device within 30 days or receive an investigational vaccine within 6 months before the planned administration of the first dose of study vaccine.

Vaccination with licensed live-attenuated vaccines within 28 days of a study vaccination (ie, before and after) is not allowed. Other licensed vaccines (eg, tetanus, hepatitis A, hepatitis B, rabies) should be given at least 14 days before (or at least 14 days after) administration of study vaccine. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

Participants can receive medications such as acetaminophen, NSAIDs, or antihistamines as needed, although their use must be documented and use of these medications as routine prophylaxis prior to study vaccination is discouraged.

Chronic (longer than 10 days) or recurrent use of immunomodulators/suppressors, eg, cancer chemotherapeutic agents, systemic corticosteroids is prohibited during the study and within 6 months before the planned administration of the first dose of study vaccine (Note: Ocular, topical or inhaled steroids are allowed). Antineoplastic and immunomodulating agents, including herbal products, or radiotherapy are prohibited during the study and within 6 months before the planned administration of the first dose of study vaccine. If chronic use of such medicines becomes medically indicated during the course of the study for any participant, the sponsor

should be contacted. The participant should remain in the study but should not receive further study vaccination[a].

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

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of immunogenicity, safety and virology measurements applicable to this study.

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

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

The diary includes instructions on how to capture the data and grading scales to assess severity of the symptoms. The study staff is responsible for providing appropriate training to the participant to avoid missing or incorrect data (refer to Study Training Manual). The diary card will be reviewed by the study personnel at visits indicated in the Time and Events Schedule.

If the diary card review is missed, the diary card will be reviewed in the following visit. If a participant misses a vaccination, the diary covering the period after the missed vaccination does not have to be filled in.

The total blood volume to be collected during the study from each participant will be approximately 485 mL, which is considered acceptable based on the US Department of Health and Human Services Office for Human Research Protections, and the US FDA guidelines.[49,50]

9.1.2. Visit Windows

Participants should be encouraged to come on the exact day planned and use the visit window only if necessary. For the following visits, windows will be allowed as indicated:

- Second vaccination: ± 7 days

[a] Depending on the time of the occurrence, any participant who receives a prohibited concomitant medication will not be included in the immunogenicity analyses.

- 7 days post-vaccination safety only visit: ± 2 days
- 21 days post-Dose 2 vaccination safety, immunogenicity and virology visit: ± 3 days
- 28 days post-vaccination safety only visit (telephone call): ± 3 days
- 2 months post-Dose 2 vaccination safety and virology visit: ± 5 days
- 6 months post-Dose 1 safety and virology visit: ± 14 days
- 6 months post-Dose 2 vaccination safety, immunogenicity and virology visit: ± 14 days
- 12 months post-Dose 1 safety, immunogenicity and virology visit: ± 14 days

If a participant cannot be vaccinated within the allowed window, then that vaccination should not be administered. However, vaccination outside of the window (in particular if the window is missed due to a study pause) can be assessed on a case-by-case basis upon discussion between investigator and sponsor.

No visit windows are applicable for telephone calls to sentinel participants at 1 day post vaccination.

The timings of the second vaccination and of Visit 12 will be determined relative to the actual day of the first vaccination. The timing of visits 7, 8, 9, 10, 11 and 13 will be determined relative to the actual day of the second vaccination.

9.1.3. Screening Period (Days -42 to -2): Visit 1

Only participants complying with the inclusion and exclusion criteria specified in Section 4.1 and Section 4.2, respectively, will be included into the study. The investigator will provide detailed information on the study to the participants and will obtain written informed consent prior to each participant's participation in the study. All the procedures described in the Time and Events Schedule will only take place after written informed consent has been signed.

The following evaluations will be performed on participants to determine overall eligibility:

- Review of inclusion/exclusion criteria
- Demographic information
- Medical history and pre-study medications
- Physical examination including vital signs measurement (supine systolic and diastolic blood pressure, heart rate and oral temperature) and height and weight
- Healthcare provider-collected cervical sample for HPV16 and HPV18 PCR (If no recent HPV16 or HPV18 Cobas® test result is available at screening, the test will be performed on a stored cervical sample [if collected within a period of 8 weeks before screening] or on a new healthcare provider-collected sample)
- Self-collected cervico-vaginal sample for HPV16 and HPV18 PCR
- Serum β-hCG pregnancy testing (women of childbearing potential only)

- Blood sampling for HIV type 1 or type 2, hepatitis B and hepatitis C serology, and for safety laboratory testing (hematology and biochemistry)

General eligibility for this clinical study will be dependent on results of laboratory tests and the medical assessment. Study participants who qualify for inclusion based on the medical history, physical examination, and laboratory results will be contacted and scheduled for enrollment and first vaccination (Visit 2) within 42 days from signing the ICF.

Participants with laboratory values or vital signs not meeting eligibility criteria at the screening visit may have one repeat testing at the discretion of the investigator using an unscheduled visit during the 42-day screening period. Enrollment of a participant with laboratory values that are outside the laboratory normal reference ranges, and additionally within the limits representing FDA toxicity Grade 1 (see Attachment 2), is allowed if the investigator considers the values to be not clinically significant and reasonable for the population under study.

9.1.4. Vaccination and Follow-up Period (Day 1 to Day 366)

9.1.4.1. Vaccination (Day 1, and Day 57)

- **Day 1/Day of Randomization/Vaccination 1: Visit 2**

  After an abbreviated physical examination (at the discretion of the investigator), measurement of vital signs, urine pregnancy test (for women of childbearing potential), self-collected cervico-vaginal sample for type-specific HPV16 and HPV18 PCR, HSV-2 serology test, and pre-vaccination symptoms check, eligible participants will be randomized as described in Section 5. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study vaccination is given such that she no longer meets all eligibility criteria, then the screening laboratory tests should be repeated and the Day 1 visit re-scheduled, or the participant should be excluded from participation in the study. Pre-dose samples for baseline immunogenicity assessments will be collected. Before vaccination, the investigator must check for any symptoms of an acute illness or oral temperature ≥38.0 °C. If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor should be contacted for further guidance.

  Administration of first dose of study vaccine.

  After vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events and will be allowed to leave the vaccination site at approximately 45 minutes post-vaccination. Any unsolicited, solicited local or systemic AEs and vital signs will be documented in the eCRF by study-site personnel following this observation period.

  Participants will be provided with a participant diary, thermometer, and ruler to measure and record oral body temperature, solicited local and systemic AEs for 7 days post-vaccination.

Unsolicited AEs will be recorded on the AE page of the eCRF from the time of ICF signature until 28 days after the first vaccination, together with information about any concomitant medications. SAEs will be collected until the study end (Day 366).

- **Day 57/Vaccination 2: Visit 6**

  An abbreviated physical examination (at the discretion of the investigator), measurement of vital signs, urine pregnancy test (for women of childbearing potential), self-collected cervico-vaginal sample for type-specific HPV16 and HPV18 PCR and pre-vaccination symptoms check will be performed for all participants pre-vaccination. Pre-dose samples for immunogenicity assessments will be collected. Before vaccination, the investigator must check for any symptoms of an acute illness or oral temperature ≥38.0 °C. If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor should be contacted for further guidance.

  Administration of second dose of study vaccine.

  After vaccination, participants will remain under observation at the study site for at least 30 minutes for presence of any acute reactions and solicited events. Any unsolicited, solicited local or systemic AEs and vital signs will be documented in the eCRF by study-site personnel following this observation period.

  Participants will be provided with a participant diary, thermometer, and ruler to measure and record oral body temperature, solicited local and systemic AEs for 7 days post-vaccination.

9.1.4.2. Post-first Vaccination Follow-Up

The randomization, vaccination process and safety evaluations described below for HPV16 infected participants will be performed in the same manner and independently among HPV18 infected participants.

- **1 Day Post-first Vaccination: Sentinel Participants: Visit 3**

  At 1 day after the first vaccination, a telephone call will be made to the 5 sentinel participants (2 in Step 1 and 3 in Step 3); vaccination of additional participants will be halted until a 24-hour and 7-day post vaccination blinded safety review of solicited and unsolicited AEs are performed by the PI and the SRP.

- **7 Days Post-first Vaccination: Visit 4**

  This visit will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, and recording of any AEs/SAEs and concomitant medications. Samples for safety laboratory testing (hematology and biochemistry) will be collected. The participant diary will be collected and reviewed.

- **28 Days Post-first Vaccination: Visit 5**

  This visit will be a telephone call to collect safety information (unsolicited AEs, SAEs and concomitant medications).

- **6 Months Post-first Vaccination (Week 26): Visit 12**

  This visit will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, self-collected cervico-vaginal sample for type-specific
  HPV16 and HPV18 PCR and recording of any SAEs and concomitant medications (related to SAEs only).

- **12 Months Post-first Vaccination (Week 52): Visit 14**

  This visit will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, healthcare provider-collected cervical sample for type-specific HPV16 and HPV18 PCR, self-collected cervico-vaginal sample for type-specific HPV16 and HPV18 PCR and recording of any SAEs and concomitant medications (related to SAEs only). At this visit all participants will undergo a colposcopic evaluation and an HSV-2 serology test. Samples will be shipped and tested in a central sponsor designated laboratory. Samples for immunogenicity assessments will be collected.

9.1.4.3. Post-second Vaccination Follow-Up

- **1 Day Post-second Vaccination (sentinel participants only): Visit 7**

  This visit will be a telephone call to check participant diaries and to collect safety information (solicited and unsolicited AEs, SAEs and concomitant medications).

- **7 Days Post-second Vaccination: Visit 8**

  This visit will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, and recording of any AEs/SAEs and concomitant medications. Samples for safety laboratory testing (hematology and biochemistry) will be collected. The participant diary will be collected and reviewed.

- **21 Days Post-second Vaccination: Visit 9**

  This visit will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, self-collected cervico-vaginal sample for type-specific
  HPV16 and HPV18 PCR and recording of any AEs/SAEs and concomitant medications. Samples for immunogenicity assessments will be collected.

- **28 Days Post-second Vaccination: Visit 10**

  This visit will be a telephone call to collect safety information (unsolicited AEs, SAEs and concomitant medications).

- **2 Months Post-second Vaccination: Visit 11**

  This visit will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, a self-collected cervico-vaginal sample for type-specific HPV16 and HPV18 PCR and recording of any SAEs and concomitant medications (related to SAEs only).

- **6 Months Post-second Vaccination: Visit 13**

  This visit will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, self-collected cervico-vaginal sample for type-specific
  HPV16 and HPV18 PCR and recording of any SAEs and concomitant medications (related to SAEs only).

  Samples for immunogenicity assessments will be collected.

9.1.4.4. Early Withdrawal – Early Exit Visit

In the event of early withdrawal from the study (ie, before Week 52), an exit visit will be conducted as soon as possible. The following procedures will be performed: an abbreviated physical examination, vital signs measurement, healthcare provider-collected cervical sample, and self-collected cervico-vaginal sample for type-specific HPV16 and HPV18 PCR, an HSV-2 serology test, recording of concomitant medications and any AEs, and collection of samples for immunogenicity assessments.

9.2. Study Evaluations

9.2.1. Safety

An IDMC will be commissioned to evaluate safety data over the course of the study and to review any events that meet a specific study pausing or stopping rule or any other safety issue that may arise. Details regarding the IDMC are provided in Section 11.8.

Any clinically relevant changes occurring from the signing of the ICF until 28 days after the first vaccination and from the second vaccination through the following 28 days must be recorded on the AE section of the eCRF. Outside these periods, reporting will be limited to all SAEs.

Any clinically significant abnormalities (including those persisting at the end of the study/early exit) will be followed by the investigator until resolution or until a clinically stable endpoint is reached. All AEs and laboratory data will be coded for severity according to the criteria presented in Section 12.1.3 (see Attachment 2).

The PI, together with the sponsor's SRP, will be responsible for the safety monitoring of the study, and will halt vaccination of further subjects in case any of the pre-specified pausing or stopping rules described in Section 11.9 have been met.

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

Adverse Events

All AEs will be reported as specified in Section 12.

For solicited AEs, the following applies.

Solicited Adverse Events

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

Solicited Injection Site (Local) Adverse Events

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

- **Injection Site Pain/Tenderness**

  Injection site pain (eg, stinging, burning) is an unpleasant sensory and emotional experience associated with actual or potential tissue damage and occurring at the immunization site (with or without involvement of surrounding tissue). Injection site tenderness is a painful sensation localized at the injection site upon palpation or movement of the limb. Due to subjective nature of the reaction, the severity assessment of pain/tenderness is self-reported (if a participant is unable to provide self-report, other reporters include parent/care giver or health care provider).[22]

- **Injection Site Erythema**

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

- **Injection Site Swelling/Induration**

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

  Note: any other injection site events not meeting the above case definitions should be reported separately as unsolicited AEs.[32,33]

Solicited Systemic Adverse Events

Participants will be instructed on how to record daily temperature using a thermometer provided for home use. Participants should record the oral body temperature in the diary in the evening of the day of vaccination, and then daily for the next 7 days approximately at the same time each day (preferably in the evening). If more than one measurement is made on any given day, the highest temperature of that day will be used in the eCRF. Temperatures to be taken 7 days after the vaccination at the end of the diary period, may be collected earlier to coincide with the clinic visit.

Fever is defined as endogenous elevation of body temperature ≥38° C, as recorded in at least one measurement.[36]

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

Unsolicited Adverse Events

The investigator or study-site staff will document any reported unsolicited AEs and perform causality evaluations from the time of ICF signature through 28 days after the first vaccination, and from the time of the second vaccination until 28 days afterwards. SAEs will be collected from the time of ICF signature until the study end.

Laboratory Safety Assessments

Blood samples will be collected for safety laboratory assessments (hematology and biochemistry) as follows on all participants:

- At screening[a]
- At 7 days post-Dose 1 and post-Dose 2

The following tests will be performed by a central laboratory:

- **Hematology Panel**

  Hemoglobin
  White blood cell count with differential
  Platelet count
  Prothrombin time[b]
  Activated partial thromboplastin time[b]

[a] Clinical laboratory tests will be collected on all participants screened for this study.

[b] Parameters only measured at screening

- **Biochemistry Panel**

  Sodium
  Potassium
  Creatinine
  Blood urea nitrogen
  Aspartate aminotransferase
  Alanine aminotransferase

Review and Grading of Laboratory Data

The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Laboratory reports must be filed with the source documents.

Laboratory values will be initially evaluated by the investigator according to central laboratory criteria. Abnormal values outside the central laboratory range of normal will be graded according to the toxicity tables from the FDA Guidance document "Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (see Attachment 2). Laboratory values within central laboratory normal limits will not be FDA graded and will be considered as normal.

Any clinically significant abnormal laboratory value occurring during the 28-day follow-up after each vaccination will be captured as an AE. For clinically significant abnormal laboratory values, the test must be repeated within a reasonable period of the site becoming aware of the abnormal value.

Additional Clinical Laboratory Assessments

Additional clinical laboratory assessments will be performed:

- Serum pregnancy testing (β-hCG) for women of childbearing potential at screening
- Urine pregnancy testing for women of childbearing potential on the day of each vaccination (pre-vaccination)
- Serology testing (HIV type 1 or type 2, hepatitis B, hepatitis C) at screening
- Serology testing (HSV-2) on the day of the first vaccination and the 12-month follow-up visit (or the early exit visit, if applicable).

Vital Signs

Vital sign measurements will be performed at time points specified in the Time and Events Schedule. Supine blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

The following measurements will be performed:

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

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

Physical Examination

Full physical examination, including height and weight, will be carried out at screening. At all other visits, an abbreviated, symptom-directed examination will be performed by the investigator based on any clinically relevant issues, clinically relevant symptoms and medical history. Symptom-directed physical examination may be repeated if deemed necessary by the investigator.

Physical examinations will be performed by the investigator or designated medically trained clinician. Any abnormalities or changes in severity noted during the review of body systems should be documented in the source document and recorded in the eCRF.

9.2.2. Immunogenicity

Venous blood samples will be collected for the determination of humoral and cellular responses, according to the Time and Events Schedule. Sample collection and processing will be performed by the staff at the clinical site according to current versions of the approved clinical site's standard procedures.

Since the vaccine targets a cellular therapeutic response, the emphasis will be on the assessment of cellular immune responses. During the study, cellular immune responses will be measured in all participants at 5 time points during the 12-month follow-up period after the first vaccination:

- pre-Dose 1, pre-Dose 2, at 21 days, 6 months post-Dose 2 and 12 months post-Dose 1

Cellular immunological assays are summarized in Table 5. Humoral immunological assays are summarized in Table 6. Exploratory analyses may be performed, including, but not limited to, the listed assays. Baseline and post-vaccination samples will be used for the characterization of immunological assays.

Table 5: Summary of Immunogenicity Assays (Cellular)

Assay	Purpose
Secondary endpoints	
ICS	Analysis of T cell responses to the separate or combined protein peptide pools of HPV16 and HPV18 E2, E6 and E7 proteins, including specific $CD4^+$ and $CD8^+$ T cells producing IFNγ, TNFα, or IL-2 (combined cytokine expression may also be assessed)
Exploratory endpoints	
ICS	Analysis of other cellular responses to the separate or combined protein peptide pools of HPV16 and HPV18 E2, E6 and E7 proteins (including, but not limited to, mucosa-homing markers, Th17, Th2, Treg, cytolytic markers, activation markers, exhaustion markers)
Transcriptome analysis	Analysis of gene expression patterns to provide phenotypic and functional characterization of PBMCs ex vivo or after stimulation with HPV16 and/or HPV18 E2, E6, and/or E7 peptide pools.
ELISpot responses	Enumeration of IFNγ-producing HPV16 and/or HPV18 E2 (complete, N-terminal, and/or C-terminal peptide pools), E6 and/or E7-specific T cells
ChipCytometry	Analysis of T cell responses to the separate or combined protein peptide pools of HPV16 and/or HPV18 E2, E6, and E7 proteins in PBMCs, including but not limited to $CD4^+$ and $CD8^+$ T cells producing IFNγ, TNFα and/or IL-2

ELISpot=enzyme-linked immunospot; HPV=human papillomavirus; ICS=intracellular cytokine staining; IFN=interferon; IL=interleukin; NK=natural killer; PBMC=peripheral blood mononuclear cell; Th=T-helper (cell); TNF=tumor necrosis factor; Treg=regulatory T cell

Table 6: Summary of Immunogenicity Assays (Humoral)

Assay	Purpose
Exploratory endpoints	
Adenovirus neutralization assay	Analysis of neutralizing antibodies to adenovirus vector
MVA neutralization assay	Analysis of neutralizing antibodies to MVA vector
L1/L2 ELISA	Analysis of L1 and/or L2 antibodies by ELISA to HPV16 and/or HPV18 or other HPV genotypes
E2, E6 and E7 ELISA	Analysis of E2, E6 and/or E7 antibodies to HPV16 and/or HPV18 or other HR-HPV genotypes

ELISA=enzyme-linked immunosorbent assay; HPV=human papillomavirus; HR-HPV=high-risk human papillomavirus; MVA=modified vaccinia Ankara

Sample collection and processing will be performed by study-site personnel according to current versions of approved SOPs.

9.2.3. Virology and Histology

HPV16 and HPV18 genotyping will be performed with a qualitative PCR test (Cobas®, Roche) on the cervical samples. Prior to vaccination, a participant will have a confirmed diagnosis of an HPV16 or HPV18 infection. More information on the identification of an HPV infection is provided in the flow chart (Figure 4).

Cervical samples will be collected by the healthcare provider and by the participant (self-sampling) at the time points indicated in the Time and Events Schedule. Healthcare provider-obtained cervical samples collected using an endocervical brush will be processed in a transport medium and send to the central laboratory. Participants will self-collect cervico-vaginal samples with a dry self-sampling device (Evalyn® Brush, Rovers Medical Devices) at the study site. Immediately after collection of the cervico-vaginal specimen for this study, the Evalyn®

Brush should be dispensed in ThinPrep® following the procedure described in the Laboratory Manual. After collection of the cervico-vaginal sample, the dry Evalyn® Brush will be suspended in transport medium at the study site and sent to the central laboratory.

Cobas® testing will be performed by a central sponsor designated laboratory.

A quantitative HPV PCR genotyping test that detects HPV16 and HPV18 together with other individual HR-HPV types will be used on all cervical samples (healthcare provider-collected and self-collected) to address the exploratory endpoints.

Colposcopy examination will occur during screening only for those participants who do not have recent (within the last 12 months) examination results. A mandatory colposcopy examination will occur 12 months after the first dose for all participants. All colposcopy biopsy specimens will be sent to a central laboratory for standardized interpretation. Histopathological reports on biopsy and excision specimens will classify findings as: negative, CIN1, CIN2, CIN3, AIS and invasive malignancy. Note: All participants will have HSV-2 serology testing on the day of the first vaccination and the 12-month follow-up visit (or the early exit visit, if applicable).

Should a participant have an examination or treatment with a non-study gynecologist, she will be asked if she consents to allow study staff to access her medical records and obtain slide and tissue for evaluation.

Management and medical follow-up after the mandatory colposcopy evaluation will be at the discretion of the investigator and local guidelines.

Participants who discontinue the study will be recommended to continue regular cervical cancer screening.

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

10.1. Completion

A participant will be considered to have completed study vaccination if she has received all study vaccinations. A participant will be considered to have completed the study if she has completed assessments through to the end of the study (ie, Day 366) even if she did not receive the second vaccination.

10.2. Discontinuation of Study Vaccine/Withdrawal from the Study

Discontinuation of Study Vaccine

Participants will discontinue further study vaccine administration for the reasons listed below. These participants must not receive any additional dose of study vaccine but should be followed-up until the end of the follow-up period at Week 52 (12 months post-Dose 1 visit) with assessments of safety, immunogenicity and virology. Additional unscheduled visits may be

performed for safety/reactogenicity reasons, if needed. In case of questions, the investigator is encouraged to contact the sponsor.

- Any related AE, worsening of health status or intercurrent illnesses that, in the opinion of the investigator, required discontinuation from study vaccine
- The participant becomes pregnant
- Unblinding on the participant level that, in the opinion of the sponsor, would compromise the integrity of the data
- Anaphylactic reaction following vaccination
- SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine
- Chronic or recurrent use of immunosuppressants (after discussion with the sponsor)
- Missing a study vaccination

Withdrawal From the Study

Each participant has the right to withdraw from the study at any time for any reason. The investigator should make an attempt to contact participants who did not return for scheduled visits or follow-up. Although the participant is not obliged to give reason(s) for withdrawing prematurely, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the participant's rights.

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

- Lost to follow-up
- Withdrawal of consent
- Death
- Repeated failure to comply with protocol requirements
- Decision by the sponsor or the investigator to stop or cancel the study
- Decision by local regulatory authorities or Institutional Review Board/Independent Ethics Committee (IRB/IEC) to stop or cancel the study

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

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study vaccine assigned to the withdrawn participant may not be assigned to another participant. In general, participants who withdraw will be replaced, as long as the participant has not been vaccinated yet. However, any randomized participant withdrawn from the study for reasons other than due to an AE after the first dose but

before the last dose might be replaced at the discretion of the sponsor. If a participant withdraws early from the study, assessments for early withdrawal should be obtained (see Section 9.1.4.4).

Participants who wish to withdraw consent from participation in the study will be offered a single Exit visit (see Section 9.1.4.4) for safety follow-up (prior to formal withdrawal of consent). They have the right to refuse.

Withdrawal From the Use of Samples in Future Research

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

10.3. Contraindications to Vaccination

The following events constitute a temporary contraindication to study vaccination. If any of these events occur at the scheduled time for vaccination, the participant may be vaccinated up to 10 days beyond the scheduled vaccination:

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

If the vaccination visit cannot be rescheduled within the allowed window or the contraindications to vaccination persist, the sponsor should be contacted for further guidance.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the safety, immunogenicity and virology data is outlined below. Specific details will be provided in the statistical analysis plan (SAP).

Planned analyses are described in Section 11.7.

11.1. Analysis Sets

Vaccination assignment will follow the as treated principle.

11.1.1. Full Analysis Set

The Full Analysis Set (FAS) will include all participants with at least 1 vaccination.

11.1.2. Per-Protocol Immunogenicity Population

The Per-Protocol Immunogenicity (PPI) population will include all randomized and vaccinated participants for whom immunogenicity data are available excluding participants with major protocol deviations expecting to impact the immunogenicity outcomes. In addition, if participants miss the second dose, but continue the planned visit schedule, samples taken after the planned but missed dose will not be taken into account.

11.2. Sample Size Determination

While mild to moderate local and systemic AEs are expected, AEs that preclude further vaccination or more serious ones that would limit product development are not anticipated. With 20 participants in 1 vaccine regimen, the observation of 0 such reactions after the first vaccination would be associated with a 95% confidence that the true rate is less than 13.9%. Across regimens (n=48), the observation of 0 such reactions after the first vaccination would be associated with a 95% confidence that the true rate is less than 6.1%.

11.3. Participant Information

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

Baseline characteristics will include HPV infection history as well as HPV infection type, the latter being categorized as follows:

- Participants with persistent infection defined as at least 2 positive cervical HPV PCR tests with an interval of at least 11 months as follows: 2 positive HPV16 (or 2 positive HPV18 tests) or, if the genotype of the first test is unknown and after consultation with the sponsor, HR-HPV positivity followed by HPV16 (or HPV18) positivity. Note: the historical positive cervical HPV PCR test will be taken into account for the definition regardless of the length of the interval (>11 months) as long as there were no known negative results in between.

- Participants with recently diagnosed (within 12 months prior to baseline) HPV infection which is not persistent as defined above.

11.4. Safety Analyses

All safety analyses will be performed on the FAS.

No formal statistical testing of safety data is planned. Safety data will be tabulated by vaccine regimens and pooled placebos and will be analyzed descriptively. The severity of abnormal symptoms, vital signs, AEs and abnormal laboratory values will be graded based on the toxicity table from the FDA "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007, see Attachment 2)".

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs (solicited local, solicited systemic, and unsolicited), event-related diary information, and all SAEs with onset or worsening within 28 days after each vaccination will be included in the analysis. For each AE, the percentage of participants who experience at least one occurrence of the given event will be summarized by vaccine schedule.

Summaries, listings, datasets, or narratives may be provided, as appropriate, for those participants who die, who discontinue study vaccine due to an AE, or who experience a severe AE or an SAE.

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

Solicited local (at injection site) and systemic AEs will be summarized descriptively. The overall frequencies per vaccine group as well as frequencies according to severity and duration will be calculated for solicited AEs. In addition, the number and percentages of participants with at least 1 solicited local (at injection site) or systemic AE will be presented. Frequencies of unsolicited AEs, separately for all and vaccination-related only, will be presented by System Organ Class and preferred term, while those of solicited AEs will be presented only by preferred term.

Clinical Laboratory Tests

Laboratory data will be reported by type of laboratory test. Actual values and changes from baseline will be summarized for each laboratory analyte at baseline and at each scheduled time point (ie, Visits 1, 4 and 8). Graphical presentation of changes in laboratory tests will be made as applicable. Baseline refers to the last value prior to first vaccination.

Laboratory abnormalities will be determined according to the FDA toxicity grading tables (see Attachment 2) or, for tests for which no grades are available, in accordance with the normal ranges of the clinical laboratory. Any laboratory value shown as a "graded" value in the FDA table that is within the institutional normal ranges will not be graded for severity.

Vital Signs

Values and changes from baseline of supine heart rate and blood pressure (systolic and diastolic) will be summarized at each scheduled time point (baseline refers to the last value prior to first vaccination). The percentage of participants with values beyond pre-specified limits will be reported.

Physical Examination

Physical examination findings at baseline will be summarized. Abnormalities during the study will be listed.

11.5. Immunogenicity Analyses

The immunogenicity analyses will be performed on the PPI set. An additional analysis will be done for the FAS.

Immunogenicity analyses for HPV16 and HPV18 participants will be performed either combined or by HPV type (HPV16 or HPV18), and by infection type (persistent or recently diagnosed).

No formal hypothesis on immunogenicity will be tested. Descriptive statistics (geometric mean and 95% CI, or median and quartile range [Q1-Q3], as appropriate) will be calculated for

continuous immunological parameters at all time points. Graphical representations of immunological parameters will be made as applicable. Frequency tabulations will be calculated for discrete (qualitative) immunological parameters as applicable.

11.6. Virology Analyses

The analyses will be performed on the FAS data set for whom virology endpoint measures are available.

Frequency and kinetics of clearance of HPV16 or HPV18 infection will be analyzed either combined or by HPV type (HPV16 or HPV18), and by infection type (persistent or recently diagnosed) using both the healthcare provider- and self-collected cervical samples and will be described for the vaccine regimens and placebo during the study duration.

11.7. Planned Analyses

A blinded interim analysis may be performed after all participants from Phase 1 of the study have completed the 21 days post-Dose 2 visit (Week 11) or have discontinued earlier. This analysis, which will include immunogenicity and safety data, will allow to identify immunogenicity and overall safety signals and guide further development of the vaccine.

The primary analysis will occur when all participants have completed the 6 months post-Dose 1 visit (Week 26) or have discontinued earlier. If enrollment is slow for HPV18-infected participants, an interim analysis may first be performed on the HPV16-infected participants. The primary analysis will then be performed on all participants when all HPV18 infected participants have completed the 6 months post-Dose 1 visit (Week 26) or have discontinued earlier. These analyses will include safety and virology data up to the 6 months post-dose 1 visit (Week 26) and immunogenicity data up to the 21 days post-Dose 2 visit (Week 11).

The final analysis will occur when the last participant completes the final visit at 12 months post-Dose 1 (Week 52, Day 366) or discontinued earlier to determine the durability of the immune response and analyze any additional safety, virology and immunological data collected after the primary analysis. If enrollment is slow for HPV18-infected participants, an interim analysis may first be performed on the HPV16-infected participants. The final analysis will then be performed on all participants when all HPV18 infected participants have completed the 12 months post-Dose 1 visit (Week 52) or have discontinued earlier.

The safety, virology and immunogenicity analysis will include the timepoints described in the TIME AND EVENTS SCHEDULE. At the time of the primary analysis, the study will be unblinded for sponsor personnel (including medical personnel, biomarker lead, virologist, statistician, programming and data management). Participants, clinical staff and study-site personnel will remain blinded to the study vaccine allocation until the end of the study.

11.8. Independent Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study. It will consist of members independent of the sponsor,

including at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The PI and SRP will inform the IDMC of any AE of concern.

The IDMC will convene to discuss any situation that meets a study vaccination pausing or stopping rule as outlined in Section 11.9. The IDMC responsibilities, authorities and procedures will be documented in its charter. In addition, the IDMC will review the 7-day safety data post-Dose 1 among all participants in Phase 1; initially in those receiving the low dose of Ad26.HPV16 or Ad26 HPV18 vaccine and then among all those dosed with high dose vaccine (Ad26.HPV16 or Ad26.HPV18) or the mixed vaccine (Ad26.HPV16/Ad26.HPV18). Further randomization and vaccination of participants will be suspended until this IDMC review is completed. The IDMC will also review 7-day safety data post-Dose 2 (MVA.HPV16/18) among all participants in Phase 1. Safety data for review will include solicited and unsolicited AEs, SAEs, and laboratory assessments. After these reviews, the IDMC will make recommendations regarding the continuation of the study. The conclusion of the IDMC will be communicate to the investigators, the IEC/IRB and the national regulatory authorities as appropriate.

The IDMC will review unblinded data. Details on the intervals of the safety evaluations and on how the integrity of the study will be maintained when the blind is broken with an IDMC analysis will be provided in the IDMC charter. Safety data from the primary analysis will be shared with the IDMC.

11.9. Study Safety Rules

Study Pausing Rules

If a study vaccination is considered to raise significant safety concerns (and a specific set of pausing criteria have been met), further vaccination of participants will be paused. The concerned data will be reviewed by the IDMC, after which the IDMC will recommend whether the pause can be lifted or not, or whether other steps are needed.

The occurrence of any of the following events will lead to a pause in further study vaccination. This list is only applicable for concerned AEs that occur up to 28 days after each vaccination and to concerned SAEs throughout the study.

1. Death of a participant; OR
2. One or more participants experience a SAE or a Grade 4 (solicited or unsolicited) AE or a persistent (upon repeat testing) Grade 4 laboratory abnormality; OR
3. One or more participants experience a diagnostic level 1, 2 or 3 criterion for anaphylaxis[43] within 24 hours of vaccination; OR
4. Two or more participants experience a Grade 3 unsolicited AE of the same type (as per medical judgment of the sponsor); OR
5. Two or more participants experience a persistent (upon repeat testing) Grade 3 laboratory abnormality; OR

6. Two or more participants experience a Grade 3 solicited AE of the same type and persisting as Grade 3 for longer than 3 consecutive days[a].

For number 2 and number 5: to assess abnormal laboratory values, the test must be repeated at least once, within 48 hours of the site becoming aware of the abnormal value.

For number 4, number 5, and number 6: after each IDMC review of similar AEs, the Committee will indicate the conditions under which it requires further notification and review of the subsequent similar AEs.

To enable prompt response to a situation that could trigger pausing rules, the investigator should notify the sponsor's medical monitor or designee (AND fax or email SAE form to Global Medical Safety Operations, if applicable), immediately and no later than 24 hours after becoming aware of any related AE of Grade 3 or above (AND update the eCRF with relevant information on the same day the AE information is collected).

A thorough analysis of all Grade 3 cases will be carried out by the sponsor's medical monitor or designee, irrespective of whether the criteria for pausing the study are met.

Based on the pausing criteria, the sponsor's medical monitor or designee then decides whether a study pause is warranted. All sites will be notified immediately in case of a study pause. The sponsor's medical monitor or designee is responsible for the immediate notification of IDMC members and coordination of a IDMC meeting in case of a study pause.

Vaccinations for an individual participant may be suspended for safety concerns other than those described in the pausing criteria, at the discretion of the investigator if he/she feels the participant's safety may be threatened. The sponsor's medical monitor or designee or the investigator(s) (upon consultation with the sponsor's medical monitor or designee) may initiate IDMC review for any single event or combination of multiple events which, in their professional opinion, could jeopardize the safety of the participants or the reliability of the data.

Vaccinations for the study may be suspended for safety concerns other than those described above, or before pausing rules are met, if, in the judgment of the IDMC, participant safety may be threatened.

Resumption of vaccinations will start only upon sponsor receipt of the written recommendations by the IDMC. The clinical site(s) will be allowed to resume activities upon receipt of a written notification from the sponsor. The communications from the IDMC will be forwarded by the investigator to the IRB/IEC and by the sponsor to the relevant health authorities, according to local standards and regulations.

[a] The day of occurrence of the AE is counted as Day 1.

Stopping Rules for Study Termination

If any of the conditions below (stopping rules) are met, further vaccination of subjects will be stopped and following consultation with the IDMC the study terminated except for the safety evaluations of already immunized participants specified in the protocol and any further safety evaluations recommended by the IDMC:

- Death of a participant, considered related to study vaccine or if the causal relationship to the study vaccine cannot be excluded; OR
- One or more participants experience diagnostic level 1 criterion for anaphylaxis[43] within 24 hours of vaccination, clearly not attributable to other causes than vaccination with study vaccine.
    - Level 1 definition of anaphylaxis:
        - ≥1 major (see below) dermatological AND
        - ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion (see below)

Major criteria

Dermatologic or mucosal	• generalized urticaria (hives) or generalized erythema • angioedema*, localized or generalized • generalized pruritus with skin rash
Cardiovascular	• measured hypotension • clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: • tachycardia • capillary refill time >3 s • reduced central pulse volume • decreased level of consciousness or loss of consciousness
Respiratory	• bilateral wheeze (bronchospasm) • stridor • upper airway swelling (lip, tongue, throat, uvula, or larynx) • respiratory distress—2 or more of the following: • tachypnoea • increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.) • recession • cyanosis • grunting

* Not hereditary angioedema.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting AEs and SAEs

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

Solicited Adverse Events

Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned and symptoms of which are noted by participants in their diary (see Section 9.1.1).

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is NOT specifically questioned in the participant diary.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the product. 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 Council 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 unsolicited AEs starting from the time of ICF signature until 28 days after the first vaccination, and from the time of the second vaccination through the following 28 days, and solicited AEs from the time of each vaccination for 7 days post-vaccination (refer to Section 12.3.1 for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and European Union (EU) Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

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

- Is Medically Important*

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Ad26.HPV16, Ad26.HPV18 and MVA.HPV16/18, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochures.

Adverse Event Associated With the Use of the Study Vaccine

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

12.1.2. Attribution Definitions

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

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

Related: there is suspicion that there is a relationship between the study vaccine and the AE (without determining the extent of probability); there is a reasonable possibility that the study vaccine contributed to the AE.

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

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

12.1.3. Severity Criteria

All AEs and laboratory data reported as AEs will be coded for severity using the FDA toxicity grading tables (see Attachment 2). Note that laboratory values within laboratory normal ranges (even if within a toxicity grade range), or laboratory values outside normal ranges that are not clinically significant in the judgment of the investigator, should not be recorded as AEs. For AEs not identified in the grading table, the following guidelines will be applied:

- Mild (Grade 1): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- Moderate (Grade 2): Sufficient discomfort is present to cause interference with normal activity.
- Severe (Grade 3): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday 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.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

The toxicity grading scale used for laboratory assessments is based on the FDA toxicity grading table (see Attachment 22), consistent with the assessment grading used throughout the protocol. If a laboratory value falls within the grading as specified in the FDA table, but also within the laboratory normal limits, the value is considered as normal. For hemoglobin, both the actual value and the change from reference will be graded.

The severity of solicited AEs will be graded in the diary by the subject based on the severity assessment provided in the diary and then verified by the investigator using the FDA toxicity grading table (see Attachment 2).

12.2. Special Reporting Situations

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

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

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.

12.3. Procedures

12.3.1. All Adverse Events

Unsolicited AEs and special reporting situations will be reported from the time of ICF signature until 28 days after the first vaccination, and thereafter, for 28 days after each subsequent dose of study vaccine. Unsolicited AEs with the onset date outside the time frame defined above (>28 days after previous study vaccination) that are ongoing on the day of the subsequent vaccination should be recorded on the eCRF AE page.

Solicited AEs will be recorded by each participant in the participant diary for 7 days after each dosing. The investigator will review each participant's diary at the subsequent in-clinic visit; diary information will be transcribed by the study personnel in the on-site assessment forms in the eCRF.

All SAEs and AEs leading to discontinuation from the study vaccination (regardless of the causal relationship) are to be reported for the duration of the study. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

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 (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion regarding the relationship of the AE to study vaccine. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

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

Participants will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

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

- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring from the time of ICF signature until the end of 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 an SAE should be made by facsimile (fax) and/or through secure email.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant'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 (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

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

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the 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 participant in a study during the entire study period, whether or not the event is expected or associated with the study vaccine, is considered an SAE and must be reported.

12.3.3. 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(s). If a participant becomes pregnant during the course of the study, no more injections of study product will be given during the pregnancy, but remaining visits and study procedures should be completed unless medically contraindicated or applicable regulations require termination from the study. If the participant terminates from the study prior to the pregnancy outcome, the site should make every effort to keep in touch with the participant in order to ascertain the pregnancy outcome. All pregnancies and pregnancy outcomes should be recorded.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies and ectopic pregnancy) are considered SAEs and must be reported using the SAE Form.

12.4. Contacting Sponsor Regarding Safety

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

13. PRODUCT QUALITY COMPLAINT HANDLING

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

13.1. Procedures

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

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

13.2. Contacting Sponsor Regarding Product Quality

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

14. STUDY VACCINE INFORMATION

14.1. Physical Description of Study Vaccine

Human replication-incompetent adenovirus-vectored vaccine candidates (manufactured and provided under the responsibility of the sponsor), as well as a MVA-based replication-incompetent vaccine (developed in collaboration with Bavarian Nordic A/S) (MVA-BN®) will be assessed in this study:

Ad26.HPV16 (JNJ-63682918)

Ad26.HPV16 is a recombinant replication-incompetent Ad26 vector encoding genetically modified HPV16 early (E2, E6 and E7) proteins.

For this study, Ad26.HPV16 will be formulated as a solution for intramuscular injection and supplied in a single use vial ($1x10^{11}$ vp/mL; 0.5 mL [extractable volume]).

Ad26.HPV18 (JNJ-63682931)

Ad26.HPV18 is a recombinant replication-incompetent Ad26 vector encoding genetically modified HPV18 early (E2, E6 and E7) proteins.

For this study, Ad26.HPV18 will be formulated as a solution for intramuscular injection and supplied in a single use vial ($1x10^{11}$ vp/mL; 0.5 mL [extractable volume]).

For Regimen 3 of this study, the monovalent Ad26.HPV16 and Ad26.HPV18 vaccine component will undergo mixing and will be given as a single injection; denoted by Ad26.HPV16/Ad26.HPV18 in this document.

MVA-mBN411B (JNJ-65195208)

MVA-mBN411B, referred to as MVA.HPV16/18 in this document, is a live vaccine which is non-replicating in human cells and encodes the same genetically modified HPV16 and HPV18 early (E2, E6 and E7) proteins.

For this study, MVA.HPV16/18 will be formulated as a suspension for intramuscular injection and supplied in a single use vial ($5x10^{8}$ Inf.U/0.5 mL; 0.5 mL [extractable volume]). The MVA.HPV16/18 vaccine will be administered at a dose of $2x10^{8}$ Inf.U by mixing with the diluent DS-TEC-138030.

Placebo

Placebo will be supplied as sterile 0.9% saline for injection in 10 mL (filled volume) vials.

Diluent

Diluent 5 (20 mM histidine, 75 mM NaCl, 0.02% [w/v] tween-80, 5% [w/v] sucrose, 0.1 mM ethylenediaminetetraacetic acid [EDTA], 0.5% [v/v] ethanol, pH 6.5), DS-TEC-79875, will be supplied in a single use vial (1 mL [extractable volume]). This diluent is to be added to the Ad26.HPV16 or Ad26.HPV18 vials for administration of the Ad26.HPV16 or Ad26.HPV18 vaccines at a dose of $5x10^{10}$ vp.

A diluent consisting of TBS (10 mM tris, 140 mM NaCl, pH 7.7), DS-TEC-138030, will be supplied in a single use vial (1.5 mL [extractable volume]). One mL of this diluent is to be added to the MVA.HPV16/18 vial for administration of the vaccine at a dose of $2x10^8$ Inf.U.

14.2. Packaging and Labeling

All study vaccines were manufactured and packaged in accordance with Current Good Manufacturing Practice. All study vaccines will be packaged and labeled under the responsibility of the sponsor. Study vaccine labels will contain information to meet the applicable regulatory requirements.

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

Further details for study vaccine packaging and labeling can be found in the Site Investigational Product Procedures Manual.

14.3. Storage and Handling

Ad26.HPV16, Ad26.HPV18, MVA.HPV16/18 and placebo must be stored as specified on the study vaccine labels.

Vials must be stored in a secured location under controlled temperature with no access for unauthorized personnel. The study refrigerator/freezer must be equipped with a continuous temperature monitor and alarm. Study refrigerators/freezers should be equipped with back-up power systems. In the event that study vaccine is exposed to temperatures outside the specified temperature range, all relevant data will be sent to the sponsor to determine if the affected study vaccine can be used or will be replaced. The affected study vaccine must be quarantined and not used until further instruction from the sponsor is received.

Blinding will be achieved by preparation of study vaccine by an unblinded pharmacist or other qualified study-site personnel with primary responsibility for study vaccine preparation and dispensing, and by the administration of vaccine in a masked syringe by a blinded study vaccine administrator.

Refer to the Site Investigational Product and Procedures Manual for additional guidance on study vaccine preparation, handling and stability, and storage.

14.4. Study Vaccine Accountability

The investigator is responsible for ensuring that all study vaccine received at the site is inventoried and accounted for throughout the study. The study vaccine administered to the participant must be documented on the vaccine accountability form. All study vaccine will be stored and disposed of according to the sponsor's instructions.

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

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

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

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure for Ad26.HPV16, Ad26.HPV18 and MVA.HPV16/18
- Site Investigational Product Procedures Manual
- Laboratory Manual
- Electronic Data Capture (eDC) eCRF completion guidelines and randomization instructions
- Sample ICF
- Diary cards
- Rulers, thermometers
- Participant wallet cards

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to

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

The total blood volume drawn from each participant will not exceed the US Department of Health and Human Services Office for Human Research Protections, and US FDA guidelines of 550 mL in any 8-week period.[49,50]

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

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

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable

recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study vaccine
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

16.2.3. Informed Consent

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the

reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF, the participant is authorizing such access. It also denotes that the participant agrees to allow her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

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

16.2.4. Privacy of Personal Data

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

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

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

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

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

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand Ad26.HPV16, Ad26.HPV18 and MVA.HPV16/18, to understand persistent HPV16 or 18 infection, and to develop tests/assays related to Ad26.HPV16, Ad26.HPV18 and MVA.HPV16/18. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 10.2).

16.2.6. Country Selection

This study will only be conducted in the US.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

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

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

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

17.3. Participant Identification, Enrollment, and Screening Logs

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

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

identification. In cases where the participant is not randomized into the study, the date seen will be used.

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

17.4. Source Documentation

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

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

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

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

An eSource system may be utilized, which contains data traditionally maintained in an hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

17.5. Case Report Form Completion

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

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

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

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

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

17.6. Data Quality Assurance/Quality Control

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

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after their return to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database, the data will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

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

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

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

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

17.8. Monitoring

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

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

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding Ad26.HPV16, Ad26.HPV18 and MVA.HPV16/18 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. 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.HPV16, Ad26.HPV18 and MVA.HPV16/18, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report (CSR) generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR. Study participant identifiers will not be used in publication of results. Any

work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: Definition of Woman of Childbearing Potential

Woman of Childbearing Potential

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

Woman Not of Childbearing Potential

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

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

Attachment 2: Toxicity Tables

From the FDA Guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007)

A: Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to Touch	Discomfort with Movement	Significant discomfort at rest	ER visit or Hospitalization
Erythema/redness*	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/swelling**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Fever** (°C) Fever** (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	>40 >104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mmHg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mmHg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) - mmHg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate - breaths per minute	17 – 20	21 – 25	>25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 - 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools or < 400 gms/24 hours	4 - 5 stools or 400 - 800 gms/24 hours	6 or more watery stools or >800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

B: Tables for Laboratory Abnormalities

The grading scale used for laboratory assessments is based on the FDA Guidance document "Toxicity Grading Scale from Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". Any laboratory value shown as a "graded" value in the table that is within the institutional normal ranges will not be graded for severity or recorded as AE. For hemoglobin, both the actual value and the change from reference will be graded. For the change from reference, the corresponding actual value should also be graded.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4) **
Sodium – Hyponatremia - mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia - mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia - mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia - mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia - mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting - mg/dL	100 – 110	111 – 125	> 125	Insulin requirements or hyperosmolar coma
Random Glucose - mg/dL	110 – 125	126 – 200	>200	
Blood Urea Nitrogen BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine - mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia - mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia - mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia - mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia - mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK - mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia - g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein –	5.5 – 6.0	5.0 – 5.4	< 5.0	--

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4) **
Hypoproteinemia - g/dL				
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	--
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life-threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4) **
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm3	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC Decrease - cell/mm3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm3	650 – 1500	1501 – 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT - increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT - increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** ULN is the upper limit of the normal range.

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Michal Sarnecki, MD

Institution: Janssen Vaccines & Prevention B.V.

Signature: [electronic signature appended at the end of the protocol] Date: _____

(Day Month Year)

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

SIGNATURES

Signed by	Date	Justification
Michal Sarnecki	20Aug2019, 12:20:32 PM, UTC	Document Approval

Janssen Vaccines & Prevention*

Clinical Protocol

COVID-19 Appendix

Protocol Title

Randomized, Double-blind, Placebo-controlled First-in-Human, Phase 1/2a Study to Evaluate the Safety, Reactogenicity and Immunogenicity of Monovalent HPV16 and HPV18 Ad26-vectored Vaccine Components and an MVA-vectored HPV16/18 Vaccine Component in Otherwise Healthy Women with HPV16 or 18 Infection of the Cervix

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Protocol VAC81623HPV1002; Phase 1/2a

VAC81623 (JNJ-63682918, JNJ-63682931 and JNJ-65195208)

*Janssen Vaccine & Prevention 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.

EudraCT NUMBER: 2018-000200-41

Status: Approved
Date: 03 July 2020
Prepared by: Janssen Research & Development, a division of Janssen Pharmaceutica NV
EDMS number: EDMS-RIM-72803 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL VAC81623HPV1002 (EDMS-ERI-146564753).

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

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/at home or delayed until such time that on-site visits can be resumed.[a] The actual visit date and the type of visit (ie, telephone or videoconference) should be captured in the electronic case report form (eCRF). The missed procedures should be recorded as "missed due to COVID-19". At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.

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

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

A remote visit is defined as a visit during which the participant and the qualified and blinded site staff interact via phone or video call in case the participant is not able to be physically present at the study site.

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

GUIDANCE SPECIFIC TO THIS PROTOCOL

The following emergency provisions are meant to ensure participant safety on study while site capabilities are compromised by COVID-19-related restrictions. Remote medical consultation and alternatives to study intervention dispensing, administration, and clinical laboratory assessments may allow continued study participation for participants in this trial. As local restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible and in accordance with any country-specific regulatory requirements. If due to the COVID-19 pandemic, screening assessments fall outside of the window allowed per protocol, re-screening would be allowed once.

Study visits and assessments

To safely maintain participants on study intervention while site capabilities are compromised by COVID-19-related restrictions, participants may have tele-health visits until such time that on-site visits can be resumed. These remote visits will be conducted by qualified and blinded study site staff via phone or video conversation as per local regulation. Note that study vaccinations should always be given on site.

- **Physical examination (PE):** PEs at study visits other than screening visits are abbreviated, symptom-directed assessments. Therefore, a protocol deviation would not be documented for a missed physical exam if there are no symptoms present. However, if it is not possible to make any PE assessments when symptoms are present, then a COVID-19 protocol deviation would be reported and the participants would need to be referred to their respective primary care physician or emergency room as required.

- **Temperature measurements**: it would be acceptable to have the patient recording his/her temperature at home and reporting that to the study site staff during remote visits in order to avoid missing data. If it is not possible for the participant to have his/her temperature measured, then a missed value would be reported as a COVID-19 protocol deviation.

- **Diary review:** it would be acceptable to review diary data with study site staff during remote visits (teleconference/videoconference) and have the data immediately entered on the eCRF.

- **Adverse events:** Standard adverse event (AE)/serious adverse event (SAE) reporting requirements apply.

- **Out of window vaccinations:** In the event site capabilities are compromised by COVID-19-related restrictions, out of window vaccinations would be allowed on a case-by-case basis and after discussion between the investigator and the sponsor.

Informed consent

A revised informed consent form (ICF) or an addendum to the ICF, arising from this amendment, is to be signed by the participants during a site visit. For any informed consent that cannot be performed in person (eg, verbal consent by telephone), the process must be documented in the

source documents and confirmed by way of normal consent procedures at the earliest opportunity. If consent is given verbally by phone, an impartial witness should be present at the study site, if required by local regulations, for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent is obtained.

Source data verification/monitoring

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

Any deviations to study procedures occurring during the COVID-19 pandemic would be captured appropriately in the clinical trial management system (or eCRF), with the prefix "COVID-19-RELATED" (including actual visit date documented or reasons for withdrawals specified; discontinuations of study interventions and withdrawal from the study if applicable).

Audits

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

INVESTIGATOR AGREEMENT

COVID-19 Appendix
VAC81623 (JNJ-63682918, JNJ-63682931 and JNJ-65195208) Clinical Protocol VAC81623HPV1002

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Michal Sarnecki, MD

Institution: Janssen Vaccines & Prevention

Signature: Michal Sarnecki Digitally signed by Michal Sarnecki
DN: c=US, o=JNJ, ou=Subscribers, 0.9.2342.19200300.100.1.1=405402, cn=Michal Sarnecki
Reason: I am approving this document.
Date: 2020.07.03 08:31:53 +02'00'
Adobe Acrobat version: 11.0.20 Date: _____
(Day Month Year)

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

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 5
Status: Approved, Date: 03 July 2020