Janssen Vaccines & Prevention B.V.

Statistical Analysis Plan
Amendment 1

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

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

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

SAP History VAC81623HPV1002			
Document Type and File Name	**Issued Date**	**Amendment Type**	**Comments**
Initial Statistical Analysis Plan VAC81623HPV1002_SAP	04/10/2018	-	
Amended Statistical Analysis Plan VAC81623HPV1002_SAP_Amendment 1	14/10/2020	Non-substantial	For details, please refer to Section SAP AMENDMENTS

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LIST OF IN-TEXT TABLES

ABBREVIATIONS

Ad26	Adenovirus serotype 26
ADaM	Analysis Data Model
AE	Adverse Event
CI	Confidence Interval
CRF	Case Report Form
CTP	Clinical Trial Protocol
DPS	Data Presentation Specifications
ELISpot	Enzyme-linked Immunospot
FDA	Food and Drug Administration
ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Committee
IFNγ	Interferon Gamma
IL-2	Interleukin 2
LLOQ	Lower Limit Of Quantification
MVA	Modified Vaccinia Ankara
NA	Not Applicable
PBMC	Peripheral Blood Mononuclear Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TFL	Tables, Figures and Listings
TNFα	Tumor Necrosis Factor Alpha

SAP AMENDMENTS

Amendment 1 (Creation date 14/10/2020)

The overall reason for the amendment: A temporary study pause on all start up and recruitment activities was initiated for study VAC81623HPV1002 in March 2020 triggered by the COVID-19 pandemic restrictions. The sponsor has continued to closely monitor developments around COVID-19 in the US and abroad. Due to ongoing impact of the pandemic and given previous challenges with recruitment to the study, it has been ultimately decided that a re-start and completion of this study is unfeasible. Therefore, all study activities were stopped. Only one final analysis will be performed where a limited number of tables, graphs and listings of results will be provided to support clinical trial disclosure, extended/exploratory analyses were therefore removed from the SAP and DPS.

In comparison to the first version of the SAP, the inclusion/exclusion criteria in the CTP have been adapted to enroll a broader population of women with any HPV16 or 18 infection of the cervix, not limited to persistent infection. Definitions of the HPV infection types were added. The immunogenicity section has been updated following additional information on assays. An update on the MVA.HPV16/18 dose was done as well. Additionally, small updates to the phase, full analysis set, and concomitant allocation definitions were made. An FDA scale to SI units conversion table and a local reaction to injectable product table were added in the attachment.

Other minor corrections were made throughout the document.

Find below the sections that are affected:

1. Introduction
1.1. Trial Objectives and Endpoints
1.2. Trial Design
1.6. Changes to Planned Analyses
2.1.1. Phase Definitions
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1. INTRODUCTION

This is the Statistical Analysis Plan (SAP) applicable for the VAC81623HPV1002 trial. This SAP is applicable for the following analyses.

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 analyze the safety, virology and immunological data collected during the study. 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.

This document contains all information needed to perform a full safety, immunogenicity and virology analysis. Which tables, figures and listing (TFL) need to be generated for this analysis is described in a separate data presentation specifications (DPS) document.

1.1. Trial Objectives and Endpoints

The following primary and secondary objectives and endpoints will be described in detail in this SAP.

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 interleukin 2 (IL-2) (combined cytokine expression may also be assessed) will be determined by flow cytometry.

1.2. Trial Design

See CTP, Section 3.1.

Table 1: Vaccine Regimen

HPV Type	Regimen	Day 1	Day 57 (Week 8)	Total
HPV16	Regimen 1a (low dose)	Ad26.HPV16 ($5x10^{10}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	4
	Regimen 2a (high dose)	Ad26.HPV16 ($1x10^{11}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	10
	Regimen 3 (pharmacy mixing)	Ad26.HPV16 ($5x10^{10}$ vp) + Ad26.HPV18 ($5x10^{10}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	10
	Control	Placebo (1.0 mL)	Placebo (0.5 mL)	9
Total HPV16				33
HPV18	Regimen 1b (low dose)	Ad26.HPV18 ($5x10^{10}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	4
	Regimen 2b (high dose)	Ad26.HPV18 ($1x10^{11}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	10
	Regimen 3 (pharmacy mixing)	Ad26.HPV16 ($5x10^{10}$ vp) + Ad26.HPV18 ($5x10^{10}$ vp)	MVA.HPV16/18 ($2x10^{8}$ Inf.U)	10
	Control	Placebo (1.0 mL)	Placebo (0.5 mL)	9
Total HPV18				33
Total				66

vp = viral particles, Inf.U = infectious units

1.3. Statistical Hypotheses for Trial Objectives

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

1.4. Sample Size Justification

See CTP, Section 11.2.

1.5. Randomization and Blinding

See CTP, Section 5.

1.6. Changes to Planned Analyses

A temporary study pause on all start up and recruitment activities was initiated for study VAC81623HPV1002 in March 2020 triggered by the COVID-19 pandemic restrictions. The sponsor has continued to closely monitor developments around COVID-19 in the US and abroad. Due to ongoing impact of the pandemic and given previous challenges with recruitment to the study, it has been ultimately decided that a re-start and completion of this study is unfeasible. Therefore, all study activities were stopped. Only the final analysis will be performed where a limited number of tables, graphs and listings of results will be provided to support clinical trial disclosure, extended/exploratory analyses were therefore removed from the SAP and DPS.

2. GENERAL ANALYSES DEFINITIONS

2.1. Study phases

A baseline (or reference) value will be defined as the value of the last available assessment prior to the first vaccination on Day 1. The safety analysis will present all results by phase. Immunogenicity and virology results will be presented per scheduled time point as appropriate. Listings will be shown per phase and time point.

Study day or relative day is defined as follows:
Study Day = visit date – date of Day 1 + 1; if visit date ≥ date of Day 1 (date of first vaccination).
Study Day = visit date – date of Day 1; if visit date < date of Day 1 (date of first vaccination).

2.1.1. Phase definitions

The phases in the study will be constructed as follows:

Table 2: Phase Definitions

Phase	Phase #	Period	Period #	Interval	
				From	To
Screening	1			Date and time of signing the informed consent form[a]	One minute prior to start of first vaccination
Regimen	2	Post-Dose 1	1	Date and time of first vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off date c) 28 days after first vaccination at 23:59 d) One minute prior to second vaccination
Follow-up 1	3			One minute after post-Dose 1 period end	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off date c) One minute prior to second vaccination
Regimen	2	Post-Dose 2	2	Date and time of second vaccination	Minimum of: a) 23:59 at the date of last contact (for early discontinuation) b) 23:59 at the date of database cut-off date c) 28 days after second vaccination at 23:59
Follow-up 2	4			One minute after post-Dose 2 period end	Minimum of: a) 23:59 at the date of last contact b) 23:59 at the date of database cut-off date

[a] In case an earlier date is available (e.g., for lab or vital signs), then use the very first date to include all data.
Note: participants who did not receive a second vaccination will not have a post-Dose 2 or follow-up 2 period.

The periods/phases will be used primarily for safety and concomitant medication allocation. The post-Dose periods (and the regimen phase) are considered active periods/phases, the screening and follow-up phases are considered non-active phases.

For immunogenicity and virology analyses no phases will be constructed. For descriptive statistics over time, assessments (regardless of the investigated parameter) will be allocated to an analysis visit based on the visit number as captured in the database.

2.2. Pooling Algorithm for Analysis Centers

Data will be pooled across the different centers.

2.3. Analysis Sets

Vaccination assignment will follow the as treated principle.

2.3.1. Full Analysis Set (FAS)

The full analysis set will include all participants with at least one vaccine administration documented, regardless of the occurrence of protocol deviations. All analyses will be based on the FAS.

2.4. Definition of Subgroups

Safety, immunogenicity and virology analyses will be performed for the active regimens versus the placebo regimen. Additionally, listings with demographics and baseline characteristics, safety, immunogenicity, and virology analyses will show infection type, according to the following definitions:

- **Persistent infection:** 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.

- **Non-persistent infection:** Participants with recently diagnosed (< 11 months prior to baseline) HPV infection which is not persistent as defined above.

The actual interval between the historical and the most recent cervical HPV PCR test will be evaluated to determine whether an HPV infection is persistent (i.e. at least 11 months).

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study. The IDMC will convene to discuss any situation that meets a study vaccination stopping or pausing rule as outlined in Section 11.9 in the CTP. The IDMC will review the unblinded 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 pharmacy mixed vaccine (Ad26.HPV16/Ad26.HPV18). The IDMC will also review the unblinded 7-day safety data post-Dose 2 (MVA.HPV16/18) among all participants in Phase 1.

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. 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. A separate SAP will be provided for the IDMC reviews.

4. PARTICIPANT INFORMATION

Participant information will be shown for the FAS.

4.1. Demographics and Baseline Characteristics

Demographic characteristics and screening/baseline characteristics will be presented in listings.

The following demographic and baseline characteristics will be summarized.

- Age (years)
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

- Marital/partner status
- Education
- Smoking status
- Age at first sexual intercourse
- Number of lifetime sexual partners
- Number of sexual partners during the last 12 months
- History of Chlamydia trachomatis

- Previous pregnancy
- Contraception
- Hormone use for other indication at study entry besides contraception
- Duration of hormone use for contraception or other indication during lifetime
- Menopausal status

- Infection type: non-persistent infection and persistent infection
- High-risk HPV coinfections, determined by Roche COBAS on the healthcare provider-collected sample

- High-risk HPV coinfections, determined by quantitative HPV PCR on the healthcare provider-collected sample
- BL quantitative HPV16 or HPV18 DNA load, determined by quantitative HPV PCR

- Previous Colposcopy results (> past 12 months to 5 years)
- Previous Cytology results (past 5 years)
- Coloscopy result/grading at baseline

The latter three baseline characteristics will be included in the colposcopy results listing.

4.2. Disposition Information

The number and percentage of participants screened, participants in the FAS, participants vaccinated and not randomized, participants randomized and not vaccinated and discontinued participants (study discontinuation and vaccination discontinuation) with the reason of discontinuation will be tabulated for the active regimens, the placebo group and overall.

Also, the number of participants and percentage per phase will be tabulated.

4.3. Treatment Compliance

The number of missed vaccinations will be tabulated. The number of vaccinations according to the time windows specified in Section 2.1.1 will also be tabulated.

4.4. Protocol Deviations

Major and minor Covid-19 related protocol deviations will be listed.

4.5. Concomitant Medications

The analysis of concomitant therapies will be done using the WHO drug coded terms.

Concomitant therapies will be listed. There will be special attention to any systemic use of analgesics/antipyretics administered during 8 days following each vaccination (00:00 of day of vaccination + 7 days). Following CMCLASCD (ATC/DD codes) will be used for this: N02A (OPIOIDS) and N02B (OTHER ANALGESICS AND ANTIPYRETICS), M01A (ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS) and M01B (ANTIINFLAMMATORY/ANTIRHEUMATIC AGENTS IN COMBINATION).

Based on their start and stop date, concomitant therapies will be reported in each applicable period/phase.

If a concomitant therapy record misses components of its start and/or stop dates (day and/or month and/or year) the following allocation rules will be applied:

- In case of partial start or stop dates, the concomitant therapy records will be allocated to periods using the available partial information, without imputations. If, for example, only month and year are available, these will be compared to the month and the year of the periods,

and the concomitant therapy record will be allocated to the period(s) where these date parts match. This rule may lead to assignment to multiple periods.

- In case of a completely missing start date, the CRF question 'medication/therapy taken prior to the study' will be used to determine whether the concomitant therapy is considered as having started before the trial or not. In case the medication/therapy did not start prior to the study and accounting for the end date, it will be assigned to the first active and all subsequent phases as applicable.
- In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial.

5. SAFETY

Safety analyses will be performed on the FAS. Continuous variables will be summarized using the following statistics, as appropriate: number of observations, arithmetic mean (mean), standard deviation (SD), median, quartiles (Q1 and Q3), minimum and maximum. Frequencies and percentages (one decimal place) will be generated for categorical variables. No formal comparisons between groups will be provided.

The minimum and maximum will be presented to the same number of decimal places as the original data. The mean, median and quartiles will be rounded to one more decimal place than the original data, while the SD will be rounded to two more decimal places.

Safety data will be analyzed for the active versus placebo regimens. Data will be presented by period (post-Dose 1 and post-Dose 2) as well as over the entire regimen. Denominator for the percentages is the number of participants in the considered population and period for a certain regimen (incidence per 100 participants/period).

5.1. Adverse Events (AE)

5.1.1. Solicited Injection Site (Local) Adverse Events

The analysis of local solicited adverse events, for all participants will include:

- Pain/Tenderness
- Erythema
- Swelling/Induration

5.1.2. Solicited Systemic Adverse Events

The analysis of systemic solicited adverse events for all participants will include:

- Fatigue
- Headache
- Myalgia

- Arthralgia
- Chills
- Nausea
- Fever (i.e., body temperature ≥ 38°C)

5.1.3. Definitions

Solicited AEs, collected during the 7-day period following each vaccination, will be extracted from the onsite assessments and the diary pages of the CRF. For unsolicited AEs, only the AEs within the 28-day period following each vaccination will be presented in the safety tables except for SAE, which will be captured and tabulated in the outputs covering the whole study period. All other collected unsolicited adverse events will be presented through listings.

Solicited local AEs will be, by definition, considered as related to the study vaccine.

The severity of the AEs will be classified as grade 1 to 4 according to the FDA grading list in Attachment 1. Solicited events that are graded less than grade 1, are not considered as AE.

5.1.4. Analysis of Adverse Events

Number and percentage of participants with at least one particular AE (unsolicited/solicited) will be tabulated. Listings for unsolicited AEs will include System Organ Class and Preferred Term. Listings for solicited AEs will include class (local, systemic) and preferred term.

For both solicited AEs and unsolicited AEs, a summary table will be provided, including SAEs, fatal outcome and discontinuation for the latter. Listings including all AEs will be provided. Note: duration is defined as the number of days from the start of the event until resolution of the event (AE end date – AE start data + 1). For the calculation of duration, imputed dates are allowed. For ongoing AEs, the imputed date will be used (see Section 5.1.5 for more details), partial dates will not be used. The time to first onset is defined as (date of first onset – reference date + 1). The reference date is the start date of each vaccination period.

5.1.5. Phase allocation of Adverse Events

Solicited events are always allocated to the respective post-Dose period.

Solicited AEs from the onsite assessments and the diary will be put in an ADaM with a similar structure and according to the same principles as the ADaM of unsolicited AEs (see below Step 2). This means the same event occurring on different days will be allocated to one row with the start date of the AE being the first date of the event and the end date for the event is the last subsequent day of the event. A change in grade will trigger a new row to be added. The same occurs in case of non-subsequent events (for example grade 1 nausea on day 1, 2 and 3 and also on day 6 and 7, which will be allocated to two rows; the duration of the event is 7 days, with 5 days of grade 1). If the on-site assessment differs in grade or relatedness (if collected per CRF) with a corresponding day (i.e., day of vaccination) of diary data, only the highest grade and relatedness assessment

indicating the highest level of relatedness to the study vaccination per AE will be kept in the analysis database and used in the tables and listings.

Step 1: Allocation of events to the periods:

Adverse events in the SDTM database are allocated to periods based on their start date/time.

1. If the start date/time of an event falls between (or on) the start and stop date/time of a period, the AE is attributed to that period (treatment-emergent principle).

2. In case of partial start or stop dates (i.e. time and/or day and/or month and/or year missing), the events are allocated to the periods using the available partial information on start and/or end date; no imputation will be done. If, for instance, for the AE start date only month and year are available, these data are compared to the month and year information of the periods. This rule may lead to multiplication of the event as a consequence of its assignment to multiple periods.

3. In case of a completely missing start date, the event is allocated to the appropriate period (post-Dose 1, post-Dose 2) and consequently the regimen period, except if the end date of the AE falls before the start of the post-Dose 1 period or post-Dose 2 period.

4. In case of a completely missing end date (for the calculation of duration), the date is imputed by the cut-off date of the analysis for participants still ongoing in the study, and by the end date of the last period for participants who discontinued or completed the trial. The imputed end dates will not be shown in the data listings.

Step 2: Combination of events:

Overlapping/consecutive events are defined as events of the same participant with the same preferred term which have at least 1 day overlap or for which the start date of an event is 1 day after the end date of the preceding event. Overlapping/consecutive events may be combined into one AE or not, according to the following rules:

1. If overlapping/consecutive events start in a non-active phase (Screening or post-Dose FU phases) followed by an AE in an active (post-Dose 1 or post-Dose 2) period, they are allocated to their respective periods/phases and are considered as separate events.

2. In case overlapping/consecutive events start within a single period, they are considered as one and the same AE. The individual events which contribute to this AE are retained as individual records in the ADaM database but are assigned the same onset, period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.

3. In case overlapping/consecutive events start in both an active period followed by a non-active period, they are allocated to the active period only and are considered as one and the same AE. The individual events which contribute to this AE are retained as individual

records in the ADaM database but are assigned the same onset, treatment period, and total duration. All related attributes to the AE/phase/period should also be consistent with the new event.

4. In case an active period is followed by another active period, and the overlapping/consecutive events start in both periods, they are allocated to their respective period and are considered as separate AEs. The same rule applies for 2 non-active periods.

Remarks:

1. Events can only be combined into one and the same AE if their start and stop dates are known.

2. In case the completely missing end date is imputed (for calculation of duration), this date is also considered as a complete date.

3. Time is not considered when determining overlap of events.

5.1.6. Missing Data

Missing data will not be imputed. Participants who do not report an event will be considered as participants without an event. An AE with a missing severity or relationship will be considered as an AE reported, but will be considered as not reported for the severity or relationship. For example, an AE with missing severity will be considered as an AE reported for the analysis of any grade but will be considered as not reported for the analysis of grade 3.

5.2. Clinical Laboratory Tests

For laboratory safety parameters, only abnormalities emerging after vaccination will be listed using the FDA table in Attachment 1.

An abnormality (toxicity grade or abnormality based on normal ranges) will be considered as emerging in a particular period if it is worse than the baseline value. If the baseline is missing, the abnormality is always considered emerging. A shift from ‘abnormally low’ at baseline to ‘abnormally high’ post baseline (or vice versa) is also emerging. In case a laboratory test result is censored (no numeric value is available, but only a verbatim term) then a numeric value will be imputed by a value exceeding the cut-off value with one unit. (<x: subtract 1 unit from x, >x: add 1 unit to x; <3.45 is imputed with 3.44).

In case no toxicity grades are defined for a test, the abnormalities (above/below normal range) will be used. In determining toxicity grades, the following rules are applied:

- Worst grades/abnormalities are determined over the whole observational period for each trial period separately, including all post-baseline measurements of that period.
- The abnormalities ‘abnormally low’ and ‘abnormally high’ are considered equally important, i.e. if a participant has both an abnormally low and an abnormally high value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%)

- Note: as the grading scale for some parameters in the grading table has some gaps (zones where no toxicity grade definition exists), laboratory results falling in these zones will be allocated to the adjacent worst-case grade.
- If a lab value falls within the grading as specified in the grading table but also within the local lab normal limits, the value is considered as normal.

5.3. Vital Signs and Physical Examination Findings

Similar to the clinical laboratory tests, only vital signs abnormalities emerging after vaccination will be listed.

Heart rate (beats per minutes, bpm), systolic blood pressure (mmHg), diastolic blood pressure (mmHg) and body temperature will be collected. The respective vital signs abnormalities are defined in ATTACHMENT 1: Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

A listing of participants with fever according to the FDA grading table will also be provided.

6. IMMUNOGENICITY ANALYSIS

The analysis of immunogenicity will use the FA set and will be performed by the defined subgroups (Section 2.4).

6.1. Parameters

Immunogenicity against the insert will be measured by the following assays:

Immunogenicity against the insert (cellular assays):
Cellular immune responses of the various regimens tested, as measured by the following assays, will be analyzed:

- Intracellular cytokine staining (ICS): specific-T cell responses to the separate or combined peptide pools of HPV16 and HPV18 E2, E6/E7 proteins will be determined by flow cytometry, including specific $CD4^+$ and $CD8^+$ T cells producing IFNγ, and/or TNFα, and/or IL-2, as well as other exploratory markers (cytotoxicity, exhaustion, Th2, Th17).

- ELISPOT: specific-IFNγ T cell responses to the separate or combined HPV16 and HPV18 E2 and E6/E7 peptide pools will be determined.

Sample interpretation and vaccine responder definition:

- ICS: the positivity and responder definition for ICS will be applied to the secondary endpoints only. This includes CD4 and CD8 T-cells expressing IFNγ only (marginal), IL-2 only (marginal) and TNFα only (marginal).
    - Sample interpretation: any background subtracted value above the LLOQ is considered positive.

- Vaccine responder definition: if baseline is negative (<LLOQ), a participant is considered as a responder if the post-vaccination value is above the LLOQ in the proportion of T-cells that express at least one of the cytokines for any of the matching peptide pools. If baseline is positive, a participant is considered as a responder if he has a 3-fold increase over baseline in the proportion of T-cells that express at least one of the cytokines for any of the matching peptide pools.

- ELISpot:

  - Sample interpretation: any background subtracted value above the LLOQ is considered positive.

  - Vaccine responder definition: if baseline is negative (<LLOQ), a participant is considered as a responder if the post-vaccination value is above the LLOQ to at least one matching peptide pool. If baseline is positive, a participant is considered a responder if he has a 2-fold increase over baseline in the number of IFNγ spots per 10^6 PBMC to at least one matching peptide pool.

6.2. Handling of Missing and/or Unquantifiable Immune Response Data

Missing immune response data will not be imputed.

Values below the LLOQ will be treated differently according to the assay:

- For ICS assays: the LLOQ will be used if available. A provisional LLOQ is put at x% (only for total cytokine response). For the individual cytokine combinations of IFNγ, TNFα and IL-2, negative values will be imputed with 0. For descriptive statistics and graphical displays, values below the LLOQ will be imputed to a value of LLOQ/2.

- For ELISpot assays: the LLOQ will be used if available. For descriptive statistics and graphical displays, values below the LLOQ will be imputed to a value of LLOQ/2.

Values above the upper limit of quantification (ULOQ) will be imputed to ULOQ.

The combined peptide pool results can be obtained by summing the background adjusted percentages of both peptide pools (E2 and E6/E7) if results for both are equal or larger than the LLOQ. If both peptide pools have results smaller than the LLOQ, a value of LLOQ/2 will be used for the combined peptide pool results. If one of the two peptide pools have a result smaller than the LLOQ, while the other peptide pool result is equal to or larger than the LLOQ, the result of the latter will be used as the combined peptide pool result.

6.3. Immune Response Analysis

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.

6.3.1. Immunogenicity against the insert

6.3.1.1. Cellular assays

For **ICS**, analyses may include:

For CD4+ and CD8+ T cells and for each peptide pools (E2 or E6/E7), the database will contain:

- Cell count (ISTEST = CD4+ or CD8+ T-Cell)
- Background adjusted percentage (ISTEST = CD4+ or CD8+ T-Cell Response)

The background adjusted percentages will be summarized for the active regimens and placebo, for each peptide pool separately and combined: n, median, quartile range, min, max, the number and percentage of positive samples and vaccine responders (see section 6.1) and corresponding 95% CIs will be tabulated for each available cytokine background adjusted percentages listed below:

CD4 T cells		
Cytokine	**Description**	**Endpoint**
IFNγ+	Marginal	Secondary
IL-2+	Marginal	Secondary
TNFα +	Marginal	Secondary
IFNγ+ or IL-2+	Boolean OR	Secondary
IFNγ+ or IL-2+ or TNFα +	Boolean OR	Secondary

CD8 T cells		
Cytokine	**Description**	**Endpoint**
IFNγ+	Marginal	Secondary
IL-2+	Marginal	Secondary
TNFα +	Marginal	Secondary
IFNγ+ or IL-2+	Boolean OR	Secondary
IFNγ+ or IL-2+ or TNFα +	Boolean OR	Secondary
CD107a+	Marginal	Exploratory

Tables with the corresponding descriptive statistics will be provided.

Internally graphical presentations will be provided by cytokine type. Different shapes will be used to show the distinction between HPV16 and HPV18 at baseline, the active and placebo regimens will be distinguished through different colors. Additionally, different panels will show E2 and E6/E7 separately, as well as combined. The graphs will show the individual percentages for each type of cytokine expressing T cells (CD4+ or CD8+) combination as dots per timepoint together with the median background adjusted percentage per regimen (active versus placebo). In the graphs the actual values will be shown. If available, the LLOQ cut-off will be visualized. Participant profiles of the actual values over time will be graphically presented.

For **ELISpot**, following results will be calculated and presented for each peptide pool separately (E2 and E6/E7), as well as combined, and for the active versus placebo regimens: N, median, quartiles, and the range of the actual values. Further, the number (N) and % of positive samples and responders and the corresponding 95% CIs will be presented according to the responder criteria in Section 6.1.

Tables with the corresponding descriptive statistics will be provided.

Internally, graphs will be generated showing the individual responses per timepoint together with the corresponding median and IQR as horizontal line. Colors will be used to distinguish between the active and placebo regimens. Three panels will be presented: peptide pool E2, E6/E7 and the combined peptide pools. Different shapes will be used to distinguish between baseline genotype HPV16 and HPV18. Each panel will show the timepoints of interest. A reference line will be used to reflect the LLOQ. For the graphs, original values will be displayed on the log10 scale. Participant profiles of the actual values over time will be graphically presented.

7. VIROLOGY

7.1. Analysis Specifications

7.1.1. Hypothesis Testing

No formal hypothesis on virology will be tested.

7.1.2. Data Collection

Cervical samples will be collected by a healthcare provider and by the participant (self-sampling) at different time points: baseline, prior to both vaccinations, 6 and 12 months post-Dose 1 and 21 days, 8 weeks and 6 months post-Dose 2. The Roche Cobas® HPV test will be performed for the specific qualitative detection of HPV16, HPV18, and/or the concurrent detection of 12 other HR-HPV types (HPV31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) by a central sponsor designated laboratory. In addition, a type-specific real-time HPV PCR test for the detection, genotyping and quantification of HPV16 and HPV18 together with other individual HR-HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), three probable HR-HPV types (HPV53, 66 and 68), two low-risk HPV types (HPV6 and 11), and one undetermined risk type (HPV67) will be used. Both tests will be performed on all cervical samples (healthcare provider-collected and self-collected). 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.

7.2. Exploratory Virology Endpoint(s)

7.2.1. Definition

To assess the frequency and kinetics of clearance of HPV16 and HPV18 infection combined, by HPV genotype (HPV16 or HPV18) and by infection type (persistent versus non-persistent) of the vaccine regimens compared to placebo over the study period, the 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, defined as:

- A negative HPV16 genotype, determined by the Cobas®, Roche test over the study period after having a baseline HPV16 infection (persistent versus non-persistent); OR

- A negative HPV18 genotype, determined by the Cobas®, Roche test over the study period after having a baseline HPV18 infection (persistent versus non-persistent).

Other definitions of viral clearance based on the quantitative HPV PCR genotyping test or a combination of this quantitative test and the qualitative Cobas®, Roche test may also be explored.

7.2.2. Analysis Methods

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

A listing will be presented showing the genotyping results per timepoint of the healthcare provider and self-collected cervical samples by a qualitative HPV genotyping test (Cobas®, Roche) and a quantitative HPV PCR genotyping test (AML). This listing will also include the results of the HSV-2 sample collected at the last visit, if available.

The results of the colposcopies will be listed descriptively.

8. ATTACHMENTS

8.1. ATTACHMENT 1: Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

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

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered as normal.

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 Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
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 – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
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	---

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
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 participant 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/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	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 (DIC)
International Normalized Ratio (INR)***	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN

* 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.
***: For INR, the values in the table are based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2014 (version 2.0)

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization forhyperglycemia
Blood (microscopic) - red blood cells per high power field (rbc/hpf)	1 - 10	11 - 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* 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.

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°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) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Participant 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 judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Ranges converted from FDA scale to SI units

Blood, Serum, or Plasma Chemistries [1]		**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Albumin (g/L)	Hypoalbuminemia	28-31	25-27	<25	
Blood urea nitrogen (mmol/L)		8.2-9.3	9.4-11.1	>11.1	
Calcium (mmol/L)	Hypocalcemia	2.00-2.10	1.87-1.99	1.75-1.86	<1.75
	Hypercalcemia	2.62-2.74	2.75-2.87	2.88-3.00	>3.00
Cholesterol (mmol/L)		5.20-5.43	5.44-5.82	>5.82	
Creatinine (µmol/L)		133-150	151-177	178-221	>221
Eosinophils (10^9/L)		0.65-1.5	1.501-5.0	>5.0	
Glucose (mmol/L)	Hypoglycemia	3.61-3.83	3.05-3.60	2.50-3.04	<2.50
	Hyperglycemia-Fasting	5.55-6.11	6.12-6.94	>6.94	
	Hyperglycemia-Random	6.11-6.94	6.95-11.10	>11.10	
Hemoglobin for male (g/L)		125-135	105-124	85-104	<85
Hemoglobin for female (g/L)		110-120	95-109	80-94	<80
Hemoglobin change from baseline (g/L)		Any decrease – 15	16-20	21-50	>50
Lymphocytes (10^9/L)		0.75-1.0	0.5-0.749	0.25-0.499	<0.25
Magnesium (mmol/L)	Hypomagnesemia	0.53-0.62	0.45-0.52	0.37-0.44	<0.37
Neutrophils (10^9/L)		1.5-2.0	1.0-1.499	0.5-0.999	<0.5
Phosphorus (mmol/L)	Hypophosphatemia	0.74-0.81	0.65-0.73	0.52-0.66	<0.52
Platelets (10^9/L)		125-140	100-124	25-99	<25
Protein (g/L)	Hypoproteinemia	55-60	50-54	<50	
WBC (10^9/L)	Increase	10.8-15	15.001-20	20.001-25	>25
	Decrease	2.5-3.5	1.5-2.499	1.0-1.499	<1.0
Coagulation					
Fibrinogen (µmol/L)	Increase	11.76-14.70	14.71-17.65	>17.65	
	Decrease	4.41-5.88	3.68-4.40	2.94-3.67	<2.94

[1] Depending upon the laboratory used, reference ranges, eligibility ranges and grading may be split out by sex and/or age.

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.