TITLE PAGE

Protocol Title: A Phase 1/2 randomized, observer-blinded, multi-country study to evaluate safety and immunogenicity of investigational adjuvanted human papillomavirus vaccine in females (16 to 26 years of age)

Protocol Number: 213749 (HPV9-AS04-001)

Amendment Number: 3

Product: Investigational adjuvanted human papillomavirus vaccine

Short Title: A study on the immune response and safety of an adjuvanted human papillomavirus vaccine when given to healthy women 16 to 26 years of age

Study Phase: 1/2

Sponsor Name: GlaxoSmithKline Biologicals SA

Legal Registered Address: Rue de l'Institut, 89, 1330 Rixensart, Belgium

EudraCT number: 2022-000090-15

Date of Original Protocol: 13 December 2021

Date of Original Protocol Version 2.0: 02 March 2022

Date of Protocol Amendment 1/DEU-1: 23 June 2022

Date of Protocol Amendment 2: 23 September 2022

Date of Protocol Amendment 3: 08 June 2023

SPONSOR SIGNATORY:

I have read this protocol in its entirety and agree to conduct the study accordingly:

PPD

Jasur Danier
VP Clinical Science, Viral Cluster
GlaxoSmithKline Biologicals SA

Date

Medical Monitor name and contact are provided in Study Reference Manual.

Investigator Agreement Page is provided in Appendix 7.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY			
Document	**Date**	**Substantial**	**Region**
Amendment 3	08 June 2023	No	Global
Amendment 2	23 September 2022	Yes	Global
Amendment 1/DEU-1	23 June 2022	Yes	Local - Germany
Version 2.0	02 March 2022	Yes	Global
Original Protocol	13 December 2021	-	-

Protocol Amendment 3:08 June 2023

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for Amendment

The purpose of the Protocol Amendment 3 is to improve participant adherence to the vaccination schedule by increasing time interval between Visit 1 (first study vaccination) and Visit 5 (third study vaccination) that will allow participants to complete HPV vaccination series during the study period. Additionally, for the analysis of anti-HPV neutralizing antibody titers at Month 2, we increased the number of participants from 160 up to 384 to collect additional immunogenicity data after the first study vaccine administration. This change applies to samples already collected and no additional Month 2 blood samples will be collected from participants. Furthermore, a change has been made in the statistical section to obtain group data (i.e., HPV9High, HPVMed and HPVLow study groups) instead of pooled data on correlation between anti-HPV IgG antibody concentration and anti-HPV neutralizing antibody titers.

Added text is ***bold italic*** and deleted text is ~~strikethrough~~.

Section and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis, 3.0 Objectives and endpoints,	Edited text in footnote #3: Anti-HPV neutralizing antibody titers at Month 2 will be performed in a subset of ~~160~~ ***384*** participants (at least ~~40~~ ***96*** participants in each group)	Increase the pool of immunogenicity data after the first vaccine administration
1.3 Schedule of Activities	Table 2 Intervals Between Study Visits Allowed Interval Range Visit 1 → Visit 5 ~~180~~***166***-194 days	Improve participants' adherence to the vaccination schedule and ensure completion of a full HPV vaccination series
4.1 Overall Design,	Edited text:	Increase immunogenicity data after

Section and Name	Description of Change	Brief Rationale
Appendix 3	Pseudovirion-based neutralization assay (PBNA) at (…) Month 2 will be performed in a subset of ~~160~~ ***384*** participants (at least ~~40~~ ***96*** participants in each group)	the first vaccine administration
9.4.2.2.1 Within Groups Assessment	Edited text: Pearson coefficient of correlation between anti-HPV IgG antibody concentration and anti-HPV neutralizing antibody titers with associated P-value will be calculated for ***each***~~pooled~~ investigational adjuvanted vaccines group and *Gardasil 9* group for each antigen for timepoint and overall.	To obtain group data instead of pooled data on correlation between anti-HPV IgG antibody concentration and anti-HPV neutralizing antibody titers
Signature page	Updated Sponsor Signatory: ~~Nadia Meyer~~ ~~Clinical and Epidemiology R&D~~ ~~Project Leader~~ ***Jasur Danier*** ***VP Clinical Science, Viral Cluster***	Updated to current signatory for this study.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1/2 randomized, observer-blinded, multi-country study to evaluate safety and immunogenicity of investigational adjuvanted human papillomavirus vaccine in females (16 to 26 years of age)

Protocol Number: 213749 (HPV9-AS04-001)

Protocol Amendment Number: 3

Product: investigational adjuvanted human papillomavirus vaccine

Short Title: A study on the immune response and safety of a human papillomavirus vaccine when given to healthy women 16 to 26 years of age.

Rationale: GlaxoSmithKline Biologicals SA (GSK) is developing an investigational adjuvanted human papillomavirus (HPV) vaccine to protect against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. This study will evaluate the reactogenicity, safety, and immunogenicity of 3 formulations of GSK's investigational adjuvanted HPV vaccine versus *Gardasil 9*, administered intramuscularly (IM) according to a 0, 2, 6 month vaccination schedule in females 16-26 years of age.

Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of GlaxoSmithKline Biologicals SA (GSK)'s investigational adjuvanted human papillomavirus (HPV) vaccine formulations	**Solicited events** • Percentage of participants reporting each solicited administration site event assessed as Grade 3 in terms of intensity within 7 days (Day 1 – Day 7) after each vaccine dose. • Percentage of participants reporting each solicited systemic event assessed as Grade 3 in terms of intensity within 7 days (Day 1 – Day 7) after each vaccine dose. **Unsolicited adverse events (AEs)** • Percentage of participants reporting unsolicited adverse event assessed as Grade 3 in terms of intensity classified by Medical Dictionary for Regulatory Activities (MedDRA) within 28 days (Day 1 – Day 28) after each vaccine dose. **Serious adverse events (SAEs)** • Percentage of participants reporting SAEs classified by MedDRA from first vaccination up to study end. **Safety laboratory parameters (Step 1 participants)** • Percentage of participants presenting clinically relevant abnormalities in each biochemical and hematological parameter at Day 7 post-dose 1.
• To evaluate the immune response to GSK's investigational adjuvanted HPV vaccine	• Anti-HPV immunoglobulin G (IgG) antibody geometric mean concentrations (GMCs), 1 month

Objectives	Endpoints
formulations	after the third dose (Month 7).
Secondary	
• To evaluate the safety and reactogenicity of GSK's investigational adjuvanted HPV vaccine formulations	**Solicited events** • Percentage of participants reporting each solicited administration site event within 7 days (Day 1 – Day 7) after each vaccine dose. • Percentage of participants reporting each solicited systemic event within 7 days (Day 1 – Day 7) after each vaccine dose. **Unsolicited AEs** • Percentage of participants reporting unsolicited symptoms within 28 days (Day 1 – Day 28) after each vaccine dose **Potential immune-mediated disease (pIMDs)** • Percentage of participants reporting pIMDs from first vaccination up to study end. **Pregnancy outcomes** • The percentage of participants who experienced pregnancy and their outcomes from Day 1 of pregnancy up to study end.
• To evaluate the immune response for all HPV vaccine types for all vaccines	• Anti-HPV IgG antibody concentration at Day 1, Month 2, Month 3, Month 6, Month 7 and Month 12. • Anti-HPV IgG antibody seroconversion[1] rate at Month 2, Month 3, Month 6, Month 7 and Month 12. • Anti-HPV neutralizing antibody titers at Day 1, Month 3 and Month 7[2] in all participants, Month 2[3] in a subset of participants. • Anti-HPV neutralizing antibody seroconversion[1] rate at Month 3 and Month 7[2]. • Correlation between anti-HPV IgG antibody concentration and anti-HPV neutralizing antibody titers at Day 1, Month 2, Month 3 and Month 7.

[1] Seroconversion is defined as the appearance of antibodies (i.e., concentrations/titer greater than or equal to the cut-off value) in the serum of participants seronegative before vaccination.

[2] At least 150 participants in each group. In case of any delay, analysis may be performed for as many participants as possible with data available at the time of the analysis. Analysis for remaining participants will be performed at the time of the next analysis.

[3] 384 participants (at least 96 participants in each group)

Note: Tertiary objectives and endpoints are available in the main text of this protocol.

Overall Design: This will be a phase 1/2 randomized, observer-blind, multi-country study with 4 groups of females 16-26 years of age at the time of vaccine administration. Participants will be

randomized in a 1:1:1:1 ratio to receive a series of 3 investigational adjuvanted intervention doses (3 different potencies [a high, medium, low potency]) or a series of the *Gardasil 9* vaccine. The investigational adjuvanted intervention or *Gardasil 9* vaccine will be administered intramuscularly (IM) at Day 1 (Month 0), Month 2, and Month 6. Blood sampling will be performed on Day 1, Month 2, Month 3, Month 6, Month 7, and Month 12 to assess for immunological response. In Germany, only adult participants between and including 18 years to 26 years of age are to be included in this clinical study.

This study is organized in to 2 steps. Forty-eight participants (12 per group) of the study Step 1 (sentinel participants) will receive the initial assigned dose prior to participants in Step 2 of the study, and sentinel participants will have an additional blood sampling visit at Day 7 to assess for biochemical and hematological parameters. The internal Safety Review Committee (iSRC) will review the accumulated safety data up to 7 days post-dose 1 for the sentinel participants* to determine whether any of the pre-defined holding rules have been met. If no safety concerns were observed and no holding rules were met, the sentinel participants will continue with study visits and dosing as scheduled and the Step 2 participants will be initiated. Vaccination of Step 2 participants with a second dose will not be initiated before all Step 1 participants have received their second vaccination dose.

CCI [redacted]

*In case not all 48 of the Step 1 participants are enrolled and vaccinated with a first dose of study vaccine by 30 September 2022, the iSRC will review the accumulated safety data up to 7 days post-dose 1 of all participants available by that date. If no safety signal is identified, these participants will be vaccinated with a second dose. To avoid any additional participants running out of the allowed interval range for their second vaccine dose, additional iSRC review(s) may need to be planned to review the safety data up to 7 days post-dose 1 of these participants, but only when all 48 Step 1 participants have been enrolled and their data have been reviewed by the iSRC, the iSRC will decide on the initiation of the vaccination of Step 2 participants.

Number of Participants: Approximately 1080 participants will be randomly assigned to the 4 study groups to provide approximately 270 participants per study group.

Intervention Groups:

Study groups	Study Interventions	Number of Participants
HPV9High	HPV9-High	270
HPV9Med	HPV9-Medium	270
HPV9Low	HPV9-Low	270
Gar9	*Gardasil 9*	270

Duration: The duration of the intervention will be approximately 6 months. Participants will be monitored until Month 12. Monitoring of pregnancies (if any) can be beyond 12 months.

Statistical Methods: Three analyses sets will be used in this study, the Enrolled Set, the Exposed Set, and the Per Protocol Set. The primary objective and all immunogenicity objectives will be evaluated descriptively. Exploratory immunologic non-inferiority analyses will be performed, to help in decision making of the formulation selection for the further phase 3 clinical studies.

Internal Safety Review Committee: An iSRC will be reviewing the accumulated safety data up to 7 days post-dose 1 for the sentinel participants to determine whether any of the pre-defined holding rules have been met in order to proceed with study schedule of activities. The iSRC will review the safety data on a monthly basis until safety data from 1-month post-dose 2 for all participants and data from 1-month post-dose 3 for Step 1 participants are reviewed.

1.2. Schema

See study schema in Figure 1.

1.3. Schedule of Activities

The schedule of activities is presented in Table 1.

Table 1 Schedule of Activities

Age	**16 – 26 years of age at the time of study intervention administration***							**Notes**
Visit	**Visit 1**	**Visit 2****	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	
Time point	**Day 1**	**Day 7**	**Month 2**	**Month 3**	**Month 6**	**Month 7**	**Month 12**	
Informed consent (and assent if applicable)	●							
Check inclusion/exclusion criteria	●							See Sections 5.1-5.2
Collect demographic data	●							See Section 8.2.1.1
Medical history	●							See Section 8.2.1.2
Vaccination history	○							See Section 8.2.1.2
Physical examination/Vital signs	●	○	●	○	●	○	○	See Section 8.2.1.3
Body temperature before study vaccination[1]	●		●		●			See Section 8.2.1.3
Pregnancy test (urine) before study vaccination	●		●		●			See Section 8.2.1.4
Randomization	○							See Section 6.3.2
Check contraindications, warnings, and precautions to study vaccine	○		○		○			See Sections 5.4, 7.2, 8.2.1.5
Administration of study vaccine	●		●		●			
Recording of administered study vaccination number	●		●		●			
Distribute and instruct participant/participant's parent(s)/LAR(s) on the use of eDiary for solicited AEs	○		○		○			
Distribute and instruct participants/participant's parent(s)/LAR(s) on the use of Memory Aid for unsolicited AEs and concomitant medication/vaccination	○		○		○			

Age	**16 – 26 years of age at the time of study intervention administration***							**Notes**
Visit	**Visit 1**	**Visit 2****	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	
Time point	**Day 1**	**Day 7**	**Month 2**	**Month 3**	**Month 6**	**Month 7**	**Month 12**	
Laboratory assessments[2]								
Blood sampling for antibody determination (~50 mL)	●		●	●	●	●	●	See Section 8.1
CCI								
Blood sampling for any hematological/biochemical laboratory abnormality for Step 1 participants (~5 mL)	●	●						See Section 8.2.2
Safety assessments								See Section 8.2
Record any concomitant medications/vaccinations	●	●	●	●	●	●	●	See Section 6.8.1
Record any intercurrent medical conditions		●	●	●	●	●	●	See Section 6.9
Review the solicited events (Days 1-7 post study vaccine administration) recorded by the participant/participant's parent(s)/LAR(s)		●		●		●		
Recording of unsolicited AEs (Days 1-28 post study vaccine administration)		●	●	●	●	●		
Return of eDiaries/disable electronic application						○		
Return of Memory Aids		○**	○	○		○		
Recording of all SAEs, including SAEs related to study intervention, to study participation, to a concurrent GSK medication/vaccine[4]	●	●	●	●	●	●	●	
Recording of AEs/SAEs leading to withdrawal of a participant from the intervention/study	●	●	●	●	●	●	●	
Recording of pregnancies and pregnancy outcomes[5]	●	●	●	●	●	●	●	
Recording of pIMDs	●	●	●	●	●	●	●	See Table 21
Study Conclusion							●	See Section 4.3

(the table footnote continues on the next page)

* 18-26 years of age for Step 1 participants.
Note: In Germany, only adult participants between and including 18 to 26 years of age are to be included in this clinical study
** For Step 1 participants only
AE = adverse event; CCI [redacted]; D = day; eDiary = electronic diary; LAR = legally authorized representative; pIMD = potential immune-mediated disease; SAE = serious adverse event
● is used to indicate a study procedure that requires documentation in the individual electronic case report form (eCRF)
○ is used to indicate a study procedure that does not require documentation in the individual eCRF

[1] The preferred location for measuring the temperature is the axilla. Fever is defined as body temperature ≥37.5°C/99.5°F.

[2] Blood samples should be collected prior to vaccine administration.

[3] Only for 200 participants (50/group) at pre-selected sites.

[4] The collection and reporting period starts once the participants' informed consent (and assent, if applicable) is obtained.

[5] Follow-up of pregnancy outcomes will be done beyond Month 12.

Table 2 Intervals Between Study Visits

Interval	Planned Visit Interval*	Allowed Interval Range
Visit 1→Visit 2**	7 days	7 – 12 days
Visit 1→Visit 3	60 days	56 – 74 days
Visit 3→Visit 4	28 days	28 – 44 days
Visit 1→Visit 5	180 days	166 – 194 days
Visit 5→Visit 6	28 days	28 – 44 days
Visit 1→Visit 7	360 days	346 – 374 days

*Number of days between the visits.
**Visit 2 is for Step 1 participants only.

2. INTRODUCTION

2.1. Background

Persistent infection with carcinogenic human papilloma virus (HPV) presents a serious risk of development of HPV-related cervical neoplasia. Of more than 100 identified HPV types, 13 are classified as oncogenic by the International Agency for Research on Cancer (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). While in low grade lesions HPV type distribution varies greatly, HPV types 16 and 18 are the predominant oncogenic types accounting for approximately 70% of all cervical cancer cases. HPV types 31, 33, 45, 52, and 58 cause an additional 20% of all cervical cancer cases worldwide (Arbyn et al, 2014; Bruni et al, 2021). Over the last decade with the increased use of molecular diagnostic techniques, growing evidence suggests HPV involvement in different anatomical sites such as anal region and the oropharynx (Bray et al, 2018; Götz et al, 2019; Hartwig et al, 2012). The low risk (non-oncogenic) HPV types 6 and 11 cause 90% of genital warts and some low grade cervical intraepithelial neoplasia and are also linked to recurrent respiratory papillomatosis.

Three HPV L1 virus-like particle (VLP) vaccines are licensed in the US, in EU and numerous countries worldwide: *Cervarix* (GSK's HPV-16/18 AS04 adjuvanted vaccine), *Gardasil* (Merck Sharp and Dohme's HPV-6/11/16/18 vaccine) and *Gardasil 9* (Merck Sharp and Dohme's HPV-6/11/16/18/31/33/45/52/58 vaccine). These vaccines have shown excellent safety and efficacy profiles.

Over a decade after first HPV vaccines (*Cervarix* and *Gardasil*) were licensed and have been widely used, disease epidemiology has evolved. Population-level impact of vaccinating girls and women against HPV infections, anogenital warts, and cervical intraepithelial neoplasia demonstrates significant evidence of effectiveness of HPV vaccines across countries (*Cervarix* and *Gardasil*) in real-world settings (Drolet MM et al, 2019; Palmer et al, 2019) as well as long-term protection (Hoes et al, 2020; Mesher et al, 2018), even in reduced dose schedule (Pasmans et al, 2019) and among different at-risk populations (Woestenberg et al, 2020).

As of 2020, less than 25% of low-income and less than 30% of lower-middle-income countries had introduced the HPV vaccine for the prevention of HPV diseases into their national immunization schedules, while more than 85% of high-income countries had done so (WHO, 2020).

In 2020, the World Health Organization (WHO) adopted a global strategy to eliminate cervical cancer and called for concerted efforts between its partners and the private sector to reach the target of 90% HPV vaccination coverage by 2030 in girls by age 15 years. One of the actions to reach this target is to overcome vaccine supply constraints and to secure sufficient HPV vaccines (WHO, 2020).

2.2. Study Rationale

This project aims at developing a new GlaxoSmithKline Biologicals SA (GSK) AS04-adjuvanted HPV vaccine. The VLP type composition will include HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. This study will evaluate the reactogenicity, safety, and immunogenicity of 3 formulations of GSK's investigational adjuvanted HPV vaccine versus *Gardasil 9*, administered intramuscularly (IM) according to a 0, 2, 6 month vaccination schedule in females 16-26 years of age (18-26 years of age in Germany). The aim of the study is to generate data to allow the selection of the investigational adjuvanted HPV vaccine formulation which will be used for the phase 3 studies. Participants who receive the selected formulation and *Gardasil 9* will be invited to participate in an additional 4-year extension study with yearly visits, to generate long-term immunogenicity and safety data.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment and Risk Mitigation Strategies

Refer to the current Investigator's Brochure (IB) for the detailed summary of potential risks and benefits of the investigational adjuvanted HPV vaccine. The investigational vaccine is expected to have a benefit risk profile similar to other known HPV vaccines. The most common side effects currently known following administration of HPV vaccines are pain, redness, or swelling at the location where the vaccine was administered, and fever, dizziness, syncope, nausea, headache, and muscle or joint pain (CDC, 2021). On very rare occasions, a person may experience allergic reaction (anaphylaxis).

For the risks associated with administration of *Gardasil 9* refer to the vaccine's prescribing information/package insert.

GSK/designee (IQVIA [see the study administrative structure in Table 20]) will immediately notify the investigators if any additional safety or toxicology information becomes available during the study.

The risk assessment and mitigation strategy for this study are outlined in Table 3. In addition to these specific mitigation strategies, the study will be conducted in a staggered manner with safety evaluations by an internal Safety Review Committee (iSRC) (Section 8.2.3). Holding rules that have been established will be applied. The project Safety Review Team (SRT) will also review blinded data on a regular basis throughout the study.

Table 3 Risk Assessment and Risk Mitigation Strategy

Important Potential/Identified Risk	Data/Rationale for Risk	Mitigation Strategy
All Study Vaccines		
Hypersensitivity reactions (including anaphylaxis).	Acute allergic reactions such as a rare case of anaphylactic event may occur with any vaccine administration. These are serious, but rare occurrences estimated in the range of 1 to 10 cases per million of vaccinations, depending on the vaccine studied (Ruggerberg et al, 2007).	Participants with known hypersensitivity to any component of the vaccine are excluded from enrollment. The onset of vaccine-related allergic symptoms occurs shortly after vaccination. In order to treat participants with a serious allergic reaction to vaccination, all participants will need to remain under observation (i.e., visibly followed; no specific procedure) at the study site for at least 60 minutes after vaccination.
Syncope	Syncope (fainting) can occur following or even before any vaccination as a psychogenic response to the needle injection.	All participants will remain under observation at the vaccination center for at least 60 minutes after vaccination.
Local inflammatory reaction due to intramuscular (IM) injection	IM vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, redness, and swelling.	All participants will remain under observation at the vaccination center for at least 60 minutes after vaccination. Solicited local adverse events (AEs) will be collected and reviewed from Day 1 to Day 7 post study vaccine administration.
GSK's investigational adjuvanted HPV vaccine		
Theoretical risk of acquiring a vaccine-induced autoimmune disease after vaccination.	Potential immune-mediated diseases (pIMDs) are a theoretical concern with adjuvanted vaccines (Tavares et al, 2013).	During the informed consent process, participants will be informed of this theoretical risk and asked to report any AEs that they consider serious/significant and/or for which they received medical attention at any point during the study. Participants with a history or with a current diagnosis of an autoimmune disease will be excluded from the study A pIMD is an adverse event of special interest (AESI) and occurrence of pIMDs will be captured and described. pIMDs will be collected throughout the study.
Study Procedures – Blood sampling		
Pain and bruising	Pain or bruising at the site where blood is drawn.	A topical analgesic may be applied to the site where blood will be collected.
Syncope	Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle injection.	All participants will remain under observation at the clinical center for at least 60 minutes after vaccination.

2.3.2. Benefit Assessment

An indirect benefit is that the information obtained in this study will aid the development of an HPV vaccine, which is intended to prevent cervical, vulvar, vaginal, anal and oropharyngeal cancers caused by high risk HPV types 16, 18, 31, 33, 45, 52, and 58 and genital warts caused by low risk HPV types 6 and 11. In addition, this vaccine aims to prevent precancerous or dysplastic lesions (cervical intraepithelial neoplasia, adenocarcinoma in situ, vulvar intraepithelial neoplasia, vaginal intraepithelial neoplasia, anal intraepithelial neoplasia) caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Another benefit for all study participants may include gaining of information and medical advice about their general health status through medical evaluations/assessments associated with this study (i.e., physical examinations and blood testing [hematology and biochemistry data]).

2.3.3. Overall Benefit/Risk Conclusion

The investigational adjuvanted HPV vaccine is currently in an early stage of clinical development and no vaccine efficacy has been demonstrated in humans. Taking into account the measures to minimize the risk to the participants, the potential risks are justified by the potential benefits linked to the development of this investigational adjuvanted HPV vaccine.

3. Objectives and Endpoints

Table 4 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and reactogenicity of GlaxoSmithKline Biologicals SA (GSK)'s investigational adjuvanted human papillomavirus (HPV) vaccine formulations.	**Solicited events** • Percentage of participants reporting each solicited administration site event assessed as Grade 3 in terms of intensity within 7 days (Day 1 – Day 7) after each vaccine dose. • Percentage of participants reporting each solicited systemic event assessed as Grade 3 in terms of intensity within 7 days (Day 1 – Day 7) after each vaccine dose. **Unsolicited adverse events (AEs)** • Percentage of participants reporting unsolicited adverse event assessed as Grade 3 in terms of intensity classified by Medical Dictionary for Regulatory Activities (MedDRA) within 28 days (Day 1 – Day 28) after each vaccine dose. **Serious adverse events (SAEs)** • Percentage of participants reporting SAEs classified by MedDRA from first vaccination up to study end. **Safety laboratory parameters (Step 1 participants)** • Percentage of participants presenting clinically relevant abnormalities in each biochemical and hematological parameter at Day 7 post-dose 1.
• To evaluate the immune response to GSK's investigational adjuvanted HPV vaccine formulations.	• Anti-HPV immunoglobulin G (IgG) antibody geometric mean concentrations (GMCs), 1 month after the third dose (Month 7).
Secondary	
• To evaluate the safety and reactogenicity of GSK's investigational adjuvanted HPV vaccine formulations.	**Solicited events** • Percentage of participants reporting each solicited administration site event within 7 days (Day 1 – Day 7) after each vaccine dose. • Percentage of participants reporting each solicited systemic event within 7 days (Day 1 – Day 7) after each vaccine dose. **Unsolicited AEs** • Percentage of participants reporting unsolicited symptoms within 28 days (Day 1 – Day 28) after each vaccine dose. **Potential immune-mediated disease (pIMDs)** • Percentage of participants reporting pIMDs from first vaccination up to study end.

Objectives	Endpoints
	Pregnancy outcomes • The percentage of participants who experienced pregnancy and their outcomes from Day 1 of pregnancy up to study end.
• To evaluate the immune response for all HPV vaccine types for all vaccines.	• Anti-HPV IgG antibody concentration at Day 1, Month 2, Month 3, Month 6, Month 7, and Month 12. • Anti-HPV IgG antibody seroconversion[1] rate at Month 2, Month 3, Month 6, Month 7, and Month 12. • Anti-HPV neutralizing antibody titers at Day 1, Month 3 and Month 7[2] in all participants, Month 2[3] in a subset of participants. • Anti-HPV neutralizing antibody seroconversion[1] rate at Month 3 and Month 7[2]. • Correlation between anti-HPV IgG antibody concentration and anti-HPV neutralizing antibody titers at Day 1, Month 2, Month 3, and Month 7.
Tertiary	
CCI [redacted]	

1 Seroconversion is defined as the appearance of antibodies (i.e., concentrations/titer greater than or equal to the cut-off value) in the serum of participants seronegative before vaccination.

2 At least 150 participants in each group. In case of any delay, analysis may be performed for as many participants as possible with data available at the time of the analysis. Analysis for remaining participants will be performed at the time of the next analysis.

3 384 participants (at least 96 participants in each group)

4 CCI [redacted]

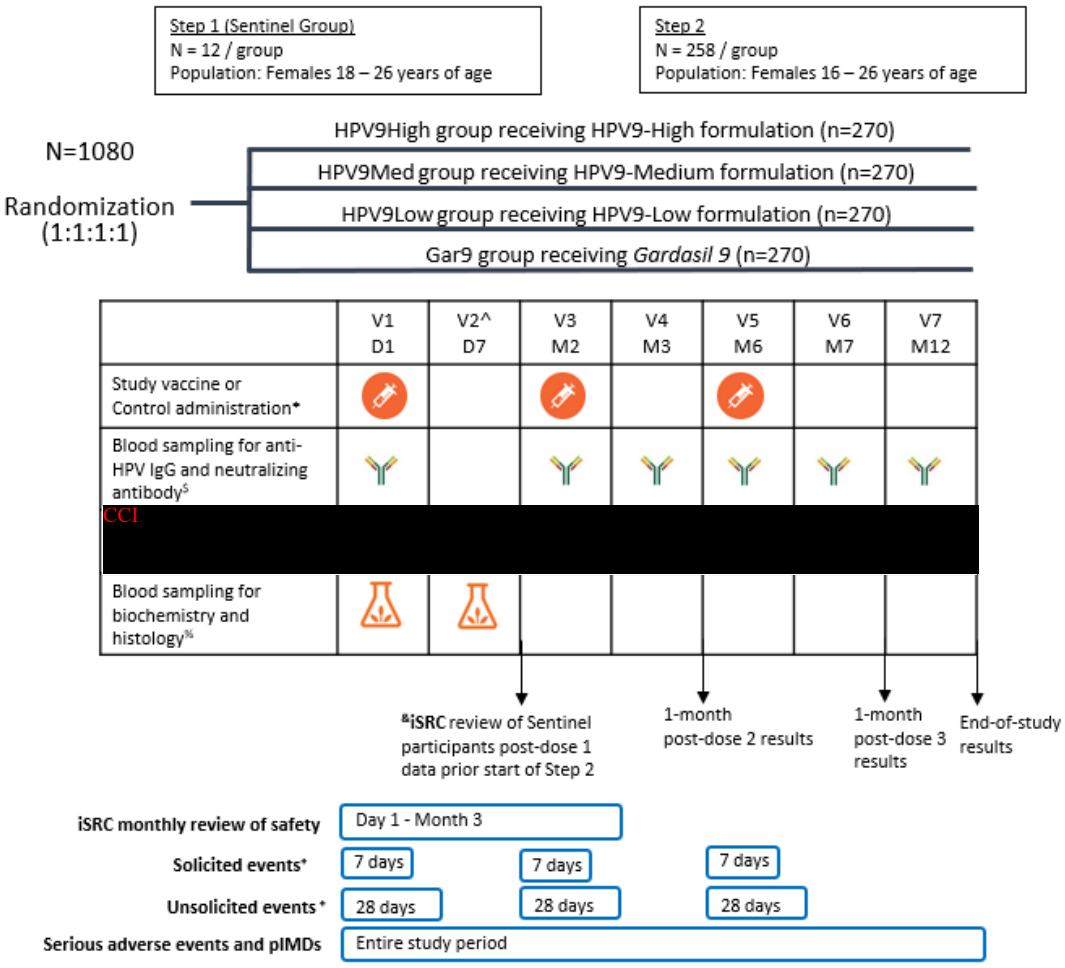
4. STUDY DESIGN

4.1. Overall Design

The study design diagram is provided in Figure 1.

Study groups are presented in Table 5.

Figure 1 Study Design Overview



D = day; iSRC = internal Safety Review Committee; M = month; IgG = immunoglobulin G; CCI [redacted]; pIMD = potential immune-mediated disease; V = visit

^V2 is only for Step 1 participants

*Pregnancy test before study vaccine administration

$Pseudovirion-based neutralization assays at D1, M2 (subset), M3 and M7

#CCI [redacted]

+Post study vaccine administration

&iSRC reviews Sentinel participants post-dose 1 safety data, then iSRC reviews the data on monthly basis until safety data from 1-month post-dose 2 for all participants and data from 1-month post-dose 3 for Step 1 participants are reviewed

%Blood sampling for biochemistry and hematology is only for Step 1 participants.

Recruitment:

A staggered enrollment will be used:

- In Step 1, 48 participants (12 per group) aged 18-26 years will be enrolled and vaccinated with the first dose, with an interval of at least 60 minutes between participants to allow sites to efficiently put on hold study vaccination in case of any safety concern.
- Unblinded safety data up to 7 days post-dose 1 in Step 1 will be reviewed by iSRC. Holding rules will apply (refer to Section 8.2.3).
- If no safety concern is identified, Step 1 participants will be allowed to complete the vaccination schedule (doses 2 and 3*), and the remaining 1032 participants aged 16-26 years** will be enrolled at the same time (Step 2).
  *In case not all 48 of the Step 1 participants are enrolled and vaccinated with a first dose of study vaccine by 30 September 2022, the iSRC will review the accumulated safety data up to 7 days post-dose 1 of all participants available by that date. If no safety signal is identified, these participants will be vaccinated with a second dose. To avoid any additional participants running out of the allowed interval range for their second vaccine dose, additional iSRC review(s) may need to be planned to review the safety data up to 7 days post-dose 1 of these participants, but only when all 48 Step 1 participants have been enrolled and their data have been reviewed by the iSRC, the iSRC will decide on the initiation of the vaccination of Step 2 participants.
  ** In Germany, only adult participants between and including 18 to 26 years of age will be included in this clinical study.

Vaccination schedule:

A 0-2-6 month vaccination schedule will be followed.

Blood sample collection:

- A 5 mL blood sample will be drawn from Step 1 (Sentinel) participants at Visit 1 (Day 1) and Visit 2 (Day 7) to assess biochemical and hematological parameters.
- For assessment of immune response, blood samples (~50 mL) will be drawn at Day 1, Month 2, Month 3, Month 6, Month 7 and Month 12 in all participants. Immunoglobulin G (IgG) antibody determination will be performed for these timepoints in all participants. Pseudovirion-based neutralization assays will be performed. Blood samples drawn at Day 1 (all participants), Month 2 (at least 96 participants in each group), Month 3 (all participants) and Month 7 (at least 150 participants in each group) will be tested.
- CCI [redacted]

Table 5 Study Groups, Vaccines, and Blinding

Study groups	Number of participants	Age (Min-Max)	Study vaccinations	Blinding*
				Visit 1 to Visit 7 (Observer-Blind)
HPV9High	270	16-26 years of age	HPV9-High	X
HPV9Med	270	16-26 years of age	HPV9-Medium	X
HPV9Low	270	16-26 years of age	HPV9-Low	X
Gar9	270	16-26 years of age	*Gardasil 9*	X

HPV = human papillomavirus
*This study is observer-blinded (double-blinded for the 3 formulations of the investigational adjuvanted HPV vaccine and observer-blinded for the investigational adjuvanted HPV vaccine vs *Gardasil 9*)
Note : In Germany, only adult participants between and including 18 to 26 years of age will be included in this clinical study.

4.2. Scientific Rationale for Study Design

4.2.1. Rationale for the use of a Comparator Vaccine and Randomization

This study is an active controlled study. *Gardasil 9* will be used as comparator. It has proven effectiveness, is approved for routine vaccinations in many countries and it is the only HPV vaccine marketed in the United States of America. It will allow the generation of data to compare the immunologic profile of the 3 investigational formulations to the one of *Gardasil 9.*

The participants will be randomized in the study in order to reduce bias of selection.

4.2.2. Selection of Study Population

The study will enroll healthy females 16-26 years of age (18-26 years of age in Germany), which is the gender and age cohort in which the efficacy of HPV vaccines has been demonstrated, at the time of the first dose, who have a lifetime history of 0-4 sexual partners and use adequate contraception. The exclusion criteria such as previous exposure to HPV vaccine or components of the investigational vaccine, history of previous HPV infection or of external genital/vaginal warts and any immunocompromised or autoimmune conditions, aim at avoiding potential immunological or clinical bias.

4.2.3. Rationale for Blinding

The study will be conducted in an observer-blind manner in order to reduce the risk of biased study outcomes. There will be a double-blind for the 3 formulations of the investigational adjuvanted HPV vaccine and an observer-blind for the investigational adjuvanted HPV vaccine versus *Gardasil 9*. A full double blinding is not possible because of the difference in the presentation of the investigational adjuvanted HPV vaccine formulations and *Gardasil 9*.

See the definitions of double blinding and observer-blind in Glossary of Terms and refer to Section 6.3.5.1 for details.

4.3. End of Study Definition

A participant is considered to have completed the study if she returns for the last visit/contact or is available for the last scheduled procedure/contact as described in the protocol.

The end of study (EoS) is defined as the date of the Last Participant Last Visit (LPLV) or date of last testing results released whichever comes last. In the latter, EoS must be achieved no later than 8 months after the LPLV.

5. STUDY POPULATION

Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria can jeopardize the scientific integrity, regulatory acceptability of the study or safety of the participant.

5.1. Inclusion Criteria

All participants must satisfy ALL the following criteria at study entry:

1. Healthy participants as established by medical history and clinical examination before entering into the study
2. **For Step 1 only**: Female between and including **18** and 26 years of age at the time of the first study intervention administration
3. **For Step 2**: Female between and including **16** and 26 years of age at the time of the first study intervention administration
4. Note: German Participants: In Germany, only adult participants between and including 18 to 26 years of age are to be included in this clinical study. Written informed consent obtained from the participant prior to performance of any study-specific procedure (for participants below the legal age of consent as per local regulations, written informed consent must be obtained from the participant/participant's parent[s]/legally acceptable representatives [LAR{s}] and, in addition, the participant should sign and personally date a written informed assent).
5. Participants and/or participants' parent(s)/LAR(s) who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the electronic diary [eDiary], return for follow-up visits).
6. Female participant with no more than 4 lifetime sexual partners prior to enrollment.
7. Female participants of non-childbearing potential may be enrolled in the study.
   Female participants of childbearing potential may be enrolled in the study if the participant:
   - has practiced adequate highly effective contraception for at least 1 month prior to study intervention administration, **and**
   - has a negative pregnancy test on the day of study intervention administration, **and**
   - has agreed to continue adequate contraception during the entire intervention period and for 2 months after completion of the study intervention administration series.

See Appendix 5 for the definition of women of childbearing potential and acceptable contraception requirements.

5.2. Exclusion Criteria

The following criteria should be checked at the time of study entry. The potential participant shall not be included in the study if any of exclusion criterion applies.

5.2.1. Medical Conditions

1. Pregnant or lactating female.
2. Female planning to become pregnant or planning to discontinue contraceptive precautions.
3. History of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention(s).
4. History or current diagnosis of autoimmune disease.
5. Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
6. Hypersensitivity to latex.
7. Major congenital defects, as assessed by the investigator.
8. History of abnormal Papanicolaou test or abnormal cervical biopsy result.
9. History of external genital/vaginal warts.
10. History of positive HPV test.
11. Acute or chronic clinically significant pulmonary, cardiovascular, neurologic, hepatic or renal functional abnormality, as determined by physical examination or laboratory tests.
12. Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.

Refer to Section 5.4 for criteria for the conditions for the temporary delay or enrollment and/or intervention.

5.2.2. Prior/Concomitant Therapy

13. Previous vaccination against HPV.
14. Previous exposure to monophosphoryl lipid A or AS04 adjuvant.
15. Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study intervention(s) during the period beginning 30 days before the first dose of study intervention(s) (Day -29 to Day 1), or their planned use during the study period.
16. Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before each dose and ending 30 days after each dose of study interventions administration*

    *In case emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organized by public health authorities outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine, provided it is licensed and used according to its Product Information.
17. Administration of long-acting immune-modifying drugs at any time during the study period (e.g., infliximab).
18. Use of systemic cytotoxic agents within the previous 3 months prior to randomization into this study or at any time during the study period.
19. Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to the first study

intervention dose(s). For corticosteroids, this will mean prednisone equivalent ≥20 mg/day for adult participants or ≥0.5 mg/kg/day with maximum of 20 mg/day for participants under 18 years of age. Inhaled and topical steroids are allowed.

20. Administration of systemic immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before the administration of the first dose of study interventions or planned administration during the study period.

5.2.3. Prior/Concurrent Clinical Study Experience

21. Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational intervention (drug/invasive medical device [see the definition in Glossary of Terms]).

5.2.4. Other Exclusions

22. History of /current chronic alcohol consumption and/or drug abuse.
23. Any study personnel or their immediate dependants, family, or household members.
24. Child in care.

5.2.5. Lifestyle Considerations

No restrictions pertaining to lifestyle and/or diet apply.

5.3. Screen Failures

Not applicable as there is no screening phase of the potential participants as part of this study.

5.4. Criteria for Temporary Delay for Enrollment and/or Intervention Administration

Enrollment and/or study intervention administration may be postponed within the permitted time interval until transient circumstances cited below are resolved and the participant stays eligible:

- Acute disease and/or fever at the time of enrollment and/or study intervention administration. Fever is defined as temperature ≥37.5°C/99.5°F. The preferred location for measuring temperature will be the axilla.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- Use of antipyretics and/or analgesics and/or antibiotics within 3 days prior to study intervention administration.
- Participants with symptoms suggestive of active Coronavirus Disease 2019 (COVID-19) infection (e.g., fever, cough, etc.) until they are free of symptoms for at least 14 days.

- Enrollment and/or study intervention administration of participants with known COVID-19-positive contacts within the past 14 days should be delayed for at least 14 days since the exposure and if the participant remains free of symptoms.

6. STUDY INTERVENTIONS

6.1. Study Interventions Administered

The details on the vaccines administered in this study are provided in Table 6.

Table 6 Study Interventions Administered

Study vaccines	HPV9-High formulation	HPV9-Medium formulation	HPV9-Low formulation	*Gardasil 9*
Study vaccines formulation	GSKVx000000031357 (Dose Aa GSKVx000000031397); GSKVx000000031399 (Dose Ba GSKVx000000031400); GSKVx000000031402 (Dose Ca GSKVx000000031327); GSKVx000000031328 (Dose Da GSKVx000000031408); GSKVx000000031409 (Dose Ea GSKVx000000031427); GSKVx000000031407 (Dose Fa GSKVx000000031360); GSKVx000000031429 (Dose Ga GSKVx000000031384); GSKVx000000031361 (Dose Ha GSKVx000000031371); GSKVx000000031363 (Dose Ia GSKVx000000031434); Excipients; Water for injections q.s. 0.5 mL	GSKVx000000031398 (Dose Ab GSKVx000000031397); GSKVx000000031382 (Dose Bb GSKVx000000031400); GSKVx000000031403 (Dose Cb GSKVx000000031327); GSKVx000000031405 (Dose Db GSKVx000000031408); GSKVx000000031410 (Dose Eb GSKVx000000031427); GSKVx000000031428 (Dose Fb GSKVx000000031360); GSKVx000000031430 (Dose Gb GSKVx000000031384); GSKVx000000031362 (Dose Hb GSKVx000000031371); GSKVx000000031433 (Dose Ib GSKVx000000031434); Excipients; Water for injections q.s. 0.5 mL	GSKVx000000031358 (Dose Ac GSKVx000000031397); GSKVx000000031401 (Dose Bc GSKVx000000031400); GSKVx000000031404 (Dose Cc GSKVx000000031327); GSKVx000000031406 (Dose Dc GSKVx000000031408); GSKVx000000031426 (Dose Ec GSKVx000000031427); GSKVx000000031359 (Dose Fc GSKVx000000031360); GSKVx000000031383 (Dose Gc GSKVx000000031384); GSKVx000000031432 (Dose Hc GSKVx000000031371); GSKVx000000031364 (Dose Ic GSKVx000000031434); Excipients; Water for injections q.s. 0.5 mL	HPV6 L1 (30 µg)[1]; HPV11 L1 (40 µg)[1]; HPV16 L1 (60 µg)[1]; HPV18 L1 (40 µg)[1]; HPV31 L1 (20 µg)[1]; HPV33 L1 (20 µg)[1]; HPV45 L1 (20 µg)[1]; HPV52 L1 (20 µg)[1]; HPV58 L1 (20 µg)[1]; [1] adsorbed on amorphous aluminum hydroxyphosphate sulfate; Amorphous aluminum hydroxyphosphate sulfate (0.5 mg Al^{3+}); Water for injections q.s. 0.5 mL
Dose form (Presentation)	Suspension for injection (syringe)	Suspension for injection (syringe)	Suspension for injection (syringe)	Suspension for injection (syringe)
Type	Biologic/Combination Product	Biologic/Combination Product	Biologic/Combination Product	Biologic/Combination Product
Route of administration	Intramuscular	Intramuscular	Intramuscular	Intramuscular
Location	Deltoid	Deltoid	Deltoid	Deltoid
Directionality	Upper	Upper	Upper	Upper
Laterality*	Nondominant	Nondominant	Nondominant	Nondominant
Number of doses to be administered	3	3	3	3
Volume to be administered	0.5 mL	0.5 mL	0.5 mL	0.5 mL
Packaging, labeling and trademark	Refer to the Study Reference Manual for details	Refer to the Study Reference Manual for details	Refer to the Study Reference Manual for details	Refer to the Study Reference Manual for details
Manufacturer	GlaxoSmithKline Biologicals SA (GSK)	GSK	GSK	Merck & Co.

*The nondominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the nondominant arm, an injection in the dominant arm may be performed.

6.2. Preparation/Handling/Storage/Accountability

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of IQVIA. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Study Reference Manual (SRM)/pharmacy manual for more details on storage of the study intervention(s).

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Participant Identification

Participant identification numbers (IDs) will be assigned sequentially to the participants who have consented or provided assent with consent from each participant's parent(s)/LAR(s) to participate in the study, according to the range of participant IDs allocated to each study center. The participant IDs will be documented in the electronic Case Report Form (eCRF).

The eligibility of the participant will be determined based on the inclusion and exclusion criteria listed in Section 5. The participant ID will be the participant's unique identification number for all eCRFs and associated study documentation that will be used for duration of the study. If the participant is terminated from the study, her participant ID cannot be re-assigned.

6.3.2. Randomization to Study Intervention

All eligible participants will be centrally randomized to the study group at a 1:1:1:1 ratio using Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) randomization (refer to Glossary of Terms for a definition of IVRS/IWRS). At study initiation, log in information and directions for the IVRS will be provided to each study center. The study and the center will be used as a minimization factor for randomization in Step 1 and the study, the center and CCI [redacted] will be used as a minimization factor for randomization in Step 2.

The participants will receive a unique treatment number (refer to Glossary of Terms for a definition of a treatment number). Once a treatment number has been assigned, it cannot be re-assigned.

6.3.3. Intervention Allocation to the Participant

Allocation of the participant to an intervention group at the study center will be performed using IVRS/IWRS through Interactive Response Tool (IRT) operated at the study level, before the first vaccination and after assessment of eligibility.

The actual randomization assignment that the participant received (to one of the groups) will be identifiable in IRT in case of unblinding.

After obtaining the signed and dated Informed Consent Form (ICF) (and informed assent form [IAF] if applicable) from the participant/participant's parent(s)/LAR(s) and having checked the eligibility of the participant, the delegated clinical study staff will access IVRS/IWRS. Upon entering the participant ID, the randomization system will determine the intervention group and provide the treatment number.

For all subsequent doses or replacement, new treatment numbers will be obtained through the IVRS/IWRS.

Refer to the IVRS/IWRS user guide or the SRM for specific instructions related to instances when IVRS/IWRS is not available.

Refer to the SRM for additional information related to the treatment number allocation.

6.3.4. Allocation of Participants to Assay Subsets

Immunogenicity assessments are planned as outlined in Section 8.1.

Refer to Section 9.3 for descriptions of analysis populations.

6.3.5. Blinding and Unblinding

6.3.5.1. Blinding

This study is observer-blind (double-blind for the 3 formulations of the investigational adjuvanted HPV vaccine and observer-blind for the investigational adjuvanted HPV vaccine versus *Gardasil 9*).

By observer-blind, it is meant that during the study, the vaccine recipient and those responsible for the evaluation of any study endpoint will be unaware of which vaccine was administered. To do so, vaccine preparation and administration will be done by a third party which will be a study center staff member who will not participate in any of the study clinical evaluation assays. The third party will know if the vaccine to dispense is the investigational adjuvanted HPV vaccine formulation or *Gardasil 9*. However, they will not know which one of the 3 investigational adjuvanted HPV vaccine formulations is dispensed (double-blind for the 3 formulations of the investigational adjuvanted HPV vaccine).

A blinded observer will participate in the participant's post injection assessments, perform clinical evaluations and record the clinical data.

The laboratory in charge of sample testing will be blinded to the study intervention assignment. Codes will be used to link the participant and study to each sample. There will be no link between the study intervention groups and the identity of the participant.

Unblinded monitors and in the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.3.5.2. Emergency Unblinding

Unblinding a participant's individual intervention number should occur ONLY in case of a medical emergency when knowledge of the intervention is essential for the clinical management or welfare of the participant.

In case of emergency, the investigator will have unrestricted, immediate, and direct access to the participant's individual study intervention through IVRS/IWRS. At activation, the study centers will be provided instructions and/or other applicable information for emergency unblinding in the SRM or other sources. The IRT used by the IVRS/IWRS provider will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention is warranted. The participant's safety must always be the first consideration in making such a determination.

If a participant's intervention assignment is unblinded, the Medical Monitor (see the definition in Glossary of Terms) must be notified WITHIN 24 HOURS after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation (see the definition in Glossary of Terms) and eCRF, as applicable. The participant may continue in the study.

In the event of a Quality Assurance audit, the auditor(s) may be allowed access to unblinded study intervention information records to verify that vaccine dispensing has been done accurately.

A non-investigator physician (e.g., physician from emergency room) or participant/participant's parent(s)/LAR(s)/caregiver (see Glossary of Terms for a definition of a caregiver)/family member may also request emergency unblinding. Instructions for this will be provided to the participant/participant's parent(s)/LAR(s) at enrollment.

6.3.5.3. Emergency Unblinding Prior to Regulatory Reporting of Serious Adverse Events

GSK policy (which incorporates the International Council for Harmonisation [ICH] E2A guideline, European Union Clinical Study Directive, and the United States Federal Regulations) is to unblind the report of any unexpected serious adverse event (SAE) that is attributable/suspected to be attributable to the investigational vaccine prior to regulatory reporting.

IQVIA will follow these policies along with IQVIA's standard procedures and will be responsible for unblinding the intervention assignment in accordance with the specified time frames for expedited reporting of SAEs.

In addition, IQVIA may unblind the intervention assignment for any participant with a Suspected Unexpected Serious Adverse Reaction or an SAE that is fatal or life-threatening. If the SAE requires an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK's policy.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive the study intervention directly from the investigator or designee, under medical supervision. The date of administration of each study intervention dose will be recorded in the source documents.

6.5. Dose Modification

Not applicable.

6.6. Continued Access to Study Intervention After the End of Study

GSK will not be providing to the participants the continuing access to either study vaccine after the conclusion of the study.

6.7. Treatment of Overdose

Any dose of either study vaccine greater than the dose advised as per protocol is considered an overdose. All cases of vaccine overdose should be reported as adverse events (AEs) (or SAEs, if SAE criteria are met) and followed accordingly.

6.8. Concomitant Medications/Products and Concomitant Vaccinations

At each study visit/contact, the investigator or designee should question the participant or participant's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the participant, whether prescribed or over the counter. Memory aids used by participant/participant's parent(s)/LAR(s) will be reviewed for any additional medication(s) and vaccination(s), which will be transcribed in eCRFs.

6.8.1. Recording of Concomitant Medications/Products and Concomitant Vaccinations

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF:

- All concomitant medications/products, except vitamins and dietary supplements, administered during the 28-day period following each dose of study vaccine.
- Any concomitant vaccination administered in the period starting from the first dose of study vaccine and ending at the last study visit.
- All concomitant medication associated with AE, including vaccines/products, except vitamins and dietary supplements, administered after the first dose of study intervention.

- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines (refer to Section 5.2.2 and Section 9.3 for further details).
- Prophylactic medication (i.e., medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  For example, an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring
- Any concomitant medications/products/vaccines relevant to an SAE/potentially immune-mediated response (pIMD) to be reported as per protocol or administered during the study period for the treatment of an SAE/pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the expedited AE report.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The record of a concomitant medication should include at a minimum the reason for use, dates of administration including start and end dates, dosage information including dose and frequency.

6.8.2. Concomitant Medications/Products/Vaccines That May Lead to Elimination of a Participant From Per Protocol Analyses

The use of the concomitant medications/products/vaccines listed in Section 5.2.2 will not require withdrawal of the participant from the study but may determine a participant's evaluability in the per protocol analysis. See Section 9.3 for cohorts to be analyzed.

6.9. Intercurrent Medical Conditions That May Lead to Elimination of a Participant From Per Protocol Analyses

At each study visit subsequent to the first vaccination, it must be verified if the participant has experienced or is experiencing any intercurrent medical condition (refer to Glossary of Terms for the definition of intercurrent medical condition). If it is the case, the condition(s) must be recorded in the AE section of the eCRF.

At the time of analysis, participants may be eliminated from the per protocol cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response or are confirmed to have an alteration of their initial immune status.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Discontinuation of study intervention refers to any participant who has not received all planned doses of study intervention. A participant who discontinued study intervention may continue other study procedures (e.g., safety or immunogenicity), planned in this protocol at the discretion of the investigator.

The primary reason for premature discontinuation of the study intervention will be documented on the eCRF and may include (but not be limited to), the following:

- Adverse event requiring expedited reporting to IQVIA
- Pregnancy
- Unsolicited non-serious AE
- Solicited AE
- Not willing to be vaccinated
- Other (specify)

7.2. Contraindications to Subsequent Study Intervention(s) Administration

The eligibility for subsequent study intervention administration must be confirmed before administering any additional dose.

All exclusion criteria have to be re-checked to ensure that the participant is still eligible. In addition, participants who meet any of the criteria listed below should not receive additional dose of study intervention.

- Study participants who experience any SAE judged to be possibly or probably related to study intervention or non-study concomitant vaccine/product, including hypersensitivity reactions.
- Study participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participant if she continues to participate in the study.
- Anaphylaxis following the administration of study intervention.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Occurrence of a new pIMD (see Table 21 for the list of pIMDs) or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the participant to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgment prior to administering the next dose of study intervention.

The participants who have become ineligible for subsequent study intervention administration should be encouraged to continue other study procedures, at the investigators' discretion. All

relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

7.3. Participant Discontinuation/Withdrawal From the Study

A participant is considered to have withdrawn from the study if no new study procedure has been performed or no new information has been collected for her since the date of withdrawal/last contact.

From an analysis perspective, a study "withdrawal" refers to any participant who did not return for the concluding visit.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses.

The primary reason for study withdrawal will be documented in the eCRF based on the list below:

- AEs requiring expedited reporting to IQVIA
- Unsolicited non-serious AEs
- Solicited AE
- Withdrawal by participant, not due to an AE*
- Migrated/moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

*If a participant is withdrawn from the study because she withdrew consent and the reason for withdrawal was provided, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved.

7.4. Lost to Follow-up

A participant will be considered "lost to follow-up" if she fails to return for scheduled visits and is unable to be contacted by the study center. Refer to the SRM for a description of the actions to be taken before considering the participant as lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are only permitted when necessary for the management of immediate safety concerns for the participant.

Immediate safety concerns should be discussed with IQVIA as soon as they occur or when the study team becomes aware of them. The purpose of this communication is to determine if the participant(s) should discontinue the study intervention.

Study procedures and their timing are summarized in the schedule of activities (SoA) (Section 1.3).

All eligibility evaluations must be completed, and the results reviewed before confirming that potential participants meet all eligibility criteria.

The SRM provides the investigator and study center personnel with detailed administrative and technical information that does not impact the participant safety.

8.1. Immunogenicity Assessments

8.1.1. Biological Samples

Collected biological samples will be used for protocol-mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol.

Additional serological assays may be performed in the future to further characterize the disease and/or the immunological response elicited by study intervention. These assays may not be represented in the objectives/endpoints of the study protocol.

Findings in this or future studies may make it desirable to use samples acquired in this study for research not planned in this protocol. In this case, all participants in countries where this is allowed will be asked to give consent to allow GSK or a contracted partner, to use the samples for further research. The further research will be subject to prior IEC/IRB approval, if required by local legislation.

Information on further investigations and their rationale can be obtained from GSK.

Sample testing will be done in accordance with the recorded consent of the individual participant/participant’s parent(s)/LAR(s).

Collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performed the last study visit, unless local rules, regulations or guidelines require different timeframes or procedures, which would then be in line with participant consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK.

Blood samples will be collected from participants as described in Table 7.

Table 7 Biological Samples

Sample Type	Quantity	Time point	Time Point	Time Point	Time Point	Time Point	Time Point	Time Point	Subset Name
Blood sampling for antibody determination	Approximately 50 mL	Visit 1 Day 1		Visit 3 Month 2	Visit 4 Month 3	Visit 5 Month 6	Visit 6 Month 7	Visit 7 Month 12	All participants
CCI [redacted]									
Blood sampling for any hematological/biochemical laboratory abnormality	Approximately 5 mL	Visit 1 Day 1	Visit 2* Day 7						Step 1 participants
CCI [redacted]									

*Visit 2 is for Step 1 participants only.

8.1.2. Laboratory Assays for Immunogenicity

The laboratory tests for immunogenicity are listed in Table 8 and Table 9. All laboratory testing will be performed at GSK laboratory or in a laboratory designated by GSK. Refer to Appendix 3 for a brief description of the assays.

Table 8 Humoral Immune Response

Assay type	System	Component	Method
Humoral Immunity (Antibody determination)	Serum	Anti-HPV-6 L1 VLP Ab IgG	ECL
	Serum	Anti-HPV-11 L1 VLP Ab IgG	ECL
	Serum	Anti-HPV-16 L1 VLP Ab IgG	ECL
	Serum	Anti-HPV-18 L1 VLP Ab IgG	ECL
	Serum	Anti-HPV-31 L1 VLP Ab IgG	ECL
	Serum	Anti-HPV-33 L1 VLP Ab IgG	ECL
	Serum	Anti-HPV-45 L1 VLP Ab IgG	ECL
	Serum	Anti-HPV-52 L1 VLP Ab IgG	ECL
	Serum	Anti-HPV-58 L1 VLP Ab IgG	ECL
	Serum	Anti-HPV-6 PSV L1/L2 neutralizing Ab	PBNA
	Serum	Anti-HPV-11 PSV L1/L2 neutralizing Ab	PBNA
	Serum	Anti-HPV-16 PSV L1/L2 neutralizing Ab	PBNA
	Serum	Anti-HPV-18 PSV L1/L2 neutralizing Ab	PBNA
	Serum	Anti-HPV-31 PSV L1/L2 neutralizing Ab	PBNA
	Serum	Anti-HPV-33 PSV L1/L2 neutralizing Ab	PBNA
	Serum	Anti-HPV-45 PSV L1/L2 neutralizing Ab	PBNA
	Serum	Anti-HPV-52 PSV L1/L2 neutralizing Ab	PBNA
	Serum	Anti-HPV-58 PSV L1/L2 neutralizing Ab	PBNA

Ab = antibody; ECL= electrochemiluminescence assay; HPV = human papilloma virus; IgG = immunoglobulin G; PBNA = pseudovirion-based neutralization assay; PSV = pseudovirion; VLP = virus-like particle

CCI

Further laboratory testing related to the investigational adjuvanted vaccine formulations and/or HPV disease may be performed if deemed necessary or if assay(s) become available.

The addresses of clinical laboratories used for sample analysis will be provided in a separate document accompanying this study protocol.

GSK clinical laboratories have established a Quality System supported by procedures. The activities of GSK clinical laboratories are audited regularly for quality assessment by an internal (GSK-dependent) but laboratory-independent Quality Department.

8.1.3. Immunological Correlates of Protection

There is no established correlate of protection with the assay(s) to be used in this study for any of the vaccines administered in the frame of this study.

8.2. Safety Assessments

The investigator and his/her designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and designees are responsible

for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant's withdrawal from the study intervention or study.

8.2.1. Pre-Intervention Administration Procedures

8.2.1.1. Collection of Demographic Data

Demographic data such as age in years, race, and ethnicity (with attention to local ethical considerations) will be collected from each participant and recorded in the eCRF.

8.2.1.2. Collection of Medical/Vaccination History

The medical and vaccination history should be checked by interviewing the participant/participant's parent(s)/LAR(s) and/or review of the participant's medical records. It should be verified that none of the exclusion criteria related to medical and vaccination history (Section 5.2) are met. Any pre-existing conditions or signs and/or symptoms present in a patient prior to the first study vaccination will be recorded in the eCRF.

8.2.1.3. Physical Examination/Vital Signs

On Day 1, a history directed physical examination (including the injection site examination) will be performed for each participant as per the standard of care. Physical examination at each study visit after the first study intervention administration will be performed only if the participant/participant's parent(s)/LAR(s) indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate. Collected information needs to be recorded in the eCRF.

On Day 1 and at each vaccination, vital signs (including temperature, systolic/diastolic blood pressure, heart rate, and respiratory rate after at least 10 minutes of rest) will be collected. Vital signs are to be taken before blood collection for laboratory tests. Collected information needs to be recorded in the eCRF

Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate healthcare provider.

If the investigator determines that the participant's health on the day of study intervention administration (Visit 1 [Day 1], Visit 3 [Month 2] and Visit 5 [Month 6]) temporarily precludes dosing, the visit will be rescheduled. Refer to Section 5.4 for the list of criteria for the temporary delay of study intervention administration.

8.2.1.4. Pregnancy Test

All study participants must perform a high sensitivity urine pregnancy test prior to each study vaccine administration. Pregnancy testing must be performed even if the participant is denying

any sexual activity, menstruating at the time of visit, or is considered infertile. The study vaccine may only be administered after the pregnancy test is negative.

Refer to Appendix 5 for the contraceptive guidance and information on study continuation for a participant who becomes pregnant during the study.

8.2.1.5. Checking Contraindications, Warnings, and Precautions to Intervention Administration

Warnings and precautions to administration of study intervention must be checked at each visit with planned administration of study intervention. Refer to Section 7.2 for contraindications to subsequent study intervention administration and to Section 5.4 for criteria for temporary delay for enrollment and/or intervention administration.

8.2.2. Clinical Safety Laboratory Tests

Blood sampling for any hematological/biochemical laboratory abnormality for Step 1 participants will be collected at Visits 1 and 2. Hematology and biochemistry tests performed in the local laboratories are listed in Table 10. The volumes of blood to be collected are shown in Table 7.

Table 10 Hematology and Biochemistry Tests

Assay type	System	Component	Method
Hematology	Whole Blood	Leukocytes (white blood cells)	As per local laboratory procedures
	Whole Blood	Neutrophils*	
	Whole Blood	Lymphocytes*	
	Whole Blood	Basophils*	
	Whole Blood	Monocytes*	
	Whole Blood	Eosinophils*	
	Whole Blood	Hemoglobin	
	Thrombocytes	Platelets	
	Red Blood Cells	Erythrocytes (red blood cells)	
Biochemistry	Serum	Blood urea nitrogen	As per local laboratory procedures
		Alanine aminotransferase (ALT)	
		Aspartate aminotransferase (AST)	

*For white blood cell differential count.

8.2.3. Study Holding Rules and Safety Monitoring

8.2.3.1. Staggered Enrollment

As this will be the first time that these investigational adjuvanted HPV vaccine formulations will be administered in humans, the enrollment will be staggered (refer to Section 8.2.3.3 for details).

In Step 1, 48 participants (12 per group) aged 18-26 years will be enrolled and vaccinated with the first dose with an interval of at least 60 minutes between participants. Safety data from Step 1 participants will be reviewed 7 days post-dose 1 by an unblinded iSRC (independent of the study team).

The solicited administration site and systemic events that will be collected during the 7-day follow-up period following each vaccination are presented in Table 11. The intensity of the solicited AEs will be assessed as described in Table 12.

Table 11 Solicited Events to be Collected in Step 1 and 2

Event	Symptoms
Solicited administration site events	Pain
	Redness
	Swelling
Solicited systemic events	Fever
	Headache
	Myalgia
	Arthralgia
	Fatigue

Note: participants/participants' parent(s)/LAR(s) will be instructed to measure and record the axillary temperature in the evening. If additional temperature measurements are taken at other times of the day, participants/participants' parent(s)/LAR(s) will be instructed to record the highest temperature in the electronic Diary.

Table 12 Intensity Scales for Solicited Events

Event	Intensity grade	Parameter
Pain	1 (Mild)	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2 (Moderate)	Moderate: Painful when limb is moved and interferes with everyday activities.
	3 (Severe)	Severe: Significant pain at rest. Prevents normal everyday activities.
Redness and Swelling at administration site (Greatest surface diameter in mm)	1 (Mild)	>0 mm to ≤20 mm
	2 (Moderate)	>20 mm to ≤50 mm
	3 (Severe)	>50 mm
Temperature* in °C	1 (Mild)	≥37.5°C (99.5°F) to ≤38.0°C (100.4°F)
	2 (Moderate)	>38.0°C (100.4°F) to ≤39.0°C (102.2°F)
	3 (Severe)	>39.0°C (102.2°F)
Headache	1 (Mild)	Headache that is easily tolerated
	2 (Moderate)	Headache that interferes with normal activity
	3 (Severe)	Headache that prevents normal activity
Fatigue	1 (Mild)	Fatigue that is easily tolerated
	2 (Moderate)	Fatigue that interferes with normal activity
	3 (Severe)	Fatigue that prevents normal activity
Arthralgia	1 (Mild)	Arthralgia that is easily tolerated
	2 (Moderate)	Arthralgia that interferes with normal activity
	3 (Severe)	Arthralgia that prevents normal activity
Myalgia	1 (Mild)	Myalgia that is easily tolerated
	2 (Moderate)	Myalgia that interferes with normal activity
	3 (Severe)	Myalgia that prevents normal activity

SoA = schedule of activities

*Refer to the SoA (Table 1) for the definition of fever and the preferred location for temperature measurement.

Biochemistry and hematology parameters will be collected in Step 1 participants (refer to Table 10). The intensity of these parameters will be assessed as described in Table 13.

Table 13 Biochemistry and Hematology Parameters Grading Component

	Grade 1	Grade 2	Grade 3	Grade 4**
Hematology				
Hemoglobin (g/dL) female	12-11	10.9-9.5	9.4-8	<8
Hemoglobin change from baseline female (g/dL)	<1.5	1.6-2	2.1-5	>5
WBC (cell/mm^3) increase	10,800-15,000	15,001-20,000	20,001-25,000	>25,000
WBC (cell/mm^3) decrease	3,500-2,500	2,499-1,500	1,499-1,000	<1,000
Lymphocyte (cell/mm^3) decrease	1,000-750	749-500	499-250	<250
Neutrophils (cell/mm^3) decrease	2,000-1,500	1,499-1,000	999-500	<500
Eosinophils (cell/mm^3)	650-1,500	1,501-5,000	>5,000	hypereosinophilic syndrome
Platelet (cell/mm^3) decrease	140,000-125,000	124,000-100,000	99,000-25,000	<25,000
Biochemistry				
ALT (increase by factor)	1.1-2.5×ULN	2.6-5×ULN	5.1-10×ULN	>10×ULN
AST (increase by factor)	1.1-2.5×ULN	2.6-5×ULN	5.1-10×ULN	>10×ULN
Blood Urea Nitrogen BUN mg/dL	23-26	27-31	>31	Requires dialysis

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FDA = Food and Drug Administration; ULN = upper limit of normal; WBC = white blood cells
Note: The laboratory values provided in the table are taken from the FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" dated September 2007. These laboratory values 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).

Besides the standard AE collection (solicited AEs, unsolicited AEs, SAEs), the study will also collect pIMDs (see Table 21) throughout the study due to presence of the adjuvant AS04.

8.2.3.2. Safety Holding Rules

The safety holding rules for the vaccination phases of the study are defined in Table 14.

For participants enrolled in Step 1, holding rules 1a-1d from Table 14 will be assessed by the investigator on a continuous basis, and meeting any of these holding rules will trigger a hold of vaccination irrespective of number of participants enrolled and/or timing of the event relative to

vaccination. Holding rules 2a-2c from Table 14 will be assessed by the iSRC during the safety evaluations on unblinded data.

These holding rules have been written under the assumption that the safety data from all participants will be available. If the data from all Step 1 participants are not available (i.e., in case a participant is lost to follow-up), then the holding rules will be assessed on a pro-rata basis (expressed as percentage of participants to be evaluated) i.e., 3 out of 12 participants per arm or 25% per arm.

Of note, no formal holding rules will be applied for other safety data such as non-life-threatening SAEs, missed visits due to study intervention-related AEs, Grade 1 and Grade 2 solicited and unsolicited AEs in the 7-day follow-up period and unsolicited AEs collected from Day 8 to Day 30 after study intervention administration. However, if available, these data will also be reviewed by the iSRC to allow an overall assessment of the benefit/risk ratio of study intervention administration.

If the investigator becomes aware of a holding rule being met, they must suspend administration of the study intervention and inform IQVIA immediately (e.g., holding rules 1a-d). IQVIA will inform the investigator if holding rules 2a-c are met. Investigators will be responsible to inform the IRB/IEC if a holding rule has been met.

The following communication sequence must be followed:

- The concerned site staff will put study intervention administration and enrollment on hold.
- The concerned site staff will immediately inform IQVIA's safety team (i.e., the events to be reported via an Electronic Data Capture system [EDC]).
- Enrollment and intervention allocation through IVRS/IWRS will then be stopped on a study level.
- IQVIA will inform all investigators about the stopping of enrollment and intervention.
- IQVIA will also provide the blinded data to GSK's Clinical Research and Development Lead and Safety Lead for further SRT and GSK Global Safety Board review.
- IQVIA will forward the relevant unblinded safety information to iSRC for evaluation.
- Based on the recommendation from iSRC, GSK's Global Safety Board will make the decision whether the study can resume, be modified, or stopped. GSK will notify IQVIA on this decision.
- IQVIA will notify all investigators on this decision.
- Depending on the outcome of the safety evaluation, the study will be re-started, terminated, or resumed under a protocol amendment.

Table 14 Study Holding Rules for Step 1 to be Assessed Post-Dose 1

Holding Rule	Event	Number of participants/group
		Step 1
1a	Death or any life-threatening serious adverse event **(SAE)**	≥1
1b	Any non-life-threatening **SAE** that cannot be reasonably attributed to a cause other than intervention as per Investigator or Sponsor assessment	≥1
1c	Any **withdrawal** from the study (by investigator or participant request) following a Grade 3 adverse event (AE)	≥1
1d	Any administration site or systemic solicited AE leading to **hospitalization**, or **fever > 40°C** (104°F), or **necrosis** at the injection site, each with an event onset within the 7-day (days 1-7) post-intervention period	≥1
2a	Any **Grade 3 solicited administration site events** (lasting 48 hours or more as Grade 3), with an event onset within the 7-day (days 1-7) post-intervention period	≥3/12 (≥25%)
2b	Any **Grade 3 solicited systemic events** (lasting 48 hours or more as Grade 3)**,** with an event onset within the 7-day (days 1-7) post-intervention period	≥3/12 (≥25%)
2c	Any **Grade 3 unsolicited** AE, that can be reasonably attributed to the vaccination as per Investigator or Sponsor assessment, with an event onset within the 7-day (days 1-7) post-vaccination period OR Any **Grade 3** or above abnormality in pre-specified hematological or biochemical **laboratory parameters** with an event onset within the 7-day (days 1-7) post-intervention period	≥3/12 (≥25%)

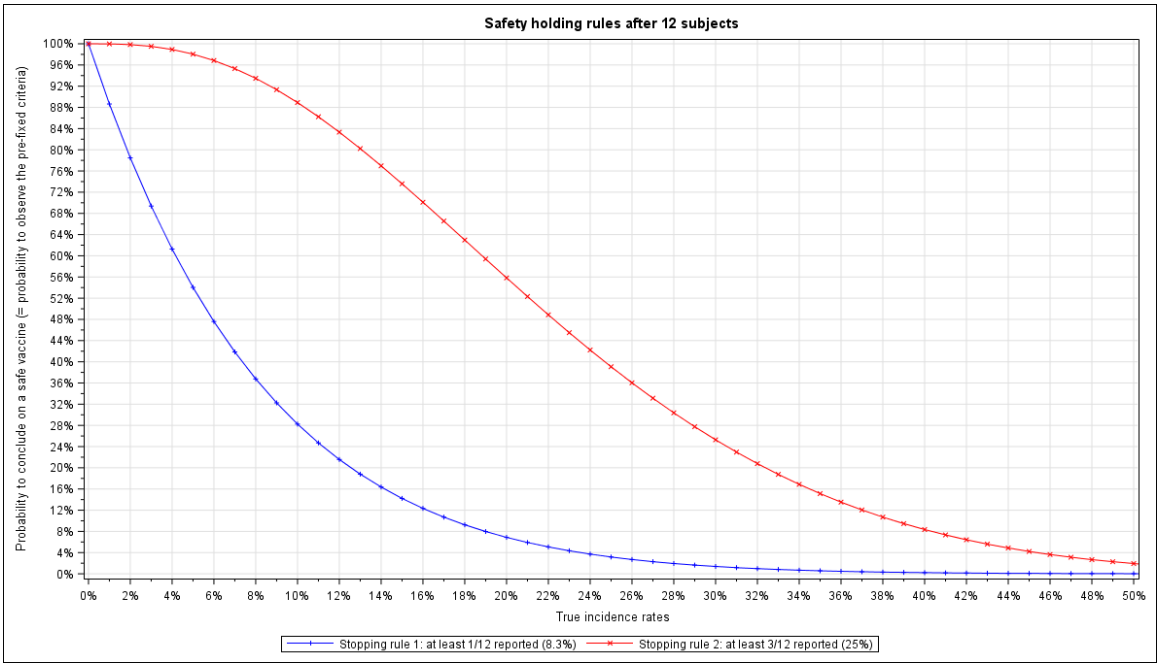
Note: by Sponsor, it means GlaxoSmithKline Biologicals SA's designee for AE recording and assessment, IQVIA

Risk Assessment for Step 1

As shown in Figure 2, with 12 participants per study group:

- Each holding rule 1a-1d has more than 89% chance of not being met for vaccination with a true incidence rate corresponding to the occurrence of holding rule event below 1%, and has more than 70% chance of being met for vaccination with a true incidence rate above 10%.
- Each holding rule 2a-2c has more than 89% chance of not being met for vaccination with a true incidence rate below 10% and more than 60% chance of being met for vaccination with a true incidence rate above 25%.

Figure 2 Probability of Not Meeting Holding Rules 1 and 2 for 12 Participants per Study Group in Step 1



8.2.3.3. iSRC Evaluation

The iSRC will review the accumulated safety data up to 7 days post-dose 1 of sentinel participants in Step 1*. The iSRC will have access to the participant randomization list and will review unblinded data. The iSRC members will determine whether any of the pre-defined holding rules are met (refer to Section 8.2.3) or if there is any other safety signal. If no safety signal is observed, vaccination of the "Step 1" participants will continue, and vaccination of the remaining participants ("Step 2" participants) will be initiated.

Following this initial review(s), the iSRC will review all available safety data on a regular basis (monthly) until data from 1-month post-dose 2 for all participants and data from 1-month post-dose 3 for Step 1 participants are reviewed. During these reviews, monitoring of safety events will be done with no holding rules assessment (refer to the iSRC charter for details). It will be up to iSRC to trigger a study hold or study change if deemed necessary. In addition to the iSRC, the project SRT will review blinded data on a regular basis throughout the study.

*In case not all 48 of the Step 1 participants are enrolled and vaccinated with a first dose of study vaccine by 30 September 2022, the iSRC will review the accumulated safety data up to 7 days post-dose 1 of all participants available by that date. If no safety signal is identified, these participants will be vaccinated with a second dose. To avoid any additional participants running out of the allowed interval range for their second vaccine dose, additional iSRC review(s) may need to be planned to review the safety data up to 7 days post-dose 1 of these participants, but

only when all 48 Step 1 participants have been enrolled and their data have been reviewed by the iSRC, the iSRC will decide on the initiation of the vaccination of Step 2 participants.

8.3. Adverse Events

The definitions and details on recording, evaluating, and reporting of AEs, SAEs, pIMDs, and also pregnancies are provided in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study/study intervention (see Section 7).

8.3.1. Time Period and Frequency for Collecting AEs/SAEs, pIMDs, and Pregnancy Information

Collection of AEs, SAEs, pregnancies, and pIMDs will be performed at the time points and periods specified in Table 15.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the medical history section of the eCRF, not the AE section.

All SAEs will be recorded and reported to IQVIA within 24 hours. The investigator will submit any updated SAE data to IQVIA within 24 hours of it being available through the Expedited Report Form.

Investigators are not obligated to actively seek AE or SAE after the participant concluded the study participation. However, if the investigator learns of any SAE, including a death, at any time after the participant has been discharged from the study, and the event is considered reasonably related to the study intervention, the investigator must notify IQVIA.

Table 15 Time Period and Frequency for Collecting AE/SAE and Pregnancy Information

	Visit 1	**Visit 2**			**Visit 3**		**Visit 4**		**Visit 5**		**Visit 6**	**Visit 7**
Event	**Day 1**	**Day 7**			**Month 2**		**Month 3**		**Month 6**		**Month 7**	**Month 12**
	Dose 1	7 days post-Dose 1	28 days post-Dose 1		**Dose 2**	7 days post-Dose 2	28 days post-Dose 2		**Dose 3**	7 days post-Dose 3	28 days post-Dose 3	**Study conclusion**
Administration site and systemic solicited events												
Unsolicited AEs												
SAEs (all, fatal, related)												
pIMDs												
AEs/SAEs leading to withdrawal from the study												
SAEs related to study participation or concurrent GSK medication/vaccine												
Pregnancies/pregnancy outcomes												

AE = adverse event; SAE = serious adverse event; pIMD = potentially immune-mediated disease

8.3.2. Method of Detecting AEs and SAEs, Pregnancies, and pIMDs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. Memory aids used by participant/participant's parent(s)/LAR(s), will be reviewed for health-related issues of participants and for potential AEs, which will be transcribed in eCRFs.

8.3.3. Clinically Significant Abnormal Laboratory Findings

The investigator must record any clinically relevant changes occurring during the study in the AE section of the eCRF. All clinically significant abnormal laboratory test values should be repeated until the values return to normal/baseline, or until they are no longer considered significantly abnormal by the investigator. If such values do not return to normal/baseline after an interval judged reasonable by the investigator, the etiology of the abnormal value should be identified, and the sponsor notified. In any case, the investigator should document they reviewed the laboratory report.

8.3.4. Follow-up of AEs and SAEs, Pregnancies, and pIMDs

After the initial AE/SAE/pIMD, or pregnancy report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and pIMDs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

8.3.5. Regulatory Reporting Requirements for SAEs, Pregnancies, and pIMDs

Once an investigator becomes aware that a study participant has experienced SAE, pIMD, or pregnancy during the study, they or designated study staff must report it to IQVIA within the timeframes provided in Table 16 via an electronic Expedited AE Report or Expedited Pregnancy Report. If the complications fulfill serious criteria, an SAE report should additionally be completed within 24 hours. This is essential for meeting legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/pIMDs, the investigator will always provide an assessment of causality at the time of the initial report.

Follow-up of relevant information on a pregnancy should be submitted the same way within 2 weeks once this information becomes available. Pregnancy outcome should be reported within 2 weeks.

Local regulatory requirements and GSK's policy for the preparation of an investigator safety report for Suspected Unexpected Serious Adverse Reactions must be followed. These reports will be forwarded to investigators as necessary.

GSK/IQVIA has a legal responsibility to notify local authorities and other regulatory agencies about the safety of a study intervention under clinical investigation. GSK/IQVIA will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Table 16 Expedited Reporting of SAEs, Pregnancies, and pIMDs

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAE	24 hours[1,2,3]	electronic Expedited AE Report	24 hours[1]	electronic Expedited AE Report
Pregnancy	2 weeks[1]	electronic Pregnancy Report	2 weeks	electronic Pregnancy Report
pIMD	24 hours[2,4]	electronic Expedited AE Report	24 hours[1]	electronic Expedited AE Report

AE = adverse event; pIMD = potentially immune-mediated disease; SAE = serious adverse event

[1] Timeframe allowed after receipt or awareness of the information by the investigator/study center staff.

[2] The investigator will confirm review of the SAE/pIMD causality by ticking the "reviewed" box in the electronic Expedited AE Report within 72 hours of submission of the SAE/pIMD.

[3] For coronavirus disease 2019 (COVID-19) related SAEs, reports should be submitted following routine procedures for SAEs.

[4] Timeframe allowed once the investigator determines that the event meets the protocol definition of an pIMD.

8.3.6. Treatment of Adverse Events

Any medication administered for the treatment of an AE should be recorded in the Expedited AE Report of the participant's eCRF.

8.3.7. Participant Card

The investigator or investigator's designee must provide the participant/participant's parent(s)/LAR(s) with a "participant card" containing information about the clinical study. The participant/participant's parent(s)/LAR(s) must be instructed to keep the participant card in her/their possession at all times throughout the study. In an emergency, this card serves to inform the responsible attending physician/LAR/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator or his/her back-up.

8.3.8. Medical Device Deficiencies

This clinical study will collect information of any device deficiencies associated with the study interventions that are combination products. Refer to Glossary of Terms for the definition of a combination product and a medical device deficiency.

8.3.8.1. Detection, Follow-up, and Reporting of Medical Device Deficiencies

The investigator is responsible for the detection, documentation and prompt reporting of any medical device deficiency occurring during the study to IQVIA. Device deficiencies should be reported within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency. New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and reported to IQVIA within 24 hours.

Refer to Appendix 4 for details on recording and reporting of medical device deficiencies.

The investigator will ensure to follow the participants with reported device deficiencies and perform any additional investigations to determine the nature and/or causality of the deficiency.

8.3.8.2. Regulatory Reporting of Medical Device Deficiency When Used as Combination Product

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for IQVIA to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. Refer to Appendix 4 for details of reporting.

The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.4. Study Procedures During Special Circumstances

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be followed. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Safety follow-up may be made by a phone call, other means of virtual contact, or home visit, if appropriate.
- If the eDiary device was provided to the participant/participant's parent(s)/LAR(s), it may be returned to the study center by conventional mail after the end of the relevant data collection period. If the application (app) was provided to the participants' parent(s)/LAR(s) for use on their personal device, the app can be disabled remotely.
- Biological samples may be collected at a different location* other than the study center or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.

*Note: It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH Good Clinical Practice (GCP) requirements, such as adequate facilities to perform study procedures, appropriate training of the staff, and documented delegation of responsibilities in this location. This alternate location may need to be covered by proper insurance for the conduct of study on participants by investigator and study center staff other than the designated study center.

Any impact of the above-mentioned measures on the study data analysis and results will be determined on a case-by-case basis and reported upon the study completion.

The impact on the Per Protocol Set (PPS) for immunogenicity will be determined on a case-by-case basis. Any impact of the above-mentioned measures on the study results will be described in the Clinical Study Report.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objective of the study will be evaluated descriptively.

In this study, exploratory immunologic non-inferiority analyses will be performed, to help in decision making of the formulation selection for phase 3.

9.2. Sample Size Determination

The target enrollment is 1080 participants (270 participants in each group).

The enrollment to the study will be performed in 2 steps. In Step 1, 48 participants (12 per group) will be enrolled and vaccinated. If no safety concern is identified, the remaining 1032 participants will be enrolled and vaccinated in Step 2 to reach 1080 participants.

9.2.1. Statistical Considerations on Safety Assessment

In Step 1, the sample size of 12 participants per group would provide a probability of at least 80% to observe at least 1 AE, if the true AE rate is equal to or greater than 12.6%.

The sample size of 270 participants per group would provide a probability of at least 93% to observe at least 1 Grade 3 AE, if the true Grade 3 AE rate is equal to or greater than 1.0%.

Table 17 provides the 2-sided 95% exact confidence interval (CI) for a range of AE rates (270 participants per group).

Table 17 2-sided 95% Exact Confidence Intervals for the True Adverse Event Rate for Various Observed Adverse Event Rates (270 Participants per Group)

Participants vaccinated	Observed number participants reporting the adverse events	Observed percentage of participants with the adverse events	2-sided 95% exact confidence interval	
			Lower limit	Upper limit
270	0	0.0	0.0%	1.4%
	1	0.4	0.0%	2.0%
	10	3.7	1.8%	6.7%
	27	10.0	6.7%	14.2%
	30	11.1	7.6%	15.5%
	50	18.5	14.1%	23.7%
	100	37.0	31.3%	43.1%
	150	55.6	49.4%	61.6%

If the true Grade 3 AE rate is 10%, with the sample size of 270 participants per group, the incidence of Grade 3 AEs above 14.2% with 97.5% confidence (14.2%=upper limit for 2-sided 95% CI) will be ruled out.

9.2.2. Statistical Considerations on Immunogenicity Assessment

All the immunogenicity objectives in the study will be evaluated descriptively.

Considering a 20% rate of non-evaluable participants, it is assumed that approximately 864 evaluable participants (216 participants in each group) will be available for the evaluation of the primary immunogenicity objective.

9.2.2.1. Exploratory Immunologic Non-Inferiority Analyses

Exploratory immunologic non-inferiority analyses will be performed in the study, to help in decision making of the formulation selection for phase 3 (Table 18).

The estimated sample size of 216 evaluable participants in each group provides at least 94% power to evaluate non-inferiority of a formulation in terms of antibody geometric mean concentrations (GMCs) measured by the electrochemiluminescence (ECL) assay.

In order to control the global type I error to below 7.5%, Bonferroni correction will be applied. The non-inferiority of each of the investigational formulations will be assessed at 2.5% type I error. That is, the non-inferiority in terms of antibody GMC for the investigational formulation will be reached, if the lower limit of the 2-sided 95% CI for the antibody GMC ratio (investigational group/*Gardasil 9* group) is not less than 0.5 for each of the 9 HPV types. To account for the multiplicity of comparison for 9 HPV types, the global type II errors are conservatively estimated as the sum of individual type II errors.

Table 18 Power to Show That the Lower Limit of the 2-sided 95% CI on Anti-HPV IgG Antibody GMC ratio (HPV-9 Vaccine Group Divided by *Gardasil 9* Group), 1 Month After Dose 3 is Not Less Than 0.5

Standard deviation (Log_{10} [concentration])	N evaluable (in each group)	Type II error for each HPV type	Overall Power
0.7	216	0.6%	94.6%

CI = confidence interval; GMC = geometric mean concentration; HPV = human papillomavirus virus; IgG = immunoglobulin G

Power was obtained using PASS 2019, non-inferiority test for 2 means, under the alternative of equal means and variances.

Since there are no immunogenicity data generated with the assay that will be used in this study, several studies with various multivalent HPV formulations in the age group 16-26 years were reviewed and a conservative standard deviation for log_{10} transformed antibody concentrations of 0.7 for each of the 9 HPV types is used for the computation of power.

If the standard deviation for log_{10} transformed antibody concentrations is ≤0.47, the sample size of 216 evaluable participants in each group provides at least 73% power to assess the non-inferiority of a formulation in terms of antibody GMCs with a non-inferiority margin of 0.67.

The study also evaluates the **immune responses using a neutralization assay** as a secondary endpoint. If the standard deviation for log_{10} transformed antibody titers is around 0.6 as observed in HPV-019 (109823) study assessing GSK's bivalent HPV-16/18 AS04-adjuvanted vaccine:

- the sample size of at least 150 participants to obtain 120 evaluable participants at Month 7 provides at least 74% power to assess the non-inferiority of a formulation to *Gardasil 9* in terms of neutralizing antibody geometric mean titers (GMTs) with a non-inferiority margin of 0.5.
- the sample size of at least 270 participants to obtain 216 evaluable participants provides at least 98% power to show the non-inferiority of a formulation to *Gardasil 9* in terms of neutralizing antibody GMTs with a non-inferiority margin of 0.5.

However, note that this does not take into account the multiplicity due to comparisons performed for antibody concentrations measured by ECL assay.

9.3. Populations for Analyses

Populations for analyses in this study are defined in Table 19.

Table 19 Study Analyses Sets

Analysis set	Description
Enrolled set	Participants who received a study vaccine or had a blood draw before study vaccine administration or were randomized. Note as per Good Clinical Practice (GCP) enrolled participants should have completed the informed consent process and participants should be eligible before initiating any study procedure.
Exposed set (ES)	All participants who received a study vaccine. Analysis per group is based on the study vaccine administered. A safety analysis based on the ES will include all vaccinated participants. An immunogenicity analysis based on ES will include all vaccinated participants for whom immunogenicity data are available.
Per Protocol set (PPS)	The per protocol set for analysis of immunogenicity will be defined by time point (to include all eligible participants' data up to the time of important protocol deviations). The PPS will include all evaluable participants in the ES: • Meeting all eligibility criteria. • For whom the administration route of the vaccine was as according to protocol. • For whom the study vaccine was administered as per protocol. • Who did not receive a concomitant medication/product leading to exclusion from a PP analysis, as described in the protocol. • Who did not present with a intercurrent medical condition leading to exclusion from a PP analysis, as described in the protocol.

Analysis set	Description
	• Who complied with the vaccination schedule, as specified in Table 1. • Who complied with the timings of the post-vaccination blood sampling for immune response evaluation, as specified in Table 1. • For whom post-vaccination immunogenicity results are available for at least one antigen at the corresponding time points.

For discontinuation of study intervention and participant discontinuation/withdrawal details, see Section 7.

9.4. Statistical Analyses

The statistical analysis plan will be prepared and will include a more technical and detailed description of the statistical analyses including the supportive analyses and demography summaries. This section is a summary of the planned statistical analyses of the most important endpoints i.e., the primary and secondary endpoints. The safety analysis for the iSRC will be described separately.

Unless otherwise mentioned, for all the planned analysis with CI, a 95% CI will be computed.

9.4.1. Primary Endpoints Analyses

9.4.1.1. Analysis Related to Safety and Reactogenicity

The safety analysis will be based on the Exposed Set (ES).

The percentage of participants reporting each solicited administration site event and systemic event assessed as Grade 3 in intensity during the solicited follow-up period (Day 1 – Day 7 after vaccine administration) will be tabulated, per dose and over the whole vaccination course, with exact 95% CI.

The percentage of participants with at least 1 report of unsolicited AE assessed as Grade 3 in intensity classified by the Medical Dictionary for Regulatory Activities (MedDRA) reported up to 28 days after vaccination will be tabulated with exact 95% CI.

The percentage of participants with at least 1 report of a SAEs classified by MedDRA from first vaccination up to Month 12, will be tabulated with exact 95% CI.

The percentage of participants in Step 1 outside the defined normal ranges for each biochemical and hematological parameter measured in the study at Day 7 post-dose 1 will be tabulated with exact 95% CI.

9.4.1.2. Immunogenicity Analyses

The immunogenicity analysis for primary endpoints will be based on PPS for analysis of immunogenicity.

9.4.1.2.1. Within Groups Assessment

For each group at Month 7 (1-month post-dose 3), antibody GMC with 95% CI and range of antibody concentrations will be tabulated for each antigen.

9.4.2. Secondary Endpoints Analyses

9.4.2.1. Analysis Related to Safety and Reactogenicity

The safety analysis will be based on the ES.

The percentage of participants reporting each solicited administration site event and systemic event during the solicited follow-up period (Day 1 – Day 7 after vaccine administration) will be tabulated, per dose and over the whole vaccination course, with exact 95% CI.

The percentage of participants with at least 1 report of unsolicited AEs classified by MedDRA reported up to 28 days after vaccination will be tabulated with exact 95% CI.

The percentage of participants with at least 1 report of a pIMD classified by MedDRA from first vaccination up to study end, will be tabulated with exact 95% CI.

The percentage of participants who experienced pregnancy during the entire study period will be reported. The percentage of pregnancies and their outcomes will be reported.

Pregnancies and their outcomes will be described in detail.

SAEs and pIMDs will be described in detail.

9.4.2.2. Immunogenicity Analyses

The immunogenicity analysis for secondary endpoints will be based on PPS for analysis of immunogenicity.

9.4.2.2.1. Within Groups Assessment

For each group at each time point for which a blood sample result is available, the following analyses will be conducted:

- Seroconversion and seropositivity rates for each antigen (with exact 95% CI) will be calculated.
    - Seroconversion is defined as the appearance of antibodies (i.e., concentrations/titer greater than or equal to the cut-off value) in the serum of participants seronegative before vaccination.
- Antibody GMCs/GMTs with 95% CI and range of antibody concentrations/titers will be tabulated for each antigen.

  - The antibody GMCs will be derived considering log-transformed concentrations are normally distributed with unknown variance. Concentration below the assay cut-off will be assigned half the cut-off for the purpose of antibody GMC computation.

- The distribution of antibody concentrations/titers for each antigen will be displayed using reverse cumulative curves for the sub-cohort of initially seronegative participants.
- Pearson coefficient of correlation between anti-HPV IgG antibody concentration and anti-HPV neutralizing antibody titers with associated P-value will be calculated for each investigational adjuvanted vaccines group and *Gardasil 9* group for each antigen for timepoint and overall. The Pearson correlation coefficient is computed by $\log_{10}$ transformation of specific antibody concentrations. Scatter plots will be generated.
- For each HPV type, the functional relationship between the pair of assay methods (pseudovirion-based neutralization assay [PBNA] versus ECL) will be estimated by timepoint using the Deming's regression model (Brown et al, 2014).

9.4.2.2.2. Exploratory Between Group Assessment

For each HPV antigen, antibody GMC ratios and the 2-sided 95% CIs of antibody GMC ratios will be computed using an analysis of variance model on the log10 transformation of the antibody concentration adjusted for country effect. This analysis will be performed at Month 3 (1-month post-dose 2) and at Month 7 (1-month post-dose 3) time points. The non-inferiority of different vaccine formulations to the control group will be assessed if the lower limit of the 2-sided 95% CI is not less than the defined non-inferiority limit.

Additional exploratory group comparisons may be performed to facilitate the formulation selection.

9.4.3. iSRC Analyses

The analysis will be based on the ES. The analyses will be further described in detail in the statistical analysis plan.

- Demographic characteristics, baseline general medical and vaccination history, withdrawals from the study.
- Study intervention exposure by group and by intervention.
- Summary tables containing information on any events considered in the holding rules and other events (SAE, any withdrawal due to intervention-related AE, any AEs causing withdrawal from the study).
- Incidence of solicited administration site AEs (pain, redness, swelling): any grade, Grade 3 (2-days or more after Dose 1, 7-day follow-up period after intervention), any solicited administration site AEs leading to hospitalization within 7 days (Day 1 – Day 7) after each vaccine dose.

- Incidence of solicited systemic AEs (fever, headache, fatigue, myalgia, and arthralgia): any grade, Grade 3, any related, Grade 3 related (2-days or more after Dose 1, 7-day follow-up period after each intervention), any solicited systemic AEs leading to hospitalization, fever >40°C (104°F), within 7 days (Day 1 – Day 7) after each vaccine dose).
- Incidence of unsolicited AEs: any, Grade 3, any related, Grade 3 related (7-day and 30-day follow-up period after each intervention).
- Any, Grade 3 or above abnormality in pre-specified hematology and biochemistry parameters with an event onset within 7 days (Day 1 – Day 7) after each vaccine dose.
- Incidence of SAEs: Any, any related, fatal, fatal related.
- Incidence of pIMDs: Any, any related.
- Any medically attended events.
- Any pregnancy and pregnancy outcomes, overall and pregnancy exposures (i.e., exposures during pregnancy).
- Summary tables containing information on concomitant medication/product during the 7-day follow-up period and during the 30-day follow-up period of each intervention.
- Safety narratives, patient profiles and laboratory reports, if required.
- Other information as deemed necessary by the iSRC.

9.5. Interim Analyses

9.5.1. Sequence of Analyses

The analyses will be performed stepwise:

- In preparation of the planned iSRC evaluations, analyses of all available safety data (as clean as possible) will be performed. The blinded and unblinded summaries will be generated. The unblinded analyses will be done by an Independent External Statistician to maintain the study blind and will be shared with iSRC members through a secured folder (refer to the iSRC charter). The outcome of the iSRC reviews will be communicated to the study team.
- A first analysis will be performed on all data available, for primary and secondary endpoints up to Month 3 (1-month post-dose 2). This includes all safety data up to 1-month post-dose 2 for all participants, anti-HPV IgG data up to 1-month post-dose 2 for all participants* and anti-HPV neutralizing titers data up to 1-month post-dose 2 with at least 150* participants/group for 1-month post-dose 2 timepoint. A clinical study report will be written. The investigators and the study team will not be provided with the individual data listings or with the randomization listings until the end-of-study analysis.
- A second analysis will be performed on all available data, for primary and secondary endpoints up to Month 7 (1-month post-dose 3). This includes all safety data up to 1-month post-dose 3 for all participants, anti-HPV IgG data up to 1-month post-dose 3 for all participants and anti-HPV neutralizing titers data up to 1-month post-dose 3 with at least 150* participants/group for 1-month post-dose 3 timepoint. Analysis will be documented in a statistical report. No clinical study report will be written. The investigators and the study

team will not be provided with the individual data listings or with the randomization listings until the end-of-study analysis.

- The final end-of-study-analysis will be performed when all data for primary and secondary endpoints up to study conclusion are available (Month 12). Individual listings will only be provided at this stage. CCI [redacted] An integrated clinical study report containing all available data will be written.

*In case of visit delay, analysis may be performed for as many participants as possible with data available at the time of the analysis. Analysis for remaining participants will be performed at the time of the next analysis.

9.5.2. Statistical Considerations for Interim Analyses

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.

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11. APPENDICES

APPENDIX 1 ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
AESI	Adverse event of special interest
app	Application
CFR	Code of Federal Regulations
CI	Confidence interval
CCI	[redacted]
COVID-19	Coronavirus disease 2019
eCRF	Electronic case report form
ECL	Electrochemiluminescence
EDC	Electronic Data Capture system
eDiary	Electronic diary
EoS	End of study
ES	Exposed set
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GSK	GlaxoSmithKline Biologicals SA
HPV	Human papillomavirus
HRT	Hormonal replacement therapy
IAF	Informed assent form
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Intracellular cytokine staining
ID number	Identification number
IEC	Independent Ethics Committee
igG	Immunoglobulin G
IM	Intramuscularly
IRB	Institutional Review Board
IRT	Interactive Response Tool
iSRC	Internal Safety Review Committee
IVRS	Interactive Voice Response System

IWRS	Interactive Web Response System
LAR	Legally acceptable representative
LPLV	Last participant last visit
MedDRA	Medical Dictionary for Regulatory Activities
PBNA	Pseudovirion-based neutralization assay
pIMD	Potential immune-mediated disease
PPS	Per protocol set
QTL	Quality tolerance limit
SADE	Serious adverse device effect
SAE	Serious adverse event
SoA	Schedule of activities
SRM	Study Reference Manual
SRT	Safety Review Team
USADE	Unanticipated serious adverse device effect
VLP	Virus-like particle
WHO	World Health Organisation

Glossary of Terms

Blinding	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In a double-blind trial, the participant, the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment. In an observer-blind study, the participant, the study center and sponsor or sponsor's designee's personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment.
Caregiver	In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol specified procedures.

Child in care	A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted.
Combination product	Combination product comprises any combination of • drug • device • biological product Each drug, device, and biological product included in a combination product is a constituent part.
Eligible (participant)	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled (participant)	"Enrolled" means a participant's/participant's parent(s)'/LAR(s)' agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are evaluated for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Evaluable (participant)	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
Immunological correlate of protection	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intercurrent medical Conditions	A condition that has the capability of altering a participant's immune response including an immunodeficiency condition diagnosed during the study.
Intervention	Term used throughout the clinical study to denote a set of investigational product or marketed product or placebo intended to be administered to a participant.

Invasive medical device	A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.
Investigational vaccine/product	A pharmaceutical form of an active ingredient being tested in a clinical study, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Investigator	A person responsible for the conduct of the clinical study at a study center. If a study is conducted by a team of individuals at a study center, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study center to qualified individual or party to perform those study-related duties and functions.
Interactive voice/web response system	The software that enables the randomizing of participants into clinical trials and allocation of the study product to them in a blinded fashion. This technology allows study centers to interact with a database by following voice/web prompts in order to enter the information.
Legally acceptable representative	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical study. The terms legal representative, legally authorized representative are used in some settings.
Medically attended AEs	Symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider.
Medical device deficiency	A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer.

Medical Monitor	IQVIA's delegate providing significant scientific contribution to the conduct of the study.
Study/Site Monitor	An individual assigned by the sponsor or sponsor's designee and responsible for assuring proper conduct of clinical studies at 1 or more study centers. The terms Clinical Research Monitor and Clinical Research Associate are used in some settings.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or participates in the clinical study, either as a recipient of the vaccine(s)/product or as a control. Synonym: subject
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Solicited event	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified post-vaccination follow-up period.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies). A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Source documents	Original legible documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries, memory aids, or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept

	at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).
Treatment number	A number identifying intervention given to a participant, according to intervention allocation.
Unsolicited adverse event	Any AE reported in addition to those solicited during the clinical study. Also, any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited AE.

APPENDIX 2 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisation of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF and IAF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- IQVIA will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of Code of Federal Regulations (CFR) Title 21, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- After reading the protocol, each investigator will sign the protocol signature page (Appendix 7) and send a copy of the signed page to IQVIA. The study will not start at any study center at which the investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-investigators will provide IQVIA with sufficient, accurate financial information as requested to allow GSK or IQVIA to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing financial interest information prior to initiation of the study center.

Investigators are responsible for providing the financial information update if their financial interests change at any point during their participation in a study and for 1 year after completion of the study.

Insurance

GSK will provide insurance in accordance with local guidelines and requirements as a minimum for the participants in this study. The terms of the insurance will be kept in the study files.

Informed Consent and Assent Process

- The investigator or his/her representative must fully explain the nature of the study to the participant/participant's parent(s)/LAR(s) and answer all questions regarding the study.
- Participant/participant's parent(s)/LAR(s) must be informed that their participation is voluntary.
- Freely given and written/witnessed/thumb printed informed consent must be obtained from each participant/participant's parent(s)/LAR(s)/witness and participant informed assent as appropriate, prior to participation in the study.
- The content of the ICF must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that informed consent and assent (if applicable) was obtained before the participant was enrolled in the study and the date the written consent and assent (if applicable) was obtained. The authorized person obtaining the informed consent and assent (if applicable) must also sign the ICF (and IAF if applicable).
- Participants must be re-consented to the most current version of the ICF(s) (and IAFs if applicable) during their participation in the study.
- Re-consent must be obtained in accordance with local laws and regulations for participants who become legally emancipated during the study, i.e., reach the legal age of consent. The participant can provide consent by signing/witnessing/thumb printing an ICF (and IAF if applicable), similar to that provided to the parent(s)/LAR(s) at study start, which summarizes the study and includes a consent statement and documents that the participant agrees to continue participating in the study.
- A copy of the ICF(s) (and IAF[s]if applicable) must be provided to the participant/participants' parent(s)/LAR(s).
- The study investigator is encouraged to obtain IAF from the minor in addition to the ICF provided by the parent(s)/LAR(s) when a minor can assent to decisions about her participation in the study. The investigator is also accountable for determining a minor's capacity to assent to participation in a research study according to the local laws and regulations.

Data Protection

Participants will be assigned a unique identifier. Any participant records or datasets transferred to IQVIA/GSK will contain only the identifier. Name and any other information which would identify the participant will not be transferred.

The participants/participants' parent(s)/LAR(s) must be informed that:

- The participant's study-related data will be used by IQVIA/GSK in accordance with local data protection law.
- The participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by GSK/IQVIA, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- IQVIA/GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study, in accordance with the Data Privacy Notice that will be sent to the site staff.
- The participants/participants' parent(s)/LAR(s) must be notified about their rights regarding the use of their personal data in accordance with the data privacy section of the ICF (and IAF if applicable).

Administrative Structure

Table 20 Study Administrative Structure

Function	Responsible Organization
Study Operations Management, Medical Monitoring, Study Master File	IQVIA
Randomization, Blinding, Unblinding	Cenduit
Clinical Supply Management, Quality Assurance Auditing	GSK
Biostatistics, Medical Writing	IQVIA
Laboratory Assessments	GSK
Internal Safety Review Committee and Safety Review Team	GSK

Medical Monitor

Refer to the SRM.

Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study register in compliance with the applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.

- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report, and provided reasonable access to statistical tables, figures, and relevant reports. IQVIA will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants and/or participant's parent(s)/LAR(s), as appropriate.
- IQVIA will provide the investigator with the randomization codes for their study center only after completion of the full statistical analysis.
- GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

Data Quality Assurance

- The investigator should maintain a record of the location(s) of their respective essential documents including source documents (see Glossary of Terms for definitions of essential documents and source documents). The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.
- Essential study documents may be added or removed where justified (in advance of study initiation) based on their importance and relevance to the study. When a copy is used to replace an original document (e.g., source documents, eCRF), the copy should fulfill the requirements for certified copies.
- All participant data relating to the study will be recorded on eCRF (or printed Case Report Form in case of an EDC failure) unless transmitted to GSK or IQVIA electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's participants that supports information entered in the eCRF.
- The completion of the eDiary will be checked by the investigator/designee at the study visits and these checks will be documented as applicable. The instructions on the review of the eDiary will be provided to the site separately (e.g., eDiary manual or SRM).
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies for such review and inspection.
- IQVIA is responsible for the data management of this study including quality checking of the source data.

- Study/Site Monitors (see the definition in Glossary of Terms) will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be fully explained if necessary (e.g., via an audit trail). The safety and rights of participants must be protected and study be conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Quality Tolerance Limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or the reliability of study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarized in the Clinical Study Report.
- Study records and source documents, including signed ICF and IAF (as applicable), pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval from GSK. No records may be transferred to another location or party without written notification to GSK/IQVIA.

Source Documents

- Source documents provide evidence to establish the existence of the participant and substantiate the integrity of the data collected. Investigator should maintain a record of the location(s) of their source documents.
- Data transcribed into the eCRF from source documents must be consistent with those source documents; any discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and source documents is provided in Glossary of Terms.

Study and Study Center Closure

GSK/IQVIA reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of GSK, provided there is sufficient notice given to account for participant's safe exit from study participation. Study center regular closure will occur upon study completion. A study center is considered closed when all required data/documents and study supplies have been collected and a study center closure visit has been performed.

The investigator may initiate study center 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 center by IQVIA/GSK or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, GSK/IQVIA's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, IQVIA shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, for the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

Publication Policy

GSK aims to submit for publication the results of the study in searchable, peer reviewed scientific literature within 18 months from LPLV for interventional studies and follows authorship and other guidance from the International Committee of Medical Journal Editors.

APPENDIX 3 CLINICAL LABORATORY TESTS

For assessment of immune response, blood sample will be drawn at Day 1, Month 2, Month 3, Month 6, Month 7 and Month 12 in all participants. IgG antibody determination by ECL multiplex methodology will be performed for all timepoints in all participants. Pseudovirion-Based Neutralization Assays (PBNA) will be performed on the following subsets: Day 1 (all participants), Month 2 (in a subset of 384 participants from Step 2 [96 participants in each group]), Month 3 (all participants) and Month 7 (at least 150 participants in each group from Step 2). CCI [redacted] For these participants collection of an additional blood sample is foreseen at Day 1 and one month after the third dose (Month 7).

Humoral Immunity

Humoral Immunity: HPV IgG concentration by multiplex immunoassay (ECL)

The anti-HPV-6/11/16/18/31/33/45/52/58 IgG response will be measured using the ECL multiplex technology from CCI [redacted]

The HPV9-AS04 ECL assay will be qualified prior the clinical testing of this study, meaning that the assay performance characteristics will be assessed, including limit of detection, precision, linearity, accuracy, specificity, robustness and stability.

The assay qualification report and assay Standard Operation Procedure will be submitted to the Investigational New Drug application when available.

The assay will be performed at GSK, Clinical Laboratory Sciences (Rixensart/Wavre, Belgium).

Humoral Immunity: HPV neutralizing assay (PBNA)

The neutralizing antibodies will be determined by the PBNA for HPV-6/11/16/18/31/33/45/52/58 performed at the CCI [redacted] with some adaptations (secondary endpoint). CCI [redacted]

The PBNAs for the 9 HPV types will be qualified at CCI [redacted] prior the clinical testing of the phase 1/2 study, meaning that assay performance characteristics including limit of detection, precision, linearity, specificity, robustness and stability will be assessed.

The assay qualification report and assay Standard Operation Procedure will be submitted to the IND when available.

The assay will be performed by CCI [redacted], Germany.

CCI [redacted]

CCI [redacted]

APPENDIX 4 ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of an AE

An AE is any untoward medical occurrence (an unfavorable/unintended sign - including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a clinical study participant that is temporally associated with the study intervention. The AE may or may not be considered related to the study intervention.

Events Meeting the AE Definition
• Significant or unexpected worsening or exacerbation of the condition/indication under study. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study vaccine(s)/product administration even though they may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccine(s)/product or a concurrent medication (overdose per se should not be reported as an AE/SAE). • Signs or symptoms temporally associated with study vaccine(s)/product administration. • Signs, symptoms that require medical attention (e.g., hospital stays, physician visits and emergency room visits). • Significant failure of an expected pharmacologic or biological action. • Pre- or post-intervention events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen). • Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. • AEs to be recorded as solicited AEs are described in the Table 11. All other AEs will be recorded as UNSOLICITED AEs. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, admission for routine examination). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Pre-existing conditions or signs and/or symptoms present in a participant prior to the first study vaccination. These events will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

Definition of an SAE

An SAE is any untoward medical occurrence that:

a) Results in death

b) Is life-threatening

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

Note: In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an outpatient setting. Complications that occur during hospitalization are also considered as AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event will also be considered serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

d) Results in disability/incapacity

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect in the offspring of a study participant

f) Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).

g) Other situations

Medical or scientific judgment should be exercised in deciding whether reporting is 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 medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

Solicited Events

Solicited events (systemic and administration site events) will include the events listed in Table 11.

Unsolicited AEs

An unsolicited AE is an AE that was not included in the list of solicited using an eDiary and that was spontaneously communicated by a participant/participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participants/participants' parents/LARs will be instructed to contact the study center as soon as possible to report medically attended events, as well as any events that, though not medically attended, are of participant/parental/LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified study center personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by participant/participant's parent(s)/LAR(s) will be collected during an interview with the participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit.

Adverse Events of Special Interest

Adverse events of special interest (AESIs) are pre-defined (serious or non-serious) AEs of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate, because such an event might warrant further investigation in order to characterize and understand it.

Potential Immune-Mediated Diseases

pIMDs are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 21.

The investigator must exercise their medical and scientific judgment to determine whether other diseases have an autoimmune origin (i.e., pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of MedDRA preferred term codes corresponding to the above diagnoses will be available to investigators at study start.

When there is enough evidence to make any of the pIMD diagnoses, the AE must be reported as pIMD. Symptoms, signs, or conditions which might (or might not) lead to one of these diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been made, and alternative diagnoses eliminated or shown to be less likely.

Table 21 List of Potential Immune-Mediated Diseases

Medical Concept	Additional Notes
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	
Evans syndrome	
Pernicious anemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/Pericarditis	• Autoimmune / Immune-mediated myocarditis • Autoimmune / Immune-mediated pericarditis • Giant cell myocarditis
Idiopathic pulmonary fibrosis	Including but not limited to: • Idiopathic interstitial pneumonia (frequently used related terms include “Interstitial lung disease”, “Pulmonary fibrosis”, “Immune-mediated pneumonitis”)
Pulmonary alveolar proteinosis (PAP)	
Pleuroparenchymal fibroelastosis (PPFE)	
Endocrine disorders	
Addison’s disease	
Autoimmune / Immune-mediated thyroiditis	Including but not limited to:

Medical Concept	Additional Notes
	• Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) • Atrophic thyroiditis • Silent thyroiditis • Thyrotoxicosis
Autoimmune diseases of the testis and ovary	
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow's disease	• Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis • Vogt-Koyanagi-Harada disease
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	Including but not limited to:

Medical Concept	Additional Notes
	• Crohn's disease • Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis • Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease

Medical Concept	Additional Notes
	• Felty's syndrome
Sjögren's syndrome	
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blennorrhagica • Psoriatic spondylitis • Reactive Arthritis (Reiter's Syndrome) • Undifferentiated spondyloarthritis
Systemic Lupus Erythematosus	• Includes lupus associated conditions (e.g., cutaneous lupus erythematosus, lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)
Systemic Scleroderma (Systemic Sclerosis)	• Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants	Includes the following: • Acute necrotizing myelitis • Bickerstaff's brainstem encephalitis • Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) • Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis
Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	Including but not limited to: • Cranial nerve neuritis (e.g., optic neuritis)

Medical Concept	Additional Notes
	• Idiopathic nerve palsies/paresis (e.g., Bell's palsy) • Melkersson-Rosenthal syndrome • Multiple cranial nerve palsies/paresis
Multiple Sclerosis (MS)	Includes the following: • Clinically isolated syndrome (CIS) • Malignant MS (the Marburg type of MS) • Primary-progressive MS (PPMS) • Radiologically isolated syndrome (RIS) • Relapsing-remitting MS (RRMS) • Secondary-progressive MS (SPMS) • Uhthoff's phenomenon
Myasthenia gravis	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy
Peripheral inflammatory-demyelinating neuropathies and plexopathies	Including but not limited to: • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) • Antibody-mediated demyelinating neuropathy • Chronic idiopathic axonal polyneuropathy (CIAP) • Chronic Inflammatory-Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g., multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) • Multifocal motor neuropathy (MMN)
Transverse myelitis (TM)	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy

Medical Concept	Additional Notes
	• Fibrillary glomerulonephritis • Anti-glomerular basement membrane disease • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	
Erythema nodosum	
Interstitial granulomatous dermatitis	
Lichen planus	• Includes lichen planopilaris
Localized Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Palisaded neutrophilic granulomatous dermatitis	
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	Including but not limited to:

Medical Concept	Additional Notes
	• Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Takayasu's arteritis
Medium sized and/or small vessels vasculitis	Including but not limited to: • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Behcet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis) • Erythema induratum (also known as nodular vasculitis) • Henoch-Schönlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis • Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Wegener's granulomatosis
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	
Goodpasture syndrome	

Medical Concept	Additional Notes
Immune-mediated enhancement of disease	• Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include “vaccine-mediated enhanced disease (VMED)”, “enhanced respiratory disease (ERD)”, “vaccine-induced enhancement of infection”, “disease enhancement”, “immune enhancement”, and “antibody-dependent enhancement (ADE)”
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	Including but not limited to: • Kawasaki’s disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Pulmonary renal syndrome	
Raynaud’s phenomenon	
Sarcoidosis	• Includes Loefgren syndrome
Susac's syndrome	

Clinical Laboratory Parameters and Other Abnormal Assessments Qualifying as AEs/SAEs

In the absence of a diagnosis, abnormal laboratory findings, assessments, or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE. The investigator must exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

COVID-19 Cases

Diagnosis of COVID-19 should be made in accordance with the World Health Organization case definition. Cases should be categorized as AEs or SAEs, and routine procedures for recording, evaluation, follow-up, and reporting of AEs, and SAEs should be followed in accordance with the time period set out in the protocol.

Events or Outcomes Not Qualifying as AEs/SAEs: Pregnancy

Female participants who become pregnant after the first study intervention dose must not receive subsequent doses of the study intervention but may continue other study procedures at the discretion of the investigator.

Assessment of Causality

All solicited administration site and systemic events will be considered causally related to administration of the study interventions. The complete list of these events is provided in Table 11.

The investigator must assess the relationship between study vaccines interventions and the occurrence of each unsolicited AE/SAE using clinical judgment.

Alternative plausible possible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccines interventions will be considered and investigated. The investigator will also consult the IB and/or the Summary of Product Characteristics and/or Prescribing Information for marketed products to assist in making his/her assessment.

Causality should be assessed by the investigator using the following question:

Is there a reasonable possibility that the unsolicited AE may have been caused by the study intervention?

- YES: There is a reasonable possibility that the study intervention contributed to the AE.
- NO: There is no reasonable possibility that the AE is causally related to the administration of the study intervention. There are other, more likely causes and administration of the study intervention is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as "serious", additional examinations/tests will be performed by the investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the study interventions, if applicable.
- An error in study intervention administration.
- Other cause (specify).

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to IQVIA. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to IQVIA. Missing causality assessment by default to be considered as possibly related to the study intervention.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may change their opinion of causality after receiving additional information and update the SAE information accordingly.

Medically Attended Visits

For each solicited and unsolicited **AE** the participant experiences, the participant/participant's parent(s)/LAR(s) will be asked if the participant received medical attention defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF/eDiary.

Assessment of Intensity

Maximum Intensity of Solicited Events

The intensity of solicited AEs will be assessed as described in Table 12.

Maximum Intensity of Unsolicited AEs and SAEs

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgment.

The intensity should be assigned to 1 of the following categories:

- 1 (mild): An AE which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- 2 (moderate): An AE which is sufficiently discomforting to interfere with normal everyday activities.
- 3 (severe): An AE which prevents normal, everyday activities (in adults/adolescents, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy).

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as "serious" when it meets 1 of the outcomes that define an SAE (see Definition of an SAE).

Assessment of Outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only)

Recording, Follow-up, and Assessment of AEs, SAEs, pIMDs, and Pregnancies

Recording AEs and SAEs

All AEs and SAEs should be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered intervention-related.

The participant/participants' parent(s)/LAR(s) will be instructed to contact the investigator immediately should the participants manifest any signs or symptoms they perceive as serious.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the participant's medical records to either GSK or IQVIA instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK or IQVIA. In this instance, all participant identifiers will be blinded on the copies of the medical records prior to submission to GSK or IQVIA.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

Use of eDiary/app

An eDiary/smartphone app will be used in this study to capture solicited administration site or systemic events. At the next visit after the end of reporting period, the investigator should check with the participant the solicited AEs entered by the participant and, if error, to correct them. The participants'/participants' parent(s)/LAR(s) should be trained on how and when to complete the eDiary/enter information into the app.

The eDiary/app may be completed in by a minor participant under the supervision of the participant's parent(s)/LAR(s) provided the minor is capable of assessing and reporting the information to be recorded on eDiary. The ultimate accountability for completion of the eDiary remains with the participant's parent(s)/LAR(s). The investigator should discuss this accountability with the participant's parent(s)/LAR(s). If the eDiary has been completed in by a minor participant, the investigator or designee should verify the reported information during a discussion with the minor participant preferably in the presence of her parent(s)/LAR(s).

Anyone who will evaluate administration site or systemic events and record the event in the eDiary/app should be trained on using the eDiary/app. This training must be documented in the participant's source documents. If any individual other than the participants/participant's parent(s)/LAR(s) is making entries in the eDiary/app, their identity must be documented in the eDiary/app/participant's source documents.

See Table 15 for the time period and frequency on collecting AEs/SAEs, pIMDs and pregnancies.

Follow-up of AEs, SAEs, and pIMDs, and Pregnancies

After the initial AE/SAE/pIMD/pregnancy or any other event of interest for the study, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs/pIMDs will be followed until the event is resolved, stabilized, or otherwise explained or the participant is lost to follow-up.

Other non-serious AEs must be followed until the last contact or until the participant is lost to follow-up.

Follow-up During the Study

AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last visit/contact of the participant.

If the participant dies during participation in the study or during a recognized follow-up period, IQVIA will be provided with any available post-mortem findings, including histopathology.

Follow-up After the Participant is Discharged from the Study

The investigator will provide any new or updated relevant information on previously reported SAE to IQVIA using electronic Expedited AE Report as applicable. The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the AE or SAE as fully as possible.

Updating of SAE, pIMD, Pregnancy Information After Removal of Write Access to the Participant's eCRF

When additional SAE, pIMD, and pregnancy information is received after removal of write access to the participant's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to IQVIA within the timeframe specified in Table 16.

Follow-up of Pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to IQVIA using the pregnancy follow-up report and the Expedited AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, if the investigator becomes aware of any SAE occurring as a result of a post-study pregnancy AND it is considered by the investigator to be reasonably related to the study intervention, they must report this information to IQVIA.

Events Requiring Expedited Reporting to IQVIA

Once an investigator becomes aware that an SAE has occurred in a study participant, the investigator or investigator's designee must complete information in the electronic Expedited AE Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. The report allows to specify that the event is serious or non-serious.

Even if the investigator does not have all information regarding an SAE, the report should still be completed WITHIN 24 HOURS. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS. The investigator will always provide an assessment of causality at the time of the initial report.

The investigator will be required to confirm the review of the SAE causality by ticking the "reviewed" box in the electronic Expedited AE Report within 72 hours of submission of the SAE.

Refer to Table 15 for the details on timeframes for reporting of SAEs.

SAE Reporting to IQVIA via EDC

- The primary mechanism/tool for reporting an SAE to IQVIA will be the EDC.
- If the EDC is unavailable for more than 24 hours, then the study center will use the paper Expedited AE Report.
- The study center staff will enter the SAE data into the EDC as soon as it become available.
- After the study is completed at a given site, the EDC will be taken offline to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE, pIMD, pregnancy from a participant or receives updated data on a previously reported SAE after the EDC has been taken offline, then the study center can report this information on a paper Expedited AE Report (see the next section) or to the Medical Monitor by phone.

Contacts of the Medical Monitor for SAE reporting can be found in the SRM.

Back-up SAE Reporting to IQVIA via Paper (in Case of EDC Failure)

- Fax transmission of the SAE paper Expedited AE Report is the preferred method to transmit this information to the Medical Monitor.
- In rare circumstances and in the absence of fax equipment, notification by phone is acceptable with a copy of the Expedited AE Report sent by overnight mail or courier service.
- Initial notification via phone does not replace the need for the investigator to complete and sign the Expedited AE Report within the designated reporting timeframes.

Contacts of the Medical Monitor for SAE reporting can be found in the SRM.

Adverse Events Related to the Use of Medical Devices

Definitions of a Medical Device AE and Adverse Device Effect

- A medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to a medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved.
- An adverse device effect (ADE) is an AE related to the use of a medical device. This definition includes any AE resulting from:

- insufficient or inadequate instructions for use (i.e., user error), or
- any malfunction of a medical device, or
- intentional misuse of the medical device.

Definition of a Medical Device SAE, Serious Adverse Device Effect, and Unanticipated Serious Adverse Device Effect

A Medical Device SAE is Any SAE That:
a. Led to death b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. c. Led to fetal distress, fetal death or a congenital abnormality or birth defect d. Is a suspected transmission of any infectious agent via a medicinal product
Serious Adverse Device Effect (SADE) Definition:
A SADE is defined as an ADE that has resulted in any of the consequences characteristic of a serious adverse event. Any device deficiency that might have led to an SAE if appropriate action had not been taken or circumstances had been less fortunate.
Unanticipated SADE (USADE) Definition
An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a SADE that by its nature, incidence, severity or outcome has not been identified in the current version of the IB.

Assessment of Severity of a Medical Device AE

Severity of medical device AE will be assessed as:

- Mild: Minor discomfort noticed but does not interfere with normal daily activity.
- Moderate: Discomfort reducing or affecting normal daily activity.
- Severe: Incapacitating with inability to work or perform normal daily activity.

Recording and Reporting of Medical Device AE, ADE, SADE, and USADE

Device deficiencies must be reported to IQVIA within 24 hours after the investigator determines that the event meets the definition of a device deficiency.

Fax transmission of the paper device deficiency/incident report form is the preferred method to transmit this information to IQVIA.

In rare circumstances and in the absence of fax equipment, notification by phone is acceptable with a copy of the device deficiency/incident report form sent by overnight mail or courier service.

Details of this process will be provided to the study centers separately (e.g., in the SRM).

IQVIA will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

APPENDIX 5 CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Definitions

Woman of Childbearing Potential

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

Women of Non-Childbearing Potential

- Premenarchal

  Menarche is the first onset of menses in a young woman. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

  Additional evaluation should be considered if a participant's fertility status is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention.

- Premenopausal woman with ONE of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

- Postmenopausal woman

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Women on HRT and whose menopausal status is in doubt will be required to use a non-hormonal, highly effective contraception method if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 22).

Table 22 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent* Failure rate of <1% per year when used consistently and correctly
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Injectable • Oral
Highly Effective Methods That Are User-Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the female participant of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Male partner sterilization prior to the female participant's entry into the study, and this male is the sole partner for that participant, The information on the male sterility can come from the site personnel's review of the participant's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. 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.

*Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Female Participants who Become Pregnant

Refer to Section 8.3 and Appendix 4 for the information on detection, recording, reporting and follow-up of pregnancies.

Any female participant who becomes pregnant during the study will need to discontinue further vaccination but may continue other study procedures at the discretion of the investigator.

APPENDIX 6 PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents.

Protocol Amendment 2: 23 September 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for Amendment

The purpose of the Protocol Amendment 2 is to allow for additional iSRC review(s) in case of enrollment delay to mitigate the risk that the iSRC for all 48 Step 1 participants may occur after the allowed interval range for their second vaccination dose. Additionally, the country-specific amendment for Germany (Protocol Amendment 1/DEU-1) to clarify that only adults between and including 18 to 26 years of age will be included in the study in Germany was incorporated. Further updates (as summarized below) were made to clarify the study procedures.

Added text is ***bold italic*** and deleted text is ~~strikethrough~~.

Section and Name	Description of Change	Brief Rationale
1.1. Synopsis 4.1 Overall Design 8.2.3.3 iSRC Evaluation	Added note: ****In case not all 48 of the Step 1 participants are enrolled and vaccinated with a first dose of study vaccine by 30 September 2022, the iSRC will review the accumulated safety data up to 7 days post-dose 1 of all participants available by that date. If no safety signal is identified, these participants will be vaccinated with a second dose. To avoid any additional participants running out of the allowed interval range for their second vaccine dose, additional iSRC review(s) may need to be planned to review the safety data up to 7 days post-dose 1 of these participants, but only when all 48 Step 1 participants have been enrolled and their data have been reviewed by the iSRC, the iSRC will decide on the initiation of the vaccination of Step 2 participants***.	To allow for additional iSRC review(s) in case of enrollment delay to mitigate the risk that the iSRC for all 48 Step 1 participants may occur after the allowed interval range for their second vaccination dose.
1.1. Synopsis	In Overall Design, the note was added: ***Vaccination of Step 2 participants with a second dose will not be***	Clarification to the study protocol

Section and Name	Description of Change	Brief Rationale
	initiated before all Step 1 participants have received their second vaccination dose.	
8.2.3.3 iSRC Evaluation	Edited text: Following this ~~first~~ ***initial*** review(s), the iSRC will review all available safety data on a regular basis (monthly) until data from 1-month post-dose 2 for all participants and data from 1-month post-dose 3 for Step 1 participants are reviewed.	Clarification to the procedures associated with iSRC review
1.3 Schedule of Activities	Added footnote: ***[2]Blood samples should be collected prior to vaccine administration.*** The footnotes were renumerated accordingly along with the associated bookmarks.	Clarification of study procedures order
4.1 Overall Design	Figure 1: Updated Solicited events (7 days) and Unsolicited events (28 days) by moving from Visit 6 to Visit 5.	Correction to align with study procedures
6.1 Study Interventions Administered	Footnote added to Table 6: ****The nondominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the nondominant arm, an injection in the dominant arm may be performed.***	Clarification to allow for flexibility in the laterality of study vaccines administration
8.2.1.3 Physical Examination/Vital Signs	~~On Day 1, a history directed physical examination will be performed for each participant.~~ ***On Day 1, a history directed physical examination (including the injection site examination) will be performed for each participant as per the standard of care.***	Clarification of study procedure.
Summary of Changes	Summary of Changes table was added to document the most recent updates made to the protocol.	Version control
Appendix 6	Appendix 6 was added to include the previous history of changes to the protocol. The Signature of Investigator was moved to Appendix 7.	Version control
Global document updates	Minor clarifications, grammar corrections, version updates have been made.	Minor edits are not summarized.
1.1 Synopsis	The note added:	

Section and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities 4.1. Overall Design 5.1. Inclusion Criteria	***In Germany, only adult participants between and including 18 years to 26 years of age are to be included in this clinical study.***	Revision to address the request of health authority of Germany
2.2. Study Rationale 4.2.2. Selection of Study Population	The note added: ***(18-26 years of age in Germany)***	

Protocol Amendment 1/DEU-1: 23 June 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

This amendment applies only to Germany.

Overall Rationale for the Amendment:

This is a country-specific amendment for Germany to clarify that only adults between and including 18 to 26 years of age will be included in the study in this country.

Added text is ***bold italic***

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3. Schedule of Activities 4.1. Overall Design 5.1. Inclusion Criteria	The note added: ***In Germany, only adult participants between and including 18 years to 26 years of age are to be included in this clinical study.***	Revision to address the request of health authority
2.2. Study Rationale 4.2.2. Selection of Study Population	The note added: ***(18-26 years of age in Germany)***	

Protocol Version 2.0: 02 March 2022

Overall Rationale for the Protocol Version 2.0

The purpose of the Protocol Version 2.0 is to increase the volume of blood sample collected for antibody determination to enable the development and quantification of laboratory assays. Further, several clarifications of the study procedures as summarized below are included.

Added text is ***bold italic*** and deleted text is ~~strikethrough~~.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Added activity to Visits 1, 3, and 5: ***Distribute and instruct participants/participant's parent(s)/LAR(s) on the use of Memory Aid for unsolicited AEs and concomitant medication/vaccination***	Clarification of study procedures
	Added activity to Visits 3, 4, and 6: ***Return of Memory Aids***	Clarification of study procedures
1.3 Schedule of Activities (Table 1) 8.1.1 Biological Samples Table 7	Blood sampling for antibody determination (~~20~~ ***50*** mL)	Higher volume of blood sample is needed for laboratory assays development and qualification
1.3 Schedule of Activities (Table 1 and Table 2) 8.1.1 Biological Samples (Table 7)	Footnote added for Visit 2**: ***** Visit 2 is for Step 1 participants only***	Clarification of study procedures
4.1 Overall Design	Edited Figure 1 Footnote: [&]iSRC reviews Sentinel participants post-dose 1 safety data, then iSRC reviews the data on monthly basis until safety data from ~~one~~***1***-month post-dose 2 for all ***participants and data from 1-month post-dose 3 for Step 1***	Clarification of data reviewed by the iSRC
	CCI [redacted]	
6.3.2 Randomization to Study Intervention	The study ***and the*** center will be used as a minimization factor for randomization ***in Step 1 and the study, the center and*** CCI [redacted] ***will be used as a minimization factor for randomization in Step 2.***	Clarification of minimization factors for randomization

6.8 Concomitant Medications/Products and Concomitant Vaccinations	***Memory aids used by participant/participant's parent(s)/LAR(s) will be reviewed for any additional medication(s) and vaccination(s), which will be transcribed in eCRFs.***	Clarification of study procedures
8.2.2.3 iSRC Evaluation	Following this first review, the iSRC will review all available safety data on a regular basis (monthly) until data from 1-month post-dose 2 for all participants ***and data from 1-month post-dose 3 for Step 1 participants*** are reviewed.	Clarification of data reviewed by the iSRC
8.3.2 Method of Detecting AEs and SAEs, Pregnancies, and pIMDs	***Memory aids used by participant/participant's parent(s)/LAR(s), will be reviewed for health-related issues of participants and for potential AEs, which will be transcribed in eCRFs.***	Clarification of study procedures
9.4.3 iSRC Analyses	The analysis will be based on the ES. ***The analyses will be further described in detail in the statistical analysis plan.*** Demographic characteristics, baseline general medical ***and vaccination*** history, ***withdrawals from the study***. […] Summary tables containing information on any events considered in the holding rules and other events (SAE, any withdrawal due to intervention-related AE, any AEs causing ~~study~~ withdrawal ***from the study***). Incidence of solicited ~~local~~ ***administration site*** AEs (pain, redness, swelling): any grade, Grade 3 (2 ~~-day period~~ ***days or more*** after Dose 1, 7-day follow-up period after intervention), ***any solicited administration site AEs leading to hospitalization within 7 days (Day 1 – Day 7) after each vaccine dose.*** Incidence of solicited ~~general AE~~***systemic AEs*** (fever, headache, fatigue, myalgia, and arthralgia): any grade, Grade 3, any related, Grade 3 related (2 ***days or more*** after Dose 1, 7-day follow-up period after ***each*** intervention), ***any solicited systemic AEs leading to hospitalization, fever >40°C (104°F), within 7 days (Day 1 – Day 7) after each vaccine dose)***. […]	Clarification of the analyses performed for the iSRC to align with the iSRC charter

	Any, ***Grade 3 or above*** abnormality in ***pre-specified*** hematology and biochemistry ***parameters with an event onset within 7 days (Day 1 – Day 7) after each vaccine dose.*** ***Incidence of SAEs: Any, any related, fatal, fatal related.*** ***Incidence of pIMDs: Any, any related.*** […] Any pregnancy and pregnancy outcomes, ***overall and pregnancy exposures (i.e., exposures during pregnancy).*** […] ***Safety narratives, patient profiles and laboratory reports, if required.*** ***Other information as deemed necessary by the iSRC.***	
Global document updates	Minor clarifications, grammar corrections, version updates have been made to this document.	Minor edits are not summarized.

APPENDIX 7 SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Phase 1/2 randomized, observer-blinded, multi-country study to evaluate safety and immunogenicity of investigational adjuvanted human papillomavirus vaccine in females (16 to 26 years of age)

PROTOCOL NO: 213749 (HPV9-AS04-001)

VERSION: Amendment 3

This protocol is a confidential communication of GSK. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from GSK.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to IQVIA.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Investigator Name: _____

Investigator Title: _____

Name/Address of Center: _____

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