TITLE PAGE

Protocol Title: A Phase II, single-blind, randomized, controlled study to evaluate the immunogenicity and safety of a measles, mumps, rubella, varicella vaccine compared with *ProQuad,* administered in healthy children 4 to 6 years of age

Protocol Number: 217715 (MMRVNS 20-001)

Product: Investigational measles, mumps, rubella, varicella vaccine (MMRVNS)

Short Title: A study on the immune response and safety of a combined measles, mumps, rubella, chickenpox vaccine compared to a marketed combined vaccine, given to healthy children 4 to 6 years of age

Study Phase: II

Sponsor Name: GlaxoSmithKline Biologicals SA

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

IND Number: 28684

EU CT Number: 2022-501564-18-00

Original Protocol Date: 01 September 2022

Amendment 1.0 Date: 15 March 2023

Approval Date: 15 March 2023

Sponsor Signatory

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

PPD

Md Ahsan Habib, MBBS, MIPH
Clinical Project Lead
GlaxoSmithKline Biologicals SA

Date

Refer to the Study Reference Manual for Medical Monitor's name and contact information.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Table 1 Document History

DOCUMENT HISTORY			
Document	**Date**	**Substantial**	**Region**
Amendment 1.0	15-March-2023	No	Global
Original Protocol	01-September-2022	-	-

Amendment 1.0 (15-March-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 the Amendment:

This protocol amendment was written to clarify the unblinding process in response to Request for Information from the European Medicines Agency.

Table 2 Description of the Most Important Changes in Amendment 1.0

(additional text in ***bold italic;*** deletions in ~~strikethrough~~)

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Edited text: A male or female between, and including, 4 years and 6 years of age (i.e., from 4-year birthday until the day before the 7-year birthday) at the time of study intervention administration***, and in accordance with local regulations***.	To ensure that within the protocol-specified age range, local regulations regarding age of vaccination are also followed.
6.3.4 Blinding and Unblinding	Added text: ***In addition, safety evaluation by IQVIA/GSK will be conducted in a blinded manner.***	Clarifying that the safety evaluation will be performed in a blinded manner.
6.3.4.1 Emergency Unblinding	Edited text: In case of emergency, the investigator ***and site staff*** will have ~~unrestricted,~~ immediate, and direct access to the participant's individual study intervention through IVRS/IWRS.	Investigator and site staff are not restricted to treatment and in order to unblind participant/caregiver investigator must use IVRS/IWRS.

Section # and Name	Description of Change	Brief Rationale
6.3.4.2 Unblinding Procedures for Safety Reporting	Edited text: In case of unblinding, blind should be maintained for ~~persons responsible for the ongoing conduct of the clinical study such as the management, monitors, investigators, and those persons responsible for data analysis and interpretation of results at the conclusion of the clinical trial, such as biometrics personnel.~~***GSK's Safety Review Team (SRT) performing blinded safety data review.***	Persons responsible for ongoing conduct of the study are not blinded for this study. Clarification is added to keep the SRT blinded during safety data review.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase II, single-blind, randomized, controlled study to evaluate the immunogenicity and safety of a measles, mumps, rubella, varicella vaccine compared with *ProQuad,* administered in healthy children 4 to 6 years of age.

Rationale:

This study is designed to evaluate the immunogenicity and safety of GlaxoSmithKline Biologicals SA (GSK)'s investigational measles, mumps, rubella, varicella vaccine (hereafter referred to MMRVNS vaccine) compared with Merck's measles, mumps, rubella, varicella vaccine, *ProQuad* (hereafter referred to as MMRV vaccine), when given as a second dose to children 4 to 6 years of age who were previously primed with a first dose of any combination of measles, mumps, rubella, and varicella-containing vaccine(s).

This study will evaluate immunogenicity and safety using 3 MMRVNS formulations which vary for some or all of the individual virus potencies. The 3 MMRVNS formulations will be compared with the MMRV vaccine. In order to ensure representative data on the comparator, participants enrolled in the MMRV group will be randomized to 2 different lots.

Concomitant administration of age-specific routine childhood diphtheria-tetanus-acellular pertussis-containing vaccines will be allowed according to the local immunization practices of the participating country.

Objectives and Endpoints:

Objectives	Endpoints
Primary (Descriptive)	
To evaluate the immune response to the MMRVNS vaccines (formulated with different potencies) and the MMRV vaccine (pooled group) in terms of GMCs for antibodies to measles, mumps, rubella, and varicella viruses.	• Anti-measles antibody GMCs at Day 43. • Anti-mumps antibody GMCs at Day 43. • Anti-rubella antibody GMCs at Day 43. • Anti-gE antibody GMCs at Day 43.
Secondary (Descriptive)	
To evaluate the immune response to the MMRVNS vaccines (formulated with different potencies) and the MMRV vaccine (pooled group) in terms of seroresponse rates for antibodies to measles, mumps, rubella, and varicella viruses.	• Anti-measles antibody seroresponse rate at Day 43. • Anti-mumps antibody seroresponse rate at Day 43. • Anti-rubella antibody seroresponse rate at Day 43. • Anti-gE antibody seroresponse rate at Day 43.
To evaluate safety and reactogenicity following administration of the MMRVNS vaccines and the MMRV vaccine (pooled group).	• Percentage of participants reporting each solicited administration site event during the 4-day period (day of administration and 3 following days) after the dose of study interventions*. • Percentage of participants reporting each solicited systemic event in terms of drowsiness and loss of appetite during the 4-day period (day of administration and 3 following days) after the dose of study interventions*. • Percentage of participants reporting each solicited systemic event in terms of fever, measles/rubella-like rash, varicella-like rash and other rash (not measles/rubella-like rash or varicella-like rash) during the 43-day period (day of administration and 42 following days) after the dose of study interventions*. • Percentage of participants reporting unsolicited AEs during the 43-day period (day of administration and 42 following days) after the dose of study interventions*. • Percentage of participants reporting SAEs after the dose of study interventions* up to study end.

Abbreviations: AE = adverse event; gE = glycoprotein E; GMC = geometric mean concentration; MMRV = comparator measles, mumps, rubella vaccine; MMRVNS = investigational measles, mumps, rubella, varicella vaccine; SAE = serious adverse event
*Study interventions: MMRV(H)NS vaccine, MM(H)RVNS vaccine, and M(L)M(L)R(L)V(L)NS (investigational vaccines) or MMRV vaccine Lot 1 and MMRV vaccine Lot 2 (comparator vaccine).

Overall Design:

This is a phase II, single-blind, randomized, controlled, multi-country study in healthy children of 4 to 6 years of age. Participants will be randomized to a single dose of MMRVNS vaccine (3 groups of participants each receiving one of the 3 different vaccine formulations [designated as MMRV(H)NS vaccine, MM(H)RVNS vaccine, and M(L)M(L)R(L)V(L)NS vaccine, respectively]) or a single dose of a comparator licensed MMRV vaccine (2 groups of

participants each receiving one of the 2 different lots of the MMRV vaccine [designated as MMRV_Lot 1 and MMRV_Lot 2], which will be pooled for the analyses). All participants will be required to have been previously primed with a first dose of any combination of measles, mumps, rubella, and varicella-containing vaccine(s). Randomization to one of the 5 intervention groups will be performed in a 2:2:2:1:1 ratio prior to intervention. There will be 3 study visits, at Day 1 (study intervention and blood sampling at Visit 1), Day 15 (virtual or in-person safety check at Visit 2), and Day 43 (blood sampling at Visit 3), as well as 1 safety call and 1 safety follow-up contact, at Day 2-3 and Day 181, respectively.

Safety monitoring will be performed by an Independent Data Monitoring Committee composed of clinical experts, independent of the study and external to GSK and GSK's designee, and an independent statistician.

Number of Participants: Approximately 800 participants will be randomly assigned to one of the 5 intervention groups to provide approximately 200 participants per each MMRVNS group and 100 participants per each MMRV group to obtain at least 640 evaluable participants (160 in each MMRVNS vaccine group and 80 in each MMRV vaccine group).

Intervention Groups and Duration:

The intervention groups will be as follows:

- MMRV(H)NS vaccine: measles, mumps, and rubella at release potency and VNS at high (H) potency
- MM(H)RVNS vaccine: measles, rubella, and varicella at release potency and mumps at high (H) potency
- M(L)M(L)R(L)V(L)NS vaccine: measles, mumps, rubella, and varicella, all at low (L) potency
- MMRV_Lot 1 vaccine: measles, mumps, rubella, and varicella Lot 1
- MMRV_Lot 2 vaccine: measles, mumps, rubella, and varicella Lot 2

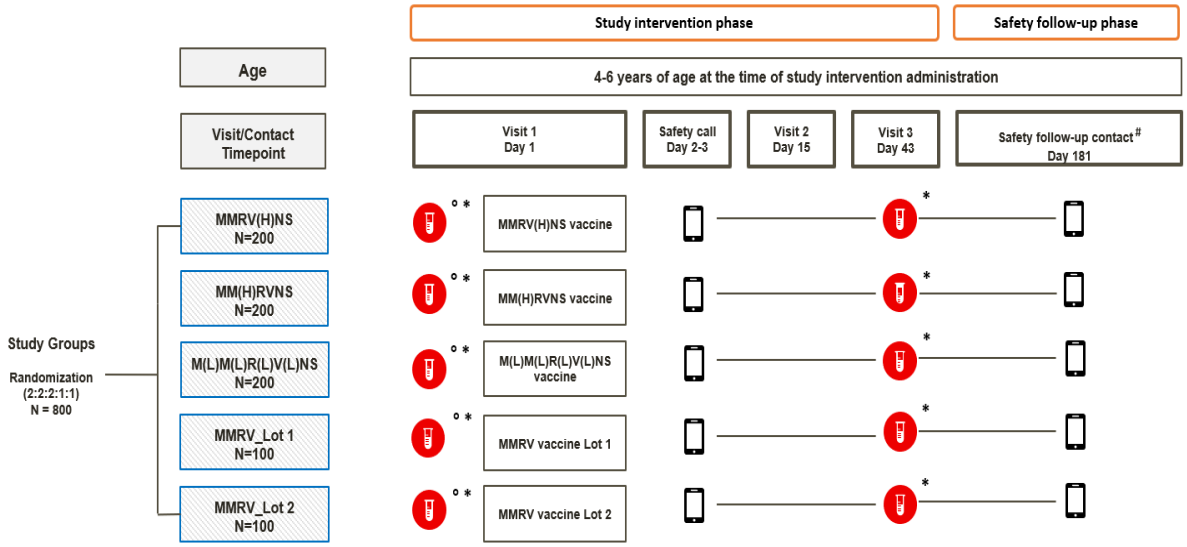
The total duration of study participation for an individual participant will be 181 days.

Data Monitoring/Other Committee: Yes

1.2 Schema

See Figure 1.

Figure 1 Study Schema



Study interventions: MMRV(H)NS, MM(H)RVNS, and M(L)M(L)R(L)V(L)NS = investigational vaccine in 3 different formulations; MMRV_Lot 1 and MMRV_Lot 2 = comparator vaccine MMRV Lot 1 and Lot 2.
Abbreviations: N = number of participants
°Before study intervention administration.
*Blood sample for anti-measles, anti-mumps, anti-rubella virus and anti-gE antibody measurements.
Contact (by telephone call or any other convenient procedure) for the safety follow-up will take place 6 months postdose of study interventions.
Note: Visit 2 (Day 15) for review of post-vaccination safety data may be a virtual visit

Healthy children aged 4 to 6 years will be enrolled in this study according to the inclusion and exclusion criteria (see Section 5.0). The participants will be randomized in a 2:2:2:1:1 ratio to one of the 5 intervention groups.

1.3 Schedule of Activities

Table 3 Schedule of Activities

Age	4 to 6 years of age at the time of study intervention administration					Notes
Type of contact	**Visit 1**	**Safety call**	**Visit 2†**	**Visit 3**	**EoS** **Safety follow-up contact**	
Timepoints	**Day 1**	**Day 2-3**	**Day 15**	**Day 43**	**Day 181**	
Informed consent/assent as appropriate	●					See Appendix 1 for details
Check inclusion/exclusion criteria	●					See Section 5.1 and Section 5.2 for details
Collect demographic data	●					See Section 8.2.1 for details
Medical history	●					See Section 8.2.1 for details
Vaccination history (protocol-specific vaccines including varicella-containing vaccine and measles-, mumps-, rubella-containing vaccine)	●					See Section 8.2.1 for details
Physical examination	●					See Section 8.2.2 for details
Randomization	○					Country and center will be used as minimization factors. See Section 6.3.2 for details
Study interventions						See Appendix 4 for the definition
Check contraindications, warnings, and precautions to study intervention administration	○					See Section 8.2.1 for details
Check criteria for temporary delay for enrollment and study intervention administration	●					See Section 5.5 for details
Study group and intervention number allocation	○					See Section 6.3.3 for details
Body temperature before study intervention administration	●					The preferred location for measuring temperature will be the axilla. Fever is defined as body temperature ≥38.0°C (100.4°F)
Study intervention (MMRVNS/MMRV vaccine) administration	●					

Age	4 to 6 years of age at the time of study intervention administration					Notes
Type of contact	**Visit 1**	**Safety call**	**Visit 2†**	**Visit 3**	**EoS** **Safety follow-up contact**	
Timepoints	**Day 1**	**Day 2-3**	**Day 15**	**Day 43**	**Day 181**	
Recording of administered study intervention number	●					
Distribute eDiaries/download the app	○					An eDiary/personal electronic device app will be used to capture solicited administration site or systemic events. The participant's parent(s)/LAR(s) should be trained on the use of the eDiary/app
Laboratory Assessment						
Blood sampling for antibody determination (~5 mL)	●*			●		See Section 8.1.1 for details
Safety assessments						
Record any concomitant medications/vaccinations	●	●	●	●		See Section 6.8 for details
Record any intercurrent medical conditions				●		See Section 9.2 for details
Phone contact for safety follow-up		●			●	Or any other convenient procedure
Recording of solicited administration site events (Days 1–4 post dosing)	○	○				Only events at the MMRVNS vaccine or MMRV vaccine administration site will be solicited
Recording of solicited systemic events (drowsiness and loss of appetite) (Days 1-4 post dosing)	○	○				See Section 8.3 for details and Appendix 3 for definitions
Safety follow-up with clinical staff to review post-vaccination safety data			●			
Recording of solicited systemic events (fever, measles/rubella-like rash, varicella-like rash and other rash [not measles/rubella-like rash or varicella-like rash]) (Days 1–43 post dosing)	○	○	○	○		See Section 8.3 for details and Appendix 3 for definitions
Recording of nonserious AEs (Days 1–43 post dosing)	●	●	●	●		See Section 8.3 for details and Appendix 3 for definitions
eDiary/app completion reminder		●				

Age	4 to 6 years of age at the time of study intervention administration					Notes
Type of contact	**Visit 1**	**Safety call**	**Visit 2†**	**Visit 3**	**EoS** **Safety follow-up contact**	
Timepoints	**Day 1**	**Day 2-3**	**Day 15**	**Day 43**	**Day 181**	
Review of eDiaries/app data		○	●	●		The study center staff should review that parent/LAR captured the info in the eDiaries/app before the eDiaries are returned or app uninstalled
Return of eDiaries/uninstall or disable the app				○		
Recording of SAEs	●	●	●	●	●	See Section 8.3 for details and Appendix 3 for definitions
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	●	The collection and reporting periods start once the participants' parent(s)/LAR(s) informed consent is obtained
Study conclusion					●	See Section 4.5 for the definition of the end of study

Abbreviations: AE = adverse event; App = application; eDiary = electronic diary; EoS = end of study; LAR = legally acceptable representative; MMRVNS = investigational measles, mumps, rubella, and varicella vaccine; MMRV = comparator measles, mumps, rubella, and varicella vaccine; SAE = serious adverse event

Notes:

The double-line border following Visit 3 (Day 43) indicates the analyses which will be performed on all data obtained up to Visit 3 (Day 43).

● 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.

† Visit 2 (Day 15) may be conducted in-person or virtually.

*Blood sampling before the study interventions.

Note: If a participant is not able to visit the study center for any reason (including coronavirus disease 2019) they should contact the study center by telephone. Adverse event and concomitant medication details may be collected during a telephone call. It may not be possible to collect all clinical laboratory samples or conduct clinical assessments during this time, but any details should be recorded in the eCRF. If alternative arrangements can be agreed for the sample collection or clinical assessments, the details should be documented in the eCRF.

Table 4 Intervals Between Study Visits

Interval	Planned visit interval*	Allowed interval range
Visit 1→Safety call	1 to 2 days	1-3 days
Visit 1→Visit 2	14 days	14-19 days
Visit 1→Visit 3	42 days	35-56 days
Visit 1→Safety follow-up contact	180 days	180-201 days

*The interval is the difference between the visit dates.

Note: Whenever possible the investigator should arrange study visits following the planned visit interval. Deviation from allowed interval between Visit 1 and Visit 3 will lead to elimination from the Per Protocol Set.

2.0 INTRODUCTION

2.1 Study Rationale

This study is designed to evaluate the immunogenicity and safety of GlaxoSmithKline Biologicals SA (GSK)'s investigational measles, mumps, rubella, varicella vaccine (MMRVNS vaccine) compared with Merck's measles, mumps, rubella, varicella vaccine, *ProQuad* (hereafter referred to as MMRV vaccine), when given as a second dose to children 4 to 6 years of age who were previously primed (previously administered) with a first dose of any combination of measles-, mumps-, rubella-, and varicella-containing vaccine(s).

This study will evaluate immunogenicity and safety using 3 MMRVNS formulations which vary for some or all of the individual virus potencies. The 3 MMRVNS formulations will be compared with the MMRV vaccine. In order to ensure representative data on the comparator, participants enrolled in the MMRV group will be randomized to 2 different lots. Throughout the study, the 2 lots will be analyzed as a pooled group.

The safety monitoring will be performed by an Independent Data Monitoring Committee composed of clinical experts, independent of the study and external to GSK and GSK's designee, and an independent statistician.

Concomitant administration of age-specific routine childhood diphtheria-, tetanus-, acellular pertussis (DTPa)-containing vaccines will be allowed according to the local immunization practices of the participating country.

2.2 Background

Measles, mumps, rubella, and varicella are viral infections which can lead to serious complications, disability, and death of infected individuals or even in unborn children.

To prevent measles, mumps, rubella, and varicella, the Advisory Committee on Immunization Practices (ACIP) in the United States (US) recommends a 2-dose measles, mumps, rubella, and varicella vaccine schedule in childhood. In the US, measles, mumps, rubella, and varicella vaccine can be administered from 12 months of age, with the routinely recommended age for the second dose at age 4 to 6 years. However, the second dose may be administered before the age of 4 years, provided that at least 3 months have elapsed since the first dose. In the US, MMRV vaccine is licensed for use among children from 12 months of age through 12 years of age [CDC, 2010].

In the European Union (EU), vaccination with 2 doses of measles, mumps, rubella, and varicella vaccine is recommended in different countries according to local and regional public health guidelines. MMRV vaccine is indicated for active immunization for the prevention of measles, mumps, rubella, and varicella in individuals over 12 months of

age. Applicable official recommendations may vary for countries regarding the interval between doses and the need for one dose or 2 doses of measles-, mumps-, and rubella- and of varicella-containing vaccines.

Refer to the current Investigator's Brochure (IB) for information regarding the MMRVNS vaccine, and to the current Prescribing Information/Package Insert/Summary of Product Characteristics for information regarding the comparator measles, mumps, rubella, and varicella vaccine, *ProQuad*.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

The investigational MMRVNS vaccine is expected to have a benefit/risk profile similar to Merck's *ProQuad* and GSK's *Priorix-Tetra* vaccines. Detailed information about the expected risks and reasonably expected adverse events (AEs) of these 2 licensed measles, mumps, rubella, and varicella vaccines are summarized in the current IB. No new significant safety concerns have been identified in clinical trials and during post-marketing use of these vaccines, at the time of finalizing this study protocol.

All study activities at the study center will be performed by trained clinical staff authorized by the study investigator. For the safety of the participants, the protocol has incorporated appropriate inclusion and exclusion criteria (see Section 5.1 and Section 5.2), checking contraindications to vaccinations (see Section 8.2.1.2) and close monitoring of participants after vaccinations.

The blinded monitoring of study data will be performed by GSK's designee/Contract Research Organization (IQVIA) (see study administrative structure in Appendix 1). Additional unblinded safety monitoring will be performed by an IDMC composed of clinical experts, independent of the study and external to GSK and IQVIA, and an independent biostatistician. Monthly Safety Review Team (SRT) review by GSK will occur up to the completion of enrollment and vaccination of the first 200 participants, to monitor cumulative, blinded safety data (including serious and nonserious AEs) (see Section 8.2.4).

IQVIA will immediately notify the investigators if any additional safety information becomes available during the study. This study will be performed in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), EU CTR, and applicable regulatory requirements.

The risk assessment and mitigation strategy for this study are outlined in Table 5.

Table 5 Risk Assessment and Risk Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Interventions – all study vaccines		
Local inflammatory reactions due to injection (i.e., pain, redness, swelling at the injection site, etc.)	Subcutaneous vaccination commonly precipitates transient and self-limiting local inflammatory reactions (see the Investigator's Brochure [IB] for details).	Solicited local adverse events will be collected from each participant.
Systemic reactions (i.e., fever, drowsiness, loss of appetite)	Systemic adverse reactions to vaccination are common but generally mild to moderate in severity.	Solicited systemic events will be collected for each participant. Medical advice as per the standard of care will be available.
Systemic reactions such as measles/rubella-like rash, varicella-like rash	Mild disease-like rashes may occur after administration of the study vaccine (see the IB for details).	Measles/rubella-like rash, varicella-like rash and other rash will be collected as solicited systemic events.
Hypersensitivity reactions (including anaphylaxis)	Acute allergic reactions such as an anaphylactic event may occur with any vaccine administration shortly after the intervention. These are serious, but rare occurrences.	Participants with known hypersensitivity to any component of the vaccines will be excluded from enrollment. All participants will remain under observation for at least 30 minutes after vaccination.
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 taken.
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 30 minutes after vaccination.

2.3.2 Benefit Assessment

By receiving the MMRVNS vaccine or *ProQuad* the participants may potentially be protected against measles, mumps, rubella, and varicella disease.

In addition, the participants will undergo a physical examination at the first study visit. In case the investigator discovers any medical condition, the participant will be referred to the local healthcare system.

2.3.3 Overall Benefit/Risk Conclusion

The apparent risks associated with the study interventions are justified by the anticipated benefits that may be afforded to participants receiving the study interventions for the prevention of the above-mentioned diseases.

3.0 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 6 Objectives and Endpoints

Objectives	Endpoints
Primary (Descriptive)	
To evaluate the immune response to the MMRVNS vaccines (formulated with different potencies) and the MMRV vaccine (pooled group) in terms of GMCs for antibodies to measles, mumps, rubella, and varicella viruses.	• Anti-measles antibody GMCs at Day 43. • Anti-mumps antibody GMCs at Day 43. • Anti-rubella antibody GMCs at Day 43. • Anti-gE antibody GMCs at Day 43.
Secondary (Descriptive)	
To evaluate the immune response to the MMRVNS vaccines (formulated with different potencies) and the MMRV vaccine (pooled group) in terms of seroresponse rates for antibodies to measles, mumps, rubella, and varicella viruses.	• Anti-measles antibody seroresponse rate at Day 43. • Anti-mumps antibody seroresponse rate at Day 43. • Anti-rubella antibody seroresponse rate at Day 43. • Anti-gE antibody seroresponse rate at Day 43.
To evaluate safety and reactogenicity following administration of the MMRVNS vaccines and the MMRV vaccine (pooled group).	• Percentage of participants reporting each solicited administration site event during the 4-day period (day of administration and 3 following days) after the dose of study interventions*. • Percentage of participants reporting each solicited systemic event in terms of drowsiness and loss of appetite during the 4-day period (day of administration and 3 following days) after the dose of study interventions*. • Percentage of participants reporting each solicited systemic event in terms of fever, measles/rubella-like rash, varicella-like rash and other rash (not measles/rubella-like rash or varicella-like rash) during the 43-day period (day of administration and 42 following days) after the dose of study interventions*. • Percentage of participants reporting unsolicited AEs during the 43-day period (day of administration and 42 following days) after the dose of study interventions*. • Percentage of participants reporting SAEs after the dose of study interventions* up to study end.

Abbreviations: AE = adverse event; gE = glycoprotein E; GMC = geometric mean concentration; MMRV = comparator measles, mumps, rubella vaccine; MMRVNS = investigational measles, mumps, rubella, varicella vaccine; SAE = serious adverse event

*Study interventions: MMRV(H)NS vaccine, MM(H)RVNS vaccine and M(L)M(L)R(L)V(L)NS (investigational vaccines) or MMRV vaccine Lot 1 and MMRV vaccine Lot 2 (comparator vaccine).

Estimands

Estimands will be defined in the statistical analysis plan (SAP).

4.0 STUDY DESIGN

4.1 Overall Design

This is a phase II, single-blind, randomized, controlled, multi-country study in healthy children of 4 to 6 years of age. Participants will be randomized to a single dose of MMRVNS vaccine (3 groups of 200 participants each receiving one of the 3 different vaccine formulations [designated as MMRV(H)NS vaccine, MM(H)RVNS vaccine, and M(L)M(L)R(L)V(L)NS vaccine, respectively]) or a single dose of a comparator licensed MMRV vaccine (2 groups of 100 participants each receiving one of the 2 different lots of the MMRV vaccine [designated as MMRV_Lot 1 and MMRV_Lot 2], which will be pooled for all analyses). All participants will be required to have been previously primed with a first dose of any combination of measles-, mumps-, rubella-, and varicella-containing vaccine(s).

The study design diagram is provided in Figure 1.

The study groups are shown in Table 7.

Table 7 Study Groups, Interventions, and Blinding

Study groups	Number of participants	Age (Min-Max)	Study interventions	Blinding
MMRV(H)NS	200	4 to 6 years	MMRV(H)NS vaccine	Single-blind
MM(H)RVNS	200	4 to 6 years	MM(H)RVNS vaccine	
M(L)M(L)R(L)V(L)NS	200	4 to 6 years	M(L)M(L)R(L)V(L)NS vaccine	
MMRV_Lot 1	100	4 to 6 years	MMRV vaccine Lot 1	
MMRV_Lot 2	100	4 to 6 years	MMRV vaccine Lot 2	

The total duration of study participation for an individual participant will be 181 days. There will be 3 study visits: Visit 1 on Day 1, when the participants receive study intervention, Visit 2 on Day 15 (either in-person or virtually, for review of post-vaccination safety data), and Visit 3 on Day 43, when blood sampling for vaccine antibody testing will be performed. A safety call will be made on Day 2 or Day 3, and a safety follow-up contact will be made to the participant on Day 181 via telephone or by any other convenient means of communication. Refer to the Study Reference Manual (SRM) which will contain a guide telephone script to be used for the Day 2-3 safety call and for the Day 181 safety follow-up call.

The visits/contacts should occur within a predefined visit window (see Table 4).

The study will be performed in a single-blind manner (see Section 6.3.4 for details). Furthermore, an IDMC comprising of clinical experts and a biostatistician will provide safety oversight during the active vaccination period, through unblinded review of the cumulative safety data. In addition, monthly SRT review by GSK will occur up to the completion of enrollment and vaccination of the first 200 participants, to monitor cumulative, blinded safety data (including serious and nonserious AEs) (see Section 8.2.4).

4.2 Scientific Rationale for Study Design

Refer to Section 2.1 for rationale and Section 2.2 for background of the study.

This is an active-controlled multi-country study. Concomitant administration of age-specific routine childhood DTPa-containing vaccines will be allowed according to the local immunization practices of the participating country to maintain the standard of care.

To prevent measles, mumps, rubella, and varicella, the ACIP recommends a 2-dose measles, mumps, rubella, and varicella (MMRV) vaccine schedule in childhood. MMRV vaccine can be administered from 12 months of age, with the routinely recommended age for the second dose at age 4 to 6 years. Participating non-US countries will be those with vaccine schedule for the second dose aligned to that of the US. Also, the participants should have received their first MMRV vaccines during their second year of life.

Because of the difference in the presentation of the investigational MMRVNS vaccine and the commercial MMRV vaccine, i.e., the difference in the labeling and presentation of the vaccine vials and diluent devices, the study will be conducted in a single-blind manner. See the definitions of single-blind in Appendix 4 and refer to Section 6.3 for details.

4.3 Participant Input into Design

Not applicable.

4.4 Justification for Dose

This study is intended to support licensure of GSK's combined measles, mumps, rubella, and varicella vaccine (MMRVNS) in the US by generating immunogenicity and safety data in children 4 to 6 years of age. Only countries with measles, mumps, rubella, and varicella vaccine schedule aligned with ACIP recommendation in the US will be selected.

The current recommendation by ACIP states that the first dose of MMRV vaccine be administered at the age of 12 to 15 months and the second dose is to be administered at the age of 4 to 6 years. Children who have not been vaccinated per the routine schedule

may be administered with the first dose of MMRV vaccine up to the age of 12 years in the US, but there is no upper age limit in the EU. Although the routinely recommended age for the second dose of MMRV vaccines is 4 to 6 years, the second dose may be administered before age 4 years, if ≥3 months have elapsed since the first dose, or up to the age of 12 years in the US.

In line with the ACIP recommendation [ACIP, 2007], participants of age 4 to 6 years who have been previously primed with a first dose of any combination of measles-, mumps-, rubella-, and varicella-containing vaccine(s), will receive a single dose of the MMRVNS vaccine or the comparator MMRV vaccine in the current study. Refer to Section 6.1 for additional details.

4.5 End of Study Definition

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

The end of the 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.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

- Healthy participants as established by medical history and clinical examination before entering into the study.
- A male or female between, and including, 4 years and 6 years of age (i.e., from 4-year birthday until the day before the 7-year birthday) at the time of study intervention administration, and in accordance with local regulations.
- Participant who previously received a first dose of varicella-containing vaccine in the second year of life.
- Participant who previously received a single dose of measles-, mumps-, rubella-containing vaccine in the second year of life.
- Written informed consent obtained from the participants' parent(s)/legally acceptable representative(s) (LAR[s]) prior to performance of any study-specific procedure (participant informed assent will be obtained from participants in line with local rules and regulations).
- 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 electronic diaries [eDiaries], return for follow-up visits).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

5.2.1 Medical Conditions

- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study interventions including hypersensitivity to neomycin or gelatin.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Hypersensitivity to latex.
- Major congenital defects, as assessed by the investigator.
- History of measles, mumps, rubella, or varicella disease.

- Recurrent history of or uncontrolled neurological disorders or seizures.
- Acute disease at the time of enrollment. Acute disease is defined as the presence of a moderate or severe illness with or without fever. Fever is defined as body temperature ≥38.0°C (100.4°F) by any age-appropriate route. All study interventions can be administered to participants with a minor illness such as diarrhea, mild upper respiratory infection without fever.
- Participant with history of coronavirus disease 2019 (COVID-19) who is still symptomatic.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study.

5.2.2 Prior/Concomitant Therapy

- Use of any investigational or non-registered product (drug, vaccine, or medical device) other than the study interventions during the period beginning 30 days before the dose of study interventions (Day -29 to Day 1), or their planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 90 days prior to the study intervention administration. For corticosteroids, this will mean prednisone equivalent ≥0.5 mg/kg/day or 20 mg/day whichever is the maximum dose for pediatric participants. Inhaled and topical steroids are allowed.
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 180 days before the dose of study interventions or planned administration during the study period.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g., infliximab).
- Previous vaccination with a second dose of varicella-containing vaccine or measles-, mumps-, rubella-containing vaccine.
- Administration or planned administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the dose and ending at 43 days after the dose of study interventions administration* (Visit 3), with the exception of:

– inactivated influenza (flu) vaccine which may be given at any time during the study and administered at a different location than the study interventions and,

– routinely recommended licensed childhood DTPa-containing vaccines which can preferably be co-administered according to the local immunization practices of the participating country.

Any other age-appropriate vaccine may be given starting at Visit 3 and anytime thereafter.

*In case an emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or 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 used according to the local government recommendations and that GSK/IQVIA is notified accordingly.

5.2.3 Prior/Concurrent Clinical Study Experience

- 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 Appendix 4]).

5.2.4 Other Exclusions

- Child in care (see the definition in Appendix 4).
- Any study personnel's immediate dependents, family, or household members.
- Participants with the following high-risk individuals in their household:
  - Immunocompromised individuals (as defined in Section 5.2.1).
  - Pregnant women without documented history of varicella.
  - Newborn infants of mothers without documented history of varicella.
  - Newborn infants born <28 weeks of gestation.

5.3 Lifestyle Considerations

No restrictions for this study.

5.4 Screen Failures

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

5.5 Criteria for Temporarily Delaying 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 ≥38.0°C (100.4°F) by any route. 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.

6.0 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

For the definition of study intervention, refer to Appendix 4.

6.1 Study Intervention(s) Administered

The study interventions that will be administered in the study are provided in Table 8.

Table 8 Study Interventions Administered

	Study intervention 1		**Study intervention 2**		**Study intervention 3**		**Study intervention 4**	
Study intervention name	MMRV(H)NS vaccine		MM(H)RVNS vaccine		M(L)M(L)R(L)V(L)NS vaccine		*ProQuad*	
Study intervention formulation (per dose)	Live attenuated measles virus (Schwarz strain) ($\geq1\times10^{3.0}$ $CCID_{50}$); Live attenuated mumps virus (RIT4385 strain) ($\geq1\times10^{4.2}$ $CCID_{50}$); Live attenuated rubella virus (Wistar RA 27/3 strain) ($\geq1\times10^{3.2}$ $CCID_{50}$); Live attenuated varicella virus (Oka strain) ($\geq1\times10^{2.9}$ pfu)	Water for injections	Live attenuated measles virus (Schwarz strain) ($\geq1\times10^{3.0}$ $CCID_{50}$); Live attenuated mumps virus (RIT4385 strain) ($\geq1\times10^{4.2}$ $CCID_{50}$); Live attenuated rubella virus (Wistar RA 27/3 strain) ($\geq1\times10^{3.2}$ $CCID_{50}$); Live attenuated varicella virus (Oka strain) ($\geq1\times10^{2.9}$ pfu)	Water for injections	Live attenuated measles virus (Schwarz strain) ($\geq1\times10^{3.0}$ $CCID_{50}$); Live attenuated mumps virus (RIT4385 strain) ($\geq1\times10^{4.2}$ $CCID_{50}$); Live attenuated rubella virus (Wistar RA 27/3 strain) ($\geq1\times10^{3.2}$ $CCID_{50}$); Live attenuated varicella virus (Oka strain) ($\geq1\times10^{2.9}$ pfu)	Water for injections	Live attenuated measles virus (Enders' Edmonston strain) ($\geq1\times10^{3.0}$ TCID50); Live attenuated mumps virus (Jeryl-Lynn [Level B] strain) ($\geq1\times10^{4.3}$ TCID50); Live attenuated rubella virus (Wistar RA 27/3 strain) ($\geq1\times10^{3.0}$ TCID50); Live attenuated varicella virus (OKA/Merck strain) ($\geq1\times10^{3.99}$ PFU)	Water for injections q.s. 0.5 mL
Presentation	Powder for suspension for injection (Vial)	Solution for suspension for injection (Syringe)	Powder for suspension for injection (Vial)	Solution for suspension for injection (Syringe)	Powder for suspension for injection (Vial)	Solution for suspension for injection (Syringe)	Powder for suspension for injection (Vial)	Solution for suspension for injection
Type	Investigational		Investigational		Investigational		Control	
Product Category	Biologic/Combination Product		Biologic/Combination Product		Biologic/Combination Product		Biologic/Combination Product	
Route of administration	Subcutaneous injection		Subcutaneous injection		Subcutaneous injection		Subcutaneous injection	
Administration site								

	Study intervention 1	Study intervention 2	Study intervention 3	Study intervention 4
Location	Arm	Arm	Arm	Arm
Directionality	Upper	Upper	Upper	Upper
Laterality	Left	Left	Left	Left
Number of doses to be administered	1	1	1	1
Volume to be administered by dose*	At least 0.5 mL	At least 0.5 mL	At least 0.5 mL	0.5 mL
Packaging and labeling	Refer to Pharmacy Manual for details	Refer to Pharmacy Manual for details	Refer to Pharmacy Manual for details	Refer to Pharmacy Manual for details
Manufacturer	GSK	GSK	GSK	Merck & Co.

Abbreviations: CCID50 = 50% cell culture infective dose; GSK = GlaxoSmithKline Biologicals SA; H = High potency; L = Low potency; PFU = plaque-forming units; q.s.= sufficient quantity; TCID50 =50% tissue culture infectious dose

*Refer to the Pharmacy Manual for the volume after reconstitution.

6.2 Preparation, Handling, Storage, and Accountability

The study interventions will be prepared as described in the Pharmacy Manual.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study can receive study intervention, and only authorized study site staff can supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

The investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study intervention using the Drug Accountability Form. These forms must be available for inspection at any time.

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.2.1 Labeling

Study vaccine will be appropriately labeled in order to ensure participant safety and the reliability and robustness of data generated in this study, and in order to allow for the distribution of vaccines to clinical study centers.

Labeling details will be provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Participant Identification

The participant identification numbers (IDs) will be assigned sequentially to the participants whose parent(s)/LAR(s) have consented to participate in the study, according to the range of participant IDs allocated to each study center.

6.3.2 Randomization to Study Intervention

Country and center will be used as minimization factors for randomization. Randomization of vaccines will be performed using Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). The participants will receive a unique treatment number

(refer to Appendix 4 for the definition). Once a treatment number has been assigned, it cannot be re-assigned.

6.3.3 Intervention Allocation to Participants

Allocation of the participant to an intervention group at the study center will be performed using IVRS/IWRS randomization through Interactive Response Tool (IRT; refer to Appendix 4 for the definition) operated at the study level, before the first vaccination and after assessment of eligibility (i.e., after screening conclusion). The country and center will be used as minimization factors.

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

After obtaining the signed and dated informed consent form (ICF) from the 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.

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 Blinding and Unblinding

Data will be collected in a single-blind manner. The investigator(s) and/or their staff will be aware of the study intervention assignment, but the participant will not. The study intervention will be prepared and administered by qualified study personnel who can be aware of the intervention assignment. In addition, safety evaluation by IQVIA/GSK will be conducted in a blinded manner.

Participants will be randomized in a 2:2:2:1:1 ratio to receive study intervention and will remain blinded to the study intervention throughout the course of the study.

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 and the identity of the participant.

6.3.4.1 Emergency Unblinding

Unblinding a participant's individual treatment 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 and site staff will have 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. 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 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 Appendix 4) 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 Appendix 4) and electronic case report form (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 treatment information records to verify that vaccine dispensing has been done accurately.

A physician other than the investigator (e.g., an emergency room physician) or participant's parent(s)/LAR(s)/caregiver (see the definition in Appendix 4)/family member may also request emergency unblinding. Instructions for this will be provided to the participants' parent(s)/LAR(s) at enrollment.

A participant may continue in the study if that participant's intervention assignment is unblinded.

6.3.4.2 Unblinding Procedures for Safety Reporting

The investigator will only unblind the treatment allocation of a participant in the course of a clinical study if unblinding is relevant to the safety of the participant.

When reporting a Suspected Unexpected Serious Adverse Reaction (SUSAR) to the European Medicines Agency (EMA), IQVIA will only unblind the treatment allocation of the affected participant to whom the SUSAR relates.

In case of unblinding, blind should be maintained for GSK's Safety Review Team (SRT) performing blinded safety data review.

Unblinded information will be accessible only to persons who need to be involved in the safety reporting to the EMA, to the IDMC, or to persons performing ongoing safety evaluations during the clinical study.

6.4 Study Intervention Compliance

When the study intervention is administered at the study center, participants will receive it directly from the investigator or designee, under medical supervision. The date of administration of each study intervention dose in the clinic will be recorded in the source documents.

6.5 Dose Modification

Dose modifications are not planned or allowed in this study.

6.6 Continued Access to Study Intervention after the End of the Study

There will be no continuing access to study intervention after the end of the study.

6.7 Treatment of Overdose

For this study, any dose of study intervention greater than the recommended dose per protocol will be considered an overdose.

Overdose in itself is not to be reported as an AE, however, any AEs associated with the overdose are to be reported in the relevant AE/serious adverse event (SAE) sections of the eCRF.

6.8 Concomitant Therapy

At each study visit/contact, the investigator(s) or their delegate(s) should question the participant's parent(s)/LAR(s) about all medications/products taken, and vaccinations received by the participant.

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

- All concomitant medication associated with an AE, including vaccines/products, administered after the first dose of study intervention (Day 1 to Day 43).
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines.
- All concomitant medication which may explain/cause/be used to treat an SAE including vaccines/products, as defined in Section 8.3.1 and Appendix 3. These must also be recorded in 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.

7.0 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Not applicable as this is a single dose study.

7.2 Contraindications to Subsequent Study Interventions Administration

Not applicable as this is a single dose study.

7.3 Participant Discontinuation/Withdrawal from the Study

The participant's parent(s)/LAR(s) may withdraw the participant from the study at any time or the investigator may decide to withdraw a participant for safety, compliance, administrative, or other reasons.

A participant is considered a "withdrawal" from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for this participant from the date of withdrawal/last contact.

From an analysis perspective, a study "withdrawal" refers to any participant who was not available for the concluding contact planned in the protocol.

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

The primary reason for study withdrawal shall be documented in the eCRF. Examples of the reasons may include:

- Adverse event requiring expedited reporting to IQVIA (see Appendix 3 for the details regarding such events)
- Unsolicited nonserious AE
- Solicited AE
- Withdrawal by the participant's parent(s)/LAR(s) but not due to AE*
- Migrated/moved from the study area
- Lost to follow-up
- Study termination
- Other (specify)

*If a participant is withdrawn from the study because the participant's parent(s)/LAR(s) have withdrawn 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 SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. The investigators should follow-up with parent(s)/LAR(s) of participants who are withdrawn from the study as a result of an SAE/AE until the event is resolved (see Appendix 3 for details regarding follow-up for AEs).

7.4 Lost to Follow-up

A participant will be considered lost to follow-up if he/she fails to return for scheduled visits and is unable to be contacted by the study center staff.

Refer to the SRM for a description of actions to be taken before considering the participant lost to follow-up.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (SoA) (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with IQVIA immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility.

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

An overall volume of ~10 mL (5 mL each at Visit 1 and Visit 3) per participant will be collected during the entire study period.

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

Findings in this study 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 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, if required by local legislation.

Information on further research and its rationale can be obtained from GSK.

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

By default, collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performs the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.

8.1.2 Laboratory Assays

All laboratory testing will be performed as indicated in Table 9 at GSK laboratory or in a laboratory designated by GSK. The assay to measure immune responses to measles, mumps, and rubella are qualified for use in this Phase II study and will be validated for future Phase III studies in the MMRVNS Clinical Development Program. The assay to measure immune response to varicella is validated and used in other GSK Clinical Development Programs.

Table 9 Laboratory Assays

Assay type	System	Component	Method
Humoral Immunity (Antibody determination)	Serum	Anti-measles Ab IgG	Multiplex Luminex based Immuno Assay
		Anti-mumps Ab IgG	
		Anti-rubella Ab IgG	
		Anti-gE Ab IgG	ELISA

Abbreviations: Ab = antibody; ELISA = enzyme-linked immunosorbent assay; gE = glycoprotein E; IgG = immunoglobulin G

8.1.3 Immunological Correlates of Protection

For measles, mumps, and rubella, there is no established correlate of protection with the anti-measles, -mumps, -rubella Multiplex Luminex based Immuno assay to be used in this study.

The following seroresponse threshold values are proposed by GSK as endpoint defining active immunization offering clinical benefit:

- 67 milli international units (mIU)/mL for anti-measles antibodies
- 296 arbitrary units (AU)/mL for anti-mumps antibodies
- 17 international units (IU)/mL for anti-rubella antibodies

For varicella, there is no established correlate of protection with the anti-glycoprotein E (gE) enzyme-linked immunosorbent assay (ELISA) assay to be used in this study. An anti-gE antibody threshold of 300 mIU/mL is accepted by the Food and Drug Administration as endpoint defining active immunization offering clinical benefit.

The investigator will be provided with the list of participants who do not achieve the pre-specified seroresponse threshold criteria in a timely manner (no later than 12 months after the last sampling date of the last participant enrolled).

At the end of the study, participants who would not achieve the pre-specified seroresponse threshold criteria will be offered re-vaccination at the investigator's discretion and depending on local recommendations, with a dose of licensed MMRV, MMR or varicella vaccine, depending on the antigen(s) for which the seroresponse threshold was not achieved.

8.2 Safety Assessments

8.2.1 Pre-intervention Administration Procedures

8.2.1.1 Collection of Demographic Data, Medical/Vaccination History

Demographic data such as age in years, sex, race, and ethnicity will be collected from each participant. Race and ethnicity will be collected as GSK seeks to have diverse clinical study participation (to see if the study vaccine works in all populations). Medical history should be collected, and it should be verified that none of exclusion criteria related to medical and vaccination history (see Section 5.2) are met. Prior vaccination history with respect to measles-, mumps-, rubella-, and varicella-containing vaccines should be obtained and recorded in the eCRF.

8.2.1.2 Checking Contraindications, Warnings, and Precautions to Intervention Administration

The body temperature of each participant will be measured prior to the study intervention administration. GSK will provide the study center with the temperature measuring device which are standard devices validated by GSK's Quality Assurance Team to ensure consistency in the data across study centers. If the participant has a fever (defined as temperature ≥38.0°C (100.4°F) regardless of the location of measurement) on the day of the intervention administration, or other health conditions that can be considered temporary, Visit 1 can be rescheduled (see Section 5.5) as long as the eligibility criteria are still met (see Section 5.1 and Section 5.2).

8.2.2 Physical Examinations

A routine physical examination as per local standard of care will be performed for each participant on Day 1. If the investigator determines that the participant's health on the day of the study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to Section 5.5 for the list of criteria for the temporary delay of study intervention administration.

8.2.3 Clinical Safety Laboratory Tests

No clinical safety laboratory tests are planned per protocol. Clinical safety laboratory tests may be performed at the investigator's discretion if deemed necessary in case of safety concerns.

8.2.4 Safety Monitoring

An IDMC comprising of clinical experts and a biostatistician will provide safety oversight during the active vaccination period, through unblinded review of the cumulative safety data. The first IDMC review meeting is planned after Day 43 safety follow-up of the first

200 vaccinated participants (approximately 50 in each group, considering pooled MMRV groups) is completed. A subsequent IDMC review meeting is planned during the study, after Day 43 safety follow-up of 400 participants is completed. The details of the review will be described in an IDMC charter.

In addition to the planned IDMC meetings, monthly SRT review by GSK will occur till the first 200 vaccinated participants complete the Day 43 safety follow-up, to monitor cumulative, blinded safety data (including serious and nonserious AEs). The blinded safety data review by the SRT may trigger an emergency ad-hoc IDMC review.

Solicited administration site events in terms of injection site redness, pain, and swelling; and solicited systemic events in terms of drowsiness, loss of appetite, fever, measles/rubella-like rash, varicella-like rash and other rash (not measles/rubella-like rash or varicella-like rash) will be collected. Unsolicited AEs, including SAEs will be encoded according to the latest version of the Medical Dictionary for Regulatory Activities dictionary.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

8.3.1 Time Period and Frequency for Collecting AE and SAEs and Other Safety Information

The definitions of an AE or SAE are provided in Appendix 3.

Collection of AEs starts on the day of the study intervention (Day 1) up to Day 43 unless the AE leads to study discontinuation. Collection of SAEs starts the day of the study intervention (Day 1) and up to study end (Day 181) unless the SAE leads to study discontinuation. The frequency for collection of AEs and SAEs is shown in the SoA (Section 1.3).

8.3.2 Method of Detecting AEs and SAEs

The methods for detecting and recording AEs and SAEs, and the assessment of AE/SAE intensity, causality and outcome are provided in Appendix 3.

The study center staff should instruct participants' parent(s)/LAR(s) on how to report signs and symptoms (e.g., pain) in the individual participant. They will be instructed to report both specific and non-specific symptoms.

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and non-leading verbal questioning of the participants' parent(s)/LAR(s) is the preferred method to inquire about AE occurrences. Examples of the open-ended questions include "Did your child have any significant medical problem since the last study visit?" The study center staff should refrain from detailed questions, e.g., "Since the last visit, has your child experienced any of the following (checklist)?"

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is provided in Appendix 3.

8.3.3 Regulatory Reporting Requirements for SAEs

Once the investigator or designee becomes aware that a study participant has experienced an SAE, they or designated study staff must report it to IQVIA within 24 hours using an electronic Expedited AE Report in the eCRF.

The investigator will provide an assessment of causality at the time of the initial report, as defined in the Appendix 3. 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. This is essential for meeting GSK's legal obligations and ethical responsibilities for the participant's safety and the safety of a study intervention under clinical investigation.

For COVID-19-related SAEs, reports should be submitted following routine procedures for SAEs.

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

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

8.3.4 Reporting of Suspected Unexpected Serious Adverse Reactions to the EudraVigilance Database

IQVIA will keep detailed records of all AEs which are reported to IQVIA by the investigators.

The sponsor will report electronically and without delay to EudraVigilance database all relevant information about any SUSAR.

The period for the reporting of SUSARs by the sponsor to the EMA will take account of the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, as soon as possible and in any event no later than 7 days after IQVIA became aware of the reaction.

- In the case of non-fatal or non-life-threatening SUSARs, no later than 15 days after IQVIA became aware of the reaction.
- In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event no later than 7 days after IQVIA became aware of the reaction being fatal or life-threatening.

Where necessary to ensure timely reporting, IQVIA may submit an initial incomplete report followed up by a complete report.

8.3.5 Annual Safety Report

Regarding investigational medicinal products, GSK/IQVIA shall submit annually through Clinical Trials Information System to all Member States concerned a report on the safety of each investigational medicinal product used in this study.

8.3.6 Urgent Safety Measures and Other Relevant Safety Reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, IQVIA and the investigator will take appropriate urgent safety measures to protect study participants. In addition, GSK/IQVIA will notify the Member States concerned, through Clinical Trials Information System, of the event and the measures taken. That notification will be made without undue delay but no later than 7 days from the date the measures have been taken.

8.3.7 Treatment of Adverse Events

Any medication administered for the treatment of an SAE should be recorded in the Expedited AE Report.

8.3.8 Participant Card

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

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 or other means of virtual contact.
- If the eDiary device was provided to the 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 (refer to the SRM for details). If the app was provided to the participants' parent(s)/LAR(s) for use on their personal device, the app can be disabled remotely.
- Visits for suspected AEs may take place in a different location* other than the study center or at participant's home. If this is not feasible, then the medical evaluation of AEs may take place remotely with documentation of symptoms by other means of communication (e.g., phone call or videoconference), if possible.
- 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 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.

The impact on the Per Protocol Set (PPS) 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.

8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Immunogenicity Assessments

Refer to Section 8.1 for details on immunogenicity assessments performed in this study.

8.10 Health Economics

Health economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

The SAP will be developed and finalized before First Participant First Visit. This section is a summary of the planned main statistical analyses of the primary and secondary immunogenicity endpoints. Analyses of safety are described in Section 9.3.3.2, and additional details will be provided in the SAP.

9.1 Statistical Hypotheses

There are no statistical hypotheses in this study. All analyses are descriptive.

9.2 Analysis Sets

Table 10 Analysis Sets

Analysis set	Description
Enrolled (ENR)	Participants who received a study intervention, had a blood draw before study intervention administration or were randomized. Note that as per Good Clinical Practice enrolled participants' parent(s)/LAR(s) should have completed the informed consent process and participants should be eligible before initiating any study procedure.
Exposed (ES)	All participants who received a study intervention. Analysis per group is based on the study intervention administered.
Per Protocol (PPS)	All eligible participants who received a study intervention as per protocol, were not unblinded, had immunogenicity results pre- and post dose for at least 1 antigen, complied with blood draw interval between study intervention and post dose blood sample, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination.

Abbreviations: LAR = legally acceptable representative

Note: Intercurrent medical conditions that may lead to elimination from the PPS are defined as confirmed immunodeficiency condition, or development of measles, mumps, rubella or varicella illness (chicken pox) or herpes zoster in the interval between study intervention administration and the collection of the blood specimen for immunogenicity at Visit 3.

9.3 Statistical Analyses

The SAP 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.

9.3.1 General Considerations

All analyses are descriptive and therefore no statistical adjustment for interim analyses is required.

9.3.2 Primary Endpoint Analysis

The immunogenicity primary endpoints are:

- Anti-measles antibody geometric mean concentrations (GMCs) at Day 43

- Anti-mumps antibody GMCs at Day 43
- Anti-rubella antibody GMCs at Day 43
- Anti-gE antibody (for varicella) GMCs at Day 43

The analysis of these immunogenicity primary endpoints will be primarily based on the PPS.

9.3.2.1 Within Group Assessments

Antibody GMCs will be summarized for each MMRV antigen (i.e., measles, mumps, rubella, and varicella) by treatment group with their 2-sided 95% confidence interval (CI), minimum and maximum, derived considering log-transformed concentrations are normally distributed with unknown variance for antibodies against each antigen. Concentration below the assay cut-off will be assigned half the cut-off for the purpose of GMC computation (Table 11).

Table 11 Assay Cut-off

Component	Assay cut-off	Method
Anti-measles Ab IgG	29.1 mIU/mL	Multiplex Luminex based Immuno Assay
Anti-mumps Ab IgG	144.3 AU/mL	
Anti-rubella Ab IgG	1.4 IU/mL	
Anti-gE Ab IgG	97 mIU/mL	ELISA

Abbreviations: Ab = antibody; AU = arbitrary unit; ELISA = enzyme-linked immunosorbent assay; IgG = immunoglobulin G; IU = international unit; mIU = milli international unit

The distribution of antibody concentrations for each antigen will be displayed using reverse cumulative curves for the sub-cohort of initially seronegative participants.

9.3.2.2 Between Group Assessments

GMC ratios of pooled MMRV group over each MMRVNS group (MMRV(H)NS, MM(H)RVNS and M(L)M(L)R(L)V(L)NS) will also be provided with nominal 2-sided 95% CI. This will be obtained for each MMRV antigen (i.e., measles, mumps, rubella, and varicella) separately using an analysis of variance model on log-transformed antibody concentrations adjusted for log-transformed pre-dose antibody concentration for the antigen. The country will be added as a covariate. Treatment group will be included in the model and group contrasts with associated 2-sided 95% CI will be exponentiated to obtain treatment group GMC ratios for antibodies against each antigen.

9.3.3 Secondary Endpoints Analysis

9.3.3.1 Immunogenicity Secondary Endpoints

The immunogenicity secondary endpoints are:

- Anti-measles antibody seroresponse rate at Day 43

- Anti-mumps antibody seroresponse rate at Day 43
- Anti-rubella antibody seroresponse rate at Day 43
- Anti-gE antibody (for varicella) seroresponse rate at Day 43

The analysis of immunogenicity will be primarily based on the PPS.

The seroresponse rates, seropositive and seronegative, will be summarized by treatment group with their 2-sided 95% exact Clopper Pearson CI for antibodies against each antigen.

Seroresponse rate for measles, mumps, and rubella is defined as the percentage of participants for whom the post dose antibody concentration (Day 43), as measured by the anti-measles, -mumps, -rubella Multiplex Luminex based Immuno assay is greater than or equal to the following threshold values:

- 67 mIU/mL for anti-measles antibodies
- 296 AU/mL for anti-mumps antibodies
- 17 IU/mL for anti-rubella antibodies

Seroresponse rate for varicella is defined as the percentage of participants for whom the post dose anti-gE antibody concentration (Day 43) is ≥300 mIU/mL as accepted by Center for Biologics Evaluation and Research in the context of the VNS vaccine IND (# 02775).

- A seronegative participant is a participant whose antibody concentration is below the assay cut-off.
- A seropositive participant is a participant whose antibody concentration is greater than or equal to the assay cut-off.

The 2-sided 95% CI on group difference in seroresponse rate will be computed based on the method of Miettinen and Nurminen.

9.3.3.2 Safety and Reactogenicity Secondary Endpoints

The safety analysis will be based on the Exposed Set.

The percentage of participants reporting each solicited administration site event during the solicited follow-up period (Day 1-4) after vaccine administration will be tabulated per treatment group and over the whole vaccination course, with exact 95% CI.

The percentage of participants reporting each solicited systemic event in terms of drowsiness and loss of appetite during the solicited follow-up period (Day 1-4) after vaccine administration will be tabulated per treatment group and over the whole vaccination course, with exact 95% CI.

The percentage of participants reporting each solicited systemic event in terms of fever, measles/rubella-like rash, varicella-like rash and other rash (not measles/rubella-like rash or varicella-like rash) up to 42 days after vaccination administration (Days 1-43) will be tabulated per treatment group and over the whole vaccination course, with exact 95% CI.

The percentage of participants reporting unsolicited AEs up to 42 days after vaccination administration (Days 1-43) after vaccine administration, will be tabulated with exact 95% CI.

Percentage of participants reporting SAEs, classified by the Medical Dictionary for Regulatory Activities, after the vaccine administration up to study end will be tabulated with exact 95% CI.

9.4 Sequence of Analyses

Apart from the analyses to be performed in support to the IDMC, a statistical analysis including safety and final immunogenicity data for all participants up to Day 43 timepoint is planned.

An EoS analysis with all safety data including those obtained until the safety follow-up contact (Day 181) will be performed.

Note: If there is a delay in availability of the immunogenicity data, leading to a window between the 2 analyses shorter than what is planned at the time of protocol writing, only one statistical analysis including all immunogenicity and safety data will be performed.

All analyses are descriptive and therefore no statistical adjustment for interim analyses is required.

9.5 Sample Size Determination

The target enrollment will be 800 participants (200 in each MMRVNS vaccine group and 100 in each MMRV vaccine group) to obtain at least 640 evaluable participants (160 in each MMRVNS vaccine group and 80 in each MMRV vaccine group) for the evaluation of the primary objective assuming that up to 20% of the enrolled participants will not be evaluable. Considering 160 evaluable participants, the study will allow generating a 1.25-fold half-width for the 2-sided 95% CI of group GMC ratio assuming a population standard error of 0.45 in log10 transformed concentration.

The randomization algorithm and handling of missing data will be detailed in the SAP.

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF and informed assent form (if applicable), IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

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 SAEs, or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

After reading the protocol, each investigator will sign the protocol signature page and send a copy of the signed page to the IQVIA. The study will not start at any study site at which the investigator has not signed the protocol.

10.1.2 Adequate Resources

The investigator is responsible for supervising any individual or party to whom the investigator delegates study-related duties and functions conducted at the study site.

If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure this individual, or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

10.1.3 Financial Disclosure

Investigators and sub-investigators will provide IQVIA with sufficient, accurate financial information as requested to allow IQVIA to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4 Recruitment Arrangements and Informed Consent and Assent Process

Recruitment Arrangements

- Potential participants will be invited to participate in this clinical study by the study personnel or clinical staff (including participants' primary health physicians) in the clinic and/or through advertisement in appropriate resources such as, but not limited to, printed media, Internet, or social media.
- Identification of potential participants can involve access to identifiable information such as medical records upon participants' parent(s)/LAR(s)' signed authorization. Clinical center personnel will follow national standards and obey local regulations for protection of sensitive patient health information.
- It is allowed that the investigator is also participant's physician or treating clinician. In such situation, there must be a separation of roles for the researcher serving as clinician and study-related interventions and clinical procedures.

Informed Consent and Assent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and participants' parent(s)/LAR(s) and answer all questions regarding the study.
- Potential participants and their parent(s)/LAR(s) must be informed that their participation is voluntary. They or their parent(s)/LAR(s) will be required to physically or digitally sign a statement of informed consent and assent (if applicable) that meets the requirements of

21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that physical or digital informed consent was obtained before the participant was enrolled in the study and the date the physical or digital consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

- A physical or digital copy of the ICF(s) must be provided to the participant and/or their parent(s)/LAR(s).

- The investigator must obtain assent from the minor participant in addition to the consent provided by the participants' parent(s)/LAR(s) when a minor can assent to participate in a 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.

10.1.5 Data Protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to GSK and/or IQVIA will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- GSK and IQVIA 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.

- The participants' parent(s)/LAR(s) must be informed that their child's study-related data will be used by GSK and IQVIA in accordance with local data protection law. The level of disclosure must also be explained to the participants' parent(s)/LAR(s) and their child's data to be used as described in the informed consent.

- The participants and participants' parent(s)/LAR(s) must be informed that participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by GSK and IQVIA, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or IQVIA and/or institutions working with GSK and IQVIA for the purposes of this study are contractually bound to protect participant coded data. GSK and IQVIA will protect participant coded data and will only share it as described in the ICF and informed assent form (if applicable).

10.1.6 Study Administrative Structure

Table 12 Study Administrative Structure

Function	Responsible organization
Clinical Supply Management, Quality Assurance Auditing	GSK
Laboratory Assessments	GSK
Randomization, Blinding, Unblinding	Cenduit
Study Operations Management, Medical Monitoring, Study Master File	IQVIA
Biostatistics, Medical Writing	IQVIA

10.1.7 Safety Data Review and Data Monitoring Committee

Besides safety monitoring by blinded Study/Center Monitors (see the definition in Appendix 4), an IDMC comprising of clinical experts and an independent biostatistician will provide safety oversight during the active vaccination period, through unblinded review of the cumulative safety data.

The first IDMC review meeting is planned after Day 43 safety follow-up of the first 200 vaccinated participants (approximately 50 in each group, considering pooled MMRV groups) is completed. A subsequent IDMC review meeting is planned during the study, after Day 43 safety follow-up of 400 participants is completed. The details of the review will be described in an IDMC charter.

In addition to the planned IDMC meetings, monthly SRT review by GSK will occur till the first 200 vaccinated participants complete the Day 43 safety follow-up, to monitor cumulative, blinded safety data (including serious and nonserious AEs). The blinded safety data review by the SRT may trigger an emergency ad-hoc IDMC review.

10.1.8 Dissemination of Clinical Study Data

The key design elements of this protocol and results summaries will be posted on ClinicalTrials.gov, GSK Clinical Study Register and Eudract.Ema.Europa.Eu in compliance with 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/study 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 study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK 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' parent(s)/LAR(s), as appropriate.

GSK will provide the investigator with the randomization codes for their site 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 to ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

Publication Policy

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

10.1.9 Data Quality Assurance

- The investigator should maintain a record of the location(s) of their respective essential documents, including source documents (see Appendix 4 for definitions of essential and source documents). The document 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 (see Appendix 4 for the definition of a certified copy).

- All participant data related to the study will be recorded on printed or eCRF unless transmitted to GSK/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 site's study participants (see Appendix 4 for the definition of source documents) that supports information entered in the eCRF.
- 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 (see Appendix 4 for the definition of source data).
- Study monitors will perform ongoing source data verification to confirm that data entered in the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be fully explained if necessary (e.g., via an audit trail). The safety and rights of participants must be protected, and the study conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Details of study monitoring, including action required due to COVID-19, will be included in a separate Study Monitoring Plan and/or other documents pertinent to study monitoring.
- Quality tolerance limits will be predefined to identify systematic issues that can impact participant safety and/or the reliability of study results.
- Study records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 25 years from issuance of the final Clinical Study Report/equivalent summary unless local/country-specific regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of GSK. No records may be transferred to another location or party without written notification to GSK.

10.1.10 Source Documents

- Source documents provide evidence to establish the existence of the participant and substantiate the integrity of collected data. The 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.
- Definitions of what constitutes source data and documents can be found in Appendix 4.

10.1.11 Study and Study Center Start and Closure

The first act of recruitment is defined as First Participant First Visit at a country level.

GSK/IQVIA reserves the right to close the study center or terminate the study at any time for any reason, provided there is sufficient notice given to account for all participants safe exit from study.

Regular closure of study centers 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 GSK/IQVIA 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's/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 IRBs/IECs, and the regulatory authorities of 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.

10.2 Appendix 2: Clinical Laboratory Tests

gE Enzyme-linked Immunosorbent Assay

Anti-gE ELISA is a 2-step ELISA based on the antibody and antigen interaction, which allows the detection and the quantification of specific immunoglobulin G (IgG) antibodies directed against gE in tested serum samples.

Briefly, diluted serum samples are added onto a 96-polystyrene-well microplate pre-coated with gE. Then goat antibodies directed against human IgG antibodies and conjugated to horseradish peroxidase (a-IgG-HRP) are added and will bind to anti-gE IgG if present. After a washing step, the addition of a chromogen-substrate solution specific for HRP will provide means of detecting the anti-gE specific for the pre-coated antigen. The HRP catalyzes an enzymatic reaction which is stopped by the addition of sulfuric acid, resulting in a color change from blue to yellow.

The optical density recorded is proportional to the concentration of the anti-gE antibodies present in the serum sample. Antibody titer is expressed in mIU/mL.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Multiplex Luminex based Immuno Assay

In the assay, inactivated native viruses from measles, mumps, rubella, and varicella are coupled to their assigned Luminex MicroPlex microsphere type. Each microsphere type has its own distinct fluorescent dye that can be recognized by excitation with a red laser. The red laser classifies the microsphere type and determines the corresponding assigned virus that is being detected. The 4 microsphere types are incubated with human serum. Following this, the microspheres are washed to remove excess sera and incubated with R-Phycoerythrin conjugated goat anti-human IgG antibody. The fluorescent signal from the PE-labeled conjugate, recognized by excitation with a green laser, is proportional to the anti-virus IgG concentration in the serum sample tested. IgG concentrations are derived from the MMRV Secondary Standard curve, which is made of pooled sera with positive reactivity to all 4 viruses and is aligned to the World Health Organization International reference standards for measles (National Institute for Biological Standards and Control [NIBSC] reference # 97/648), rubella (NIBSC reference # RUBI-1-94) and varicella zoster virus (NIBSC reference# W1044), and to NIBSC QC Reagent for mumps (NIBSC reference # 15/B664). The MMRV Secondary Standard is 2-fold serially diluted in duplicate to create a 10-point (STD1 to STD10) standard curve for each of the MMRV antigens. Standard curve for each virus is calculated using a 3 Parameter Logistic curve fit. Results are expressed in mIU/mL for measles and varicella, AU/mL for mumps, and IU/mL for rubella. Samples are quantified at 2 pre-dilutions in singlet.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting for Study Intervention

10.3.1 Definition of 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.

10.3.1.1 Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after administration of the study intervention even though they may have been present before study start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- 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 Section 10.3.3.
- 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.

10.3.1.2 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Preexisting conditions or signs and/or symptoms present in a participant before the first dose of study intervention. These events will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a preexisting condition (known or diagnosed before signing the informed consent) 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.

10.3.2 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, if it were 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 outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
d. Results in persistent or significant 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Other situations Medical or scientific judgment must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the

above definition should 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; and convulsions that do not result in hospitalization.

10.3.3 Solicited Events

a. Solicited administration site events

The following administration site events will be solicited:

Table 13 Solicited Administration Site Events

Participants 4-6 years of age
Injection site redness
Pain
Swelling

b. Solicited systemic events

The following systemic events will be solicited:

Table 14 Solicited Systemic Events

Participants 4 to 6 years of age
Drowsiness
Loss of appetite
Fever
Measles/rubella-like rash
Varicella-like rash
Other rash (not measles/rubella-like rash or varicella-like rash)

Note: Participants' parent(s)/legally acceptable representative(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' parent(s)/ legally acceptable representative(s) will be instructed to record the highest temperature in the electronic diary/application.

10.3.4 Unsolicited Adverse Events

An unsolicited AE is an AE that was either not included in the list of solicited events or could be included in the list of solicited events but with an onset outside the specified period of follow-up for solicited events. Unsolicited AEs must have been communicated by a participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include both serious and nonserious AEs.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or an emergency room visit, or visit to/by a health care provider). The participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to

report medically attended event(s), as well as any events that, though not medically attended, are of participant's parent(s)/LAR(s)' concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended or perceived as a concern by the participant's parent(s)/LAR(s) will be collected during an interview with the participant's parent(s)/LAR(s) and by review of available medical records at the next visit.

10.3.5 Coronavirus Disease 2019 Cases

Diagnosis of COVID-19 should be made in accordance with the World Health Organization case definition. Cases should be categorized as AEs (unsolicited or AEs leading to withdrawal) 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.

10.3.6 Assessment of Intensity

The intensity of the following solicited AEs will be assessed as described in Table 15.

Table 15 Intensity Scales for Solicited Symptoms in Children (4 to 6 Years of Age)

Children (4 to 6 years of age)		
Adverse Event	**Intensity Grade**	**Parameter**
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Redness at injection site		Greatest surface diameter in mm
Swelling at injection site		Greatest surface diameter in mm
Fever*		Temperature in °C/°F
Measles/rubella-like rash**		Number of lesions
Varicella-like rash***		Number of lesions
Other rash (not measles/rubella-like rash or varicella-like rash)	0	None
	1	Mild: Rash which is easily tolerated by the child, causing minimal discomfort and not interfering with everyday activities
	2	Moderate: Rash which is sufficiently discomforting to interfere with normal everyday activities
	3	Severe: Rash which prevents normal, everyday activities (in a young child, such an adverse events would, for example, prevent attendance at school/day care and would cause the parent(s)/legally authorized representative(s) to seek medical advice)
Drowsiness	0	Behavior as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all

*Fever is defined as temperature ≥38.0°C (100.4°F) by any route. The preferred location for measuring temperature will be the axilla.

**A measles/rubella-like rash manifests as presence of macules, discolored small patches or spots of the skin, neither elevated nor depressed below the skin's surface and/or papules, raised bumps on the skin usually <1 cm in diameter.
***A typical varicella-like rash manifests as a rash/lesion that may appear within 2 weeks (or sometimes later) after the varicella vaccination. Lesions may contain spots, bumps, blisters, or crusts.
Refer to the SRM for detailed guidelines about the rashes.

The maximum intensity of administration site redness/swelling/measles/rubella-like rash/varicella-like rash/fever/will be scored as follows:

Intensity Grade	**Redness/swelling**	**Measles/rubella-like rash and varicella-like rash***	**Fever****
0	None	None	<38.0°C (100.4°F)
1	>0 - ≤5 mm	1-25 lesions	≥38.0°C (100.4°F) - ≤39.0°C (102.2°F)
2	>5 - ≤20 mm	26-50 lesions	>39.0°C (102.2°F) - ≤39.5°C (103.1°F)
3	>20mm	≥51 lesions	>39.5°C. (103.1°F)

*Including injection site varicella-like rash
**Temperature will be analyzed in 0.5°C increments from ≥38.0°C (100.4°F).

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 that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

2 (moderate) = An AE that is sufficiently discomforting to interfere with normal everyday activities.

3 (severe) = An AE that prevents normal everyday activities. Such an AE would, for example, prevent attendance at a childcare facility and would cause the parent(s)/LAR(s) to seek medical advice.

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 one of the predefined outcomes as described above.

10.3.7 Assessment of Causality

The investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgment. Where several different interventions were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific intervention. When a causal relationship to a specific study

intervention cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all interventions.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention 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" (see Section 10.3.2), 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 intervention, 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 AE Report to IQVIA.

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

10.3.8 Medically Attended Visits

For each solicited and unsolicited AE the participant experiences, the 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 in the participant's eDiary (for solicited AEs) and in the participant's eCRF as part of normal AE reporting (for unsolicited AEs). Medical attention received for SAEs will have to be reported using the normal AE reporting process in the eCRF.

10.3.9 Assessment of Outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

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

10.3.10 Reporting, Follow-up, and Assessment of AEs

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 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 the sponsor or IQVIA instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor or IQVIA. In this instance, all participant identifiers will be blinded on the copies of the medical records prior to submission to the

sponsor 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.

The Use of eDiary/Personal Electronic Device App

An eDiary will be used in this study to capture solicited administration site or systemic events. The participants' parent(s)/LAR(s) should be trained on how and when to complete the eDiary/enter information into the app.

Anyone who measures administration site or systemic events and who will 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 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.

Time Period for Collecting and Recording of AEs and SAEs

All solicited administration site events that occur during 4 days (Day 1 to Day 4), and solicited systemic events that occur during 4 days (Day 1 to Day 4; for drowsiness and loss of appetite) or 43 days (Day 1 to Day 43; other solicited systemic events) following administration of the study intervention, must be recorded into the eDiary/personal electronic device app, irrespective of intensity. Unsolicited events occurring from Day 1 to Day 43 and SAEs occurring up the end of the study should be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination related.

Follow-up of AEs and SAEs

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

Other nonserious 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 Information After Removal of Write Access to the Participant's eCRF

When additional SAE 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 as described within the timeframes specified in Section 8.3.1.

Events Requiring Expedited Reporting to IQVIA:

SAE(s) throughout the study

- Once the investigator or designee becomes aware that study participant(s) have experienced an SAE, the investigator or designated study staff must complete information in the electronic Expedited AE Report in the eCRF WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event.
- 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.
- Refer to Section 8.3.1 for the details on timeframes for reporting of SAEs.

SAE Reporting to IQVIA via an Electronic Data Capture Tool
• The primary mechanism for reporting an SAE to IQVIA will be the electronic Data Capture (EDC) Tool. • 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 becomes 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 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.

Backup 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.

10.4 Appendix 4: Abbreviations and Definitions

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
App	Application
AU	Arbitrary unit
CFR	Code of Federal Regulations
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
DTPa	Diphtheria-tetanus-acellular pertussis
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture Tool
eDiary	Electronic diary
ELISA	Enzyme-linked immunosorbent assay
EoS	End of study
EU	European Union
GCP	Good Clinical Practice
gE	Glycoprotein E
GMC	Geometric mean concentration
GSK	GlaxoSmithKline Biologicals SA
HRP	Horseradish peroxidase
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Participant identification number
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IRB	Institutional Review Board
IRT	Interactive Response Tool
IU	International unit
IVRS	Interactive Voice Response System

Abbreviation	Definition
IWRS	Interactive Web Response System
LAR	Legally acceptable representative
LPLV	Last Participant Last Visit
mIU	Milli international unit
MMRVNS	Measles, mumps, rubella, and varicella vaccine (investigational vaccine)
MMRV	Measles, mumps, rubella, and varicella vaccine (comparator vaccine)
NIBSC	National Institute for Biological Standards and Control
PPS	Per Protocol Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States (of America)
VZV	Varicella zoster virus
WHO	World Health Organization

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 an SAE. In a single-blind study, the investigator(s) and/or their staff are aware of the intervention assignment but the participant/parent(s)/LAR(s) is not.
Caregiver:	A caregiver is someone who • lives in the close surroundings of a participant and has a continuous caring role or

	• has substantial periods of contact with a participant and is engaged in his/her daily health care (e.g., a relative of the participant).
Certified copy:	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.
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 or has an appointed legal guardian/LAR(s).
Combination product:	Combination product comprises any combination of a. drug b. device c. biological product Each drug, device, and biological product included in a combination product is a constituent part.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrollment:	The process of registering a participant into a clinical study by assigning participant identification number after signing the ICF.
Enrolled participant:	"Enrolled" means a participant's parent(s)'/LAR(s)' agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for determining eligibility for the study, but do not participate in the study, are not considered enrolled.
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Evaluable:	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.
Intervention:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
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 pressing keypad buttons on a phone and following voice or online prompts in order to enter in 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 trial. The terms legal representative and legally authorized representative are used in some settings.
Medical Monitor	IQVIA’s delegate providing significant scientific contribution to the conduct of the study. The terms Medical Officer, Medical Advisor are also used in some settings.
Medically attended AEs:	Symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider.
Participant:	An individual whose parent(s)/LAR(s) has been contacted to participate or participates in the clinical trial, either as a recipient of the vaccine(s)/product or as a control.
Participant ID:	A unique identification number assigned to each participant who consents to participate in the study.

Protocol amendment:	The ICH defines a protocol amendment as "A written description of a change(s) to or formal clarification of a protocol." GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Safety Review Team:	This team lead by safety comprises of core representatives from GSK global safety, clinical, epidemiology, regulatory, and statistics departments, who are also part of the study team. For this study, the team is responsible for reviewing observed safety concerns based on blinded safety data.
Solicited events:	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 follow-up period following study intervention administration.
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).
Source documents:	Original legible documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries 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).
Study/Center Monitor:	An individual assigned by IQVIA (see the study administrative structure in Appendix 1 [Table 12]) 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.
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Treatment number:	A number identifying intervention given to a participant, according to intervention allocation.

Unsolicited event:	Any AE reported in addition to those solicited during the clinical study. Also, any “solicited” symptom with onset outside of the specified period of follow-up for solicited symptoms will be reported as an unsolicited AE.

11.0 REFERENCES

Advisory Committee on Immunization Practices (ACIP). Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control, Atlanta, GA. MMWR. 2007;56 (No. RR-4).

CDC Morbidity and Mortality Weekly Report (MMWR). Use of Combination Measles, Mumps, Rubella, and Varicella Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). 2010; 59(RR03):1-12. Accessed 23 May 2022

Signature of Investigator

PROTOCOL TITLE: A Phase II, single-blind, randomized, controlled study to evaluate the immunogenicity and safety of a measles, mumps, rubella, varicella vaccine compared with *ProQuad,* administered in healthy children 4 to 6 years of age

PROTOCOL NO: 217715 (MMRVNS 20-001)

Date of protocol: 15 March 2023

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 the 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: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____