Statistical Analysis Plan

Study ID: 217715

Official Title of Study: 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.

NCT number: NCT05630846

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STATISTICAL ANALYSIS PLAN

217715 (MMRVNS 20-001)

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.

AUTHOR: PPD

VERSION NUMBER AND DATE: V5.0, 09DEC2024

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V5.0 (Dated 09DEC2024) for Protocol 217715 (MMRVNS 20-001)

	Name	Signature	Date (DDMmmYYYY)
Author:	PPD	PPD	
Position:	Associate Director Biostatistics		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date (DDMmmYYYY)
Approved By:	PPD	PPD	
Position:	Lead Statistician		
Company:	GlaxoSmithKline Biologicals SA		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	16AUG2022	PPD	Not Applicable – First Version
2.0	07SEP2022	PPD	Update assay cut off values following update in protocol
3.0	25NOV2022	PPD	Update seroresponse values following update in protocol Update appendix 2 to be consistent with section 13 Update labelling of treatment groups in the table and listings.
4.0	25JUN2024	PPD	Updated Protocol version – No impact on analyses. Increased precision for assay cut off values for measles, mumps and rubella, based on laboratory information. Updated the MedDRA version number and Preferred Term for Loss of appetite. Updated Preferred Terms for unsolicited

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			adverse events that are synonymous with solicited adverse events. Added details for handling duplicate solicited adverse events. Explained handling of solicited events recorded beyond the end of the solicited periods. Added definition of immediate unsolicited AEs. Added Section 16.1.1.1 eCOA Compliance.
5.0	09DEC2024	PPD	Updated the seroresponse thresholds for measles and rubella in Section 6.6 and added the change from Protocol in Section 3.3. Removed the filter of initially seronegative participants for the reverse cumulative curves, in Section 15.1.3 and added the change from Protocol in Section 3.3. The assay cut-offs were updated in Table E (Section 15.1.3) for mumps and rubella and added the change from Protocol in Section 3.3. Added detail for handling of duplicates with differing results, in Section 16.1.1. Added detail for handling "no symptoms to

			report" records, in Section 16.1.1.1. Added detail if the imputed start date falls after the event end date, in Appendix 2.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
eCOA	Electronic Diary
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
ENR	Enrolled Set
ES	Exposed Set
gE	Glycoprotein E

GCP	**Good Clinical Practice**
GMC	**Geometric Mean Concentration**
IDMC	**Independent Data Monitoring Committee**
IgG	**Immunoglobulin G**
LAR	**Legally Acceptable Representative**
LLOQ	**Lower Limit Of Quantification**
MedDRA	**Medical Dictionary for Regulatory Activities**
MMRVNS	**Measles, mumps, rubella and varicella vaccine (investigational vaccine)**
MMRV	Measles, mumps, rubella and varicella vaccine (comparator vaccine)
PD	Protocol Deviation
PDMP	Protocol Deviations Management Plan
PI	Principal Investigator
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

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SD	Standard Deviation
SOC	System Organ Class
SRT	Safety Review Team
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures and Listings
ULOQ	Upper Limit Of Quantification

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of immunogenicity and safety at final analyses for Protocol 217715 (MMRVNS 20-001). It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This Statistical Analysis Plan (SAP) is based on final protocol amendment 1.0 dated 15 March 2023.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. Primary Objective

The primary objective is

- To evaluate the immune response of measles, mumps, rubella and varicella vaccine (investigational vaccine) (MMRVNS) vaccine (formulated with different potencies) and the measles, mumps, rubella and varicella (comparator vaccine) (MMRV) vaccine (pooled group) in terms of geometric mean concentrations (GMCs) at Day 43 for antibodies to measles, mumps, rubella and varicella viruses.

2.2. Secondary Objectives

The secondary objectives are

- To evaluate the immune response to the MMRVNS vaccine (formulated with different potencies) and the MMRV vaccine (pooled group) in terms of seroresponse rates at Day 43 for antibodies to measles, mumps, rubella and varicella viruses.
- To evaluate safety and reactogenicity following administration of the MMRVNS vaccine (formulated with different potencies) and MMRV vaccine (pooled group)

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2.3. Estimands

The primary and secondary estimands to support regulatory decisions are described in the following table:

Table A: Objectives and Estimands

	Study Intervention	Population	Variable (or endpoint)	Intercurrent events (ICEs)		Population level summary
				Description	Handling strategy	
Primary	Randomized MMRVNS vaccine or MMRV vaccine	Healthy children of 4 to 6 years of age	Anti-measles antibody GMC at Day 43	1. Permanently discontinued from study due to any reasons prior to Day 43 blood sampling 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition 4. Vaccine or blood sample taken out of window 5. No post-vaccine immunogenicity result available	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis. 3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	Antibody GMC with exact 95% CI and range of antibody concentrations will be tabulated.
Primary	Randomized MMRVNS vaccine or MMRV vaccine	Healthy children of 4 to 6 years of age	Anti-mumps antibody GMC at Day 43	1. Permanently discontinued from study due to any reasons prior to Day 43 blood sampling 2. Study intervention not administered per protocol 3. Prohibited medication	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis. 3. Participant excluded from the immunogenicity analysis.	Antibody GMC with exact 95% CI and range of antibody concentrations will be tabulated.

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				or intercurrent medical condition 4. Vaccine or blood sample taken out of window 5. No post-vaccine immunogenicity result available	4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	
Primary	Randomized MMRVNS vaccine or MMRV vaccine	Healthy children of 4 to 6 years of age	Anti-rubella antibody GMC at Day 43	1. Permanently discontinued from study due to any reasons prior to Day 43 blood sampling 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition 4. Vaccine or blood sample taken out of window 5. No post-vaccine immunogenicity result available	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis. 3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	Antibody GMC with exact 95% CI and range of antibody concentrations will be tabulated.
Primary	Randomized MMRVNS vaccine or MMRV vaccine	Healthy children of 4 to 6 years of age	Anti-Glycoprotein E (gE) antibody GMC at Day 43	1. Permanently discontinued from study due to any reasons prior to Day 43 blood sampling	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity	Antibody GMC with exact 95% CI and range of antibody concentrations will be tabulated.

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				2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition 4. Vaccine or blood sample taken out of window 5. No post-vaccine immunogenicity result available	analysis. 3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	
Secondary	Randomized MMRVNS vaccine or MMRV vaccine	Healthy children of 4 to 6 years of age	Anti-measles antibody seroresponse rate at Day 43	1. Permanently discontinued from study due to any reasons prior to Day 43 blood sampling 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition 4. Vaccine or blood sample taken out of window 5. No post-vaccine immunogenicity result available	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis. 3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	Seroresponse rates for each antigen will be tabulated with exact 95% CI
Secondary	Randomized	Healthy children	Anti-mumps antibody	1. Permanently	1. Missing data won't be	Seroresponse rates for each

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	MMRVNS vaccine or MMRV vaccine	of 4 to 6 years of age	seroresponse rate at Day 43	discontinued from study due to any reasons prior to Day 43 blood sampling 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition 4. Vaccine or blood sample taken out of window 5. No post-vaccine immunogenicity result available	imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis. 3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	antigen will be tabulated with exact 95% CI
Secondary	Randomized MMRVNS vaccine or MMRV vaccine	Healthy children of 4 to 6 years of age	Anti-rubella antibody seroresponse rate at Day 43	1. Permanently discontinued from study due to any reasons prior to Day 43 blood sampling 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition 4. Vaccine or blood sample taken out of window	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis. 3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity	Seroresponse rates for each antigen will be tabulated with exact 95% CI

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				5. No post-vaccine immunogenicity result available	analysis.	
Secondary	Randomized MMRVNS vaccine or MMRV vaccine	Healthy children of 4 to 6 years of age	Anti-gE antibody seroresponse rate at Day 43	1. Permanently discontinued from study due to any reasons prior to Day 43 blood sampling 2. Study intervention not administered per protocol 3. Prohibited medication or intercurrent medical condition 4. Vaccine or blood sample taken out of window 5. No post-vaccine immunogenicity result available	1. Missing data won't be imputed. Summaries will present the actual data. 2. Participant excluded from the immunogenicity analysis. 3. Participant excluded from the immunogenicity analysis. 4. Participant excluded from the immunogenicity analysis. 5. Participant excluded from the immunogenicity analysis.	Seroresponse rates for each antigen will be tabulated with exact 95% CI
Secondary	Randomized MMRVNS vaccine or MMRV vaccine	Healthy children of 4 to 6 years of age	Each solicited administration site event within 4 days after dose of study intervention	1. eDiary not completed on each day	1. Missing data won't be imputed. Compliance to eDiary will be captured	Percentage of participants with event will be summarized with exact 95% Confidence Interval (CI)
Secondary	Randomized MMRVNS vaccine or MMRV vaccine	Healthy children of 4 to 6 years of age	Each solicited systemic event (drowsiness and loss of appetite) within 4 days after dose of	1. eDiary not completed on each day	1. Missing data won't be imputed. Compliance to eDiary will be captured	Percentage of participants with event will be summarized with exact 95% Confidence Interval (CI)

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			study intervention			
Secondary	Randomized MMRVNS vaccine or MMRV vaccine	Healthy children of 4 to 6 years of age	Each solicited systemic event (fever, measles/rubella-like rash, varicella-like rash and other rash) within 43 days after dose of study intervention	1. eDiary not completed on each day	1. Missing data won't be imputed. Compliance to eDiary will be captured	Percentage of participants with event will be summarized with exact 95% Confidence Interval (CI)
Secondary	Randomized MMRVNS vaccine or MMRV vaccine	Healthy children of 4 to 6 years of age	Each unsolicited adverse event within 43 days after dose of study intervention	1. Permanently discontinued from study due to any reasons prior to Day 43 blood sampling	1. Missing data won't be imputed. Summaries will present the actual data.	Percentage of participants with event will be summarized with exact 95% CI
Secondary	Randomized MMRVNS vaccine or MMRV vaccine	Healthy children of 4 to 6 years of age	Serious Adverse Events from dose of study intervention up to study end	1. Permanently discontinued from study due to any reasons	1. Missing data won't be imputed. Summaries will present the actual data.	Percentage of participants with event will be summarized with exact 95% CI

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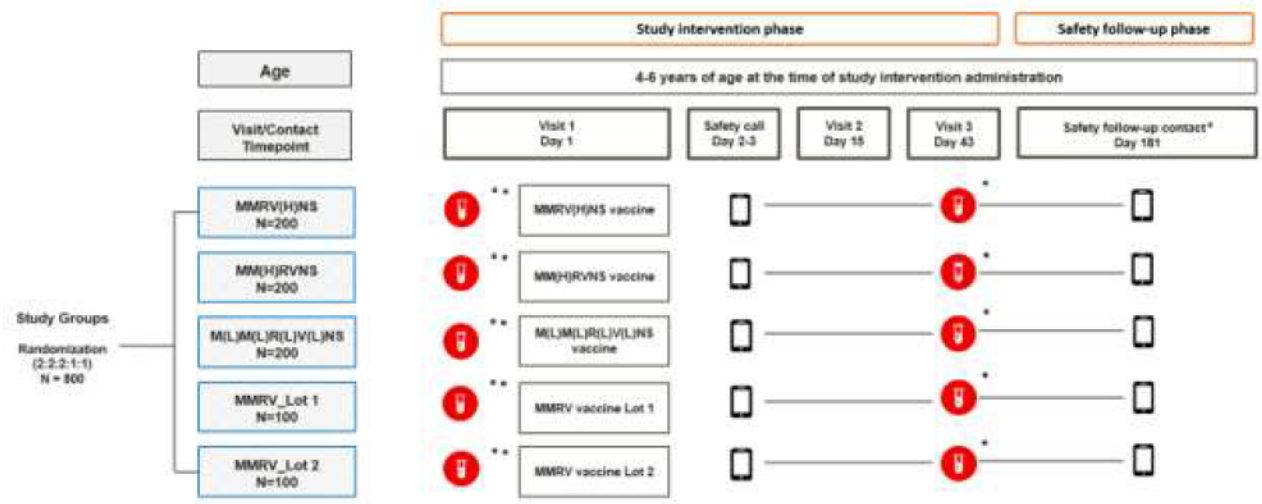
3. STUDY DESIGN

3.1. General Description

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 [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 MMVR vaccine (2 groups of 100 participants each receiving one of the 2 different lots of the MMRV vaccine [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).

Figure A; 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

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°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 post-dose of study intervention

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 protocol Section 5.0). Approximately 800 participants will be randomly assigned to the 5 study interventions in a 2:2:2:1:1 ratio prior to intervention to provide approximately 200 enrolled participants in each MMRVNS group and 100 enrolled participants in each MMRV group (MMRV_Lot 1 and MMRV_Lot 2).

Treatments will be allocated using a minimization algorithm for 90% of the participants, with the remaining 10% of treatments allocated randomly. Center and country will be used as minimization factors.

Table B: Study Groups

Study groups	Number of participants	Age (Min-max)	Study interventions
MMRV(H)NS	200	4 to 6 years	MMRV(H)NS vaccine
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-contact will be made to the participant on Day 181 via telephone or by any other convenient means of communication.

3.2. Schedule of Activities

Schedule of events can be found in Section 1.3 of the protocol.

3.3. Changes to Analysis from Protocol

The seroresponse thresholds for anti-measles antibodies and anti-rubella antibodies offering clinical benefit were updated and communicated to the FDA. The SAP was updated with the new thresholds but the Protocol was not

updated.

The assay cut-offs were updated during assay validation for anti-mumps antibodies and anti-rubella antibodies. The SAP was updated but the Protocol was not updated.

The distribution of antibody concentrations for each antigen display using reverse cumulative curves will no longer be for the sub-cohort of initially seronegative participants, due to an expectation of a low number of participants in this sub-cohort.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses for Independent Data Monitoring Committee (IDMC) meetings
- Analyses for Safety Review Team (SRT) review
- Interim Analysis
- Final Analysis

4.1. Independent Data Monitoring Committee (IDMC)

An IDMC SAP, describing the methodology and the presentation of, and access to, results will be provided by IQVIA as a separate document.

An IDMC will provide safety oversight during the active vaccination period, through unblinded review of the cumulative safety data.

The first IDMC review is planned after Day 43 safety follow-up of the first 200 vaccinated participants

(approximately 50 participants in each group, considering pooled MMRV groups) is completed. The analysis will take place once all 200 participants have returned for their Day 43 visit (Visit 3) within the allowed interval for the visit or have withdrawn from the study. A subsequent IDMC review meeting is planned during the study, after Day 43 safety follow-up of 400 participants is completed.

4.2. SRT Review

The SRT is responsible for ongoing safety monitoring. Monthly SRT reviews will occur up to the enrollment and vaccination of the first 200 participants through their Day 43 follow-up, to monitor cumulative, blinded safety data (including serious and non-serious AEs). The blinded safety data review by the SRT may trigger an emergency ad-hoc IDMC review before the 200 participants are enrolled and vaccinated.

4.3. Interim Analysis

One interim analysis will take place for this study. A statistical analysis including safety and final immunogenicity data for all participants up to Day 43 timepoint is planned, the results of which will be based on the unblinded intervention groups. All analyses are descriptive and therefore no statistical adjustment for interim analyses is required.

4.4. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of intervention group.

This SAP is focused/limited to planned interim and final analyses. Outputs required for the interim and final

analyses will be flagged in the tables, figures and listings (TFL) mock shells document.

5. ANALYSIS SETS

Agreement and authorization of participants included/excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. Process for Analysis Set Assignment

- Definitions for analysis sets are provided below.
- Prior to database lock, a transfer of raw data from the electronic Case Report Form (eCRF) will occur, and participants will be assigned to analysis sets in accordance with the definitions in this SAP and the available data at that time. However, the protocol deviations will be monitored continuously throughout the study.
- Listings presenting participants excluded from each preliminary analysis set and reasons for exclusion will be prepared for sponsor review ahead of database lock in order to allow appropriate related data queries to be issued.
- Listings presenting participants excluded from each final analysis set and reasons for exclusion will be prepared for sponsor review ahead of unblinding for a final review and approval. However, for deviations that can only be assessed after unblinding such as vaccination errors these will be reviewed after unblinding.
- A Data Review meeting will be held to confirm analysis set assignment for each participant and any changes will be recorded. Changes will be implemented, and an updated analysis set assignment will be approved by the sponsor.
- Sponsor authorization of the analysis sets will be necessary to unblind the data after database lock. Once approved, the study will be unblinded, analysis sets will be finalized including additional eliminations requiring unblinding, and the database will be locked.

- After database lock, the final analysis sets will be derived using the final study data, i.e., clinical database (eCRF), external vendor data (immunogenicity results), protocol deviations log and blinded data report.

5.2. Enrolled Set [ENR]

All participants who received a study intervention, had a blood draw before study intervention or were randomized. Note that as per Good Clinical Practice (GCP) enrolled participants' parent(s)/ legally acceptable representative (LAR) should have completed the informed consent process and participants should be eligible before initiating any study procedure.

5.3. Exposed Set [ES]

All participants who received a study intervention. Analysis per group is based on the study intervention administered.

5.4. Per Protocol Set [PPS]

All eligible participants who received 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 medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination*.

*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.

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6. GENERAL CONSIDERATIONS

Data will be summarized descriptively (frequency and percentage for categorical data and mean, standard deviation [SD] and range for continuous data, unless specified otherwise). In summary tables for categorical data for which categories are defined on the eCRF, all categories will be presented as specified, even if the participant count within that category is zero.

In all the summary tables intervention MMRV lot 1 and MMRV lot 2 will be analyzed as pooled lots.

Unless otherwise specified, all data collected during the trial will be presented in listings for the ENR.

6.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the dose of study intervention and will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the date of study intervention then:

Study Day = (date of event – date of study intervention) + 1.

If the date of the event is prior to the date of study intervention then:

Study Day = (date of event – date of study intervention).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear as missing in the listings.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline.

6.3. Retests, Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries.

Listings will include all scheduled, and early termination discontinuation data.

6.4. Windowing Conventions

Allowed time window for each visit will be performed as mentioned in "Schedule of Activities", section 1.3 of protocol.

Table C: Intervals between Study Visits

Interval	Planned visit interval	Allowed interval range
Visit 1 → Safety call	1 to 2 days	1 to 3 days
Visit 1 → Visit 2	14 days	14 to 19 days

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Visit 1 → Visit 3	42 days	35 to 56 days
Visit 1→ Safety follow-up contact	180 days	180 to 201 days

Table D: Window convention

Assigned Study Day	Visit label as per protocol	Visit assigned
Day 1	Visit 1	Visit 1 (Day 1)
Day 2 to 3 (Day 1 + 1 to 3 days)	Safety Call	Safety Call (Day 2 – 3)
Day 15 (Day 1 + 14 to 19 days)	Visit 2	Visit 2 (Day 15)
Day 43 (Day 1 + 35 to 56 days)	Visit 3	Visit 3 (Day 43)
Day 181 (Day 1 + 180 to 201 days)	Safety Follow-up contact	Safety Follow-up (Day 181)

6.5. Statistical Tests

The default significant level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.6. Common Calculations

Geometric Mean Concentration (GMC):

Distributions of antibodies are generally skewed to the right (Nauta, 2010). Therefore, prior to any statistical analysis that assumes normally distributed observations, antibody titers or concentrations will be log10-transformed.

GMCs and their 95% CI are computed by exponentiating (base 10) the least squares mean and 95% CI of the log10 concentrations.

The GMC will be calculated using the following formula:

$$10^{\left(\frac{\sum_{i=1}^{n} \log 10(t_i)}{n}\right)}$$

Where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity concentrations.

Concentration below assay cut-off (i.e., <lower limit of quantification or < LLOQ) will be replaced by half the assay cut-off (LLOQ/2) for the purpose of GMC computation. Concentrations above the upper limit of quantification (ULOQ) will be replaced by the ULOQ value.

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 ≥ to the following threshold values:

- 116 mIU/mL for anti-measles
- 296 AU/mL for anti-mumps
- 24 IU/mL for anti-rubella

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.

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6.7. Software Version

All analyses will be conducted using SAS version 9.4.

7. STATISTICAL CONSIDERATIONS

7.1. Adjustments for Covariates and Factors to be Included in Analyses

The following factors will be used in the analyses: country. For details, refer to section 15.1 and 15.2. The model will include all groups as fixed categorical effects in the Analysis of Variance (ANOVA) model.

For the interim analysis an Analysis of Covariance (ANCOVA) model on log-transformed anti-measles, anti-mumps, anti-rubella and anti-gE with MMRVNS dose level will be used as covariate in addition to the indicator of investigational vaccine. Likewise, seroresponse will be analyzed using a logistic regression with the same covariate. The dose effect will be constrained to be positive.

7.2. Multicenter Studies

This study will be conducted by multiple investigators in multiple countries. The participants will be randomized to one of the 5 groups (refer to Table B: in section 3.1) which will be performed in a 2:2:2:1:1 ratio prior to intervention to provide approximately 200 enrolled participants per each MMRVNS group and 100 enrolled participants per each MMRV group (MMRV Lot 1 and MMRV lot 2).

7.3. Missing Data

Missing data (missing, incomplete or partial dates, AE measurement [including missing AE severity and relationship], prior and concomitant medications and death date) will be handled as per APPENDIX 2 of this

analysis plan.

Missing immunogenicity data will not be imputed. Concentration below assay cut-off (i.e., lower limit of quantification or < LLOQ) will be replaced by half the assay cut-off (LLOQ/2) for the purpose of GMC computation.

7.4. Examination of Subgroups

No subgroup analyses will be performed for this study. Some analysis will be repeated by country, further details will be included in the relevant sections.

8. Output Presentations

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics. Statistical output numbering will follow 'ICH E3 Structure and Content of Clinical Study Reports'.

9. Disposition and Withdrawals

All participants who are enrolled in the study (those who received a study intervention, had a blood draw before study intervention administration, or were randomized), i.e., those accounted for in the ENR, will be accounted for in this study.

9.1. Disposition

Participant disposition, withdrawals, and reasons for exclusion from each analysis set, including inclusion as well as exclusion criteria will be presented for the ENR. Specifically, the number of participants, vaccinated, completed the study, discontinued from the study and the reason for discontinuation will be summarized by study intervention for the ENR. Additionally, the number of participants returning for each visit for the ES will be presented. A summary of the number of participants that discontinued from the study due to Coronavirus Disease 2019 (COVID-19) will be presented.

A listing of the disposition for all participants with early withdrawal or discontinuation due to having COVID-19 related issues information will be provided.

9.2. Protocol Deviations

Protocol deviations (PDs) will be collected in a PD log, as detailed in the Protocol Deviations Management Plan (PDMP). All PDs will be assessed as either important or non-important. PDs will be reviewed by the sponsor, and their status confirmed by the time that all data are cleaned for the Final Analysis. A summary table presenting the number and percentage of participants with important PDs (i.e., those PDs associated to elimination from PPS) will be presented for participants in the ES. A listing of all PDs including an indicator of those excluded from the PPS and an indicator of COVID-19 causality will be provided.

9.2.1. Protocol Deviations Related To Study Conduct

A PD is any non-compliance with the clinical trial protocol, GCP, or protocol deviation guidelines requirements. The non-compliance may be either on the part of the participant, the site principal investigator (PI), the study site staff or the sponsor.

9.2.2. Protocol Deviations Related To Immunogenicity Analysis

Changes to the procedures or events, which may impact the quality of the immunogenicity data, will be considered significant PDs and will be described within the CSR. This includes any circumstances that could alter the evaluation of the immunogenicity results such as sample processing errors that lead to inaccurate immunogenicity results, and/or inaccurate dosing which could exclude them from the PPS. In addition, participants may also be eliminated from the PPS based on usage of certain concomitant medications or vaccines as described in Section 5.2.2 of the Protocol.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for ES and PPS. The following demographic and other baseline characteristics will be reported for this study:

- Age (years) – at the time of study intervention
- Sex
- Race (as per Clinical Data Interchange Standards Consortium [CDISC] categories)
- Ethnicity

Descriptive statistics (mean, median, standard deviation and range) will be presented for continuous variables and frequency counts and percentages for categorical variables.

Age category (preterm newborn infants (gestational age < 37 weeks), newborn (0-27 days), infant and toddlers (28 days – 23 months), children (2-11 years), adolescents (12-17 years), adults (18-64 years), 65-84 years and >=85 years) will be summarized by study intervention for ES.

CCI [redacted]

PPD [redacted] CCI [redacted]

The number of participants enrolled at each country will be summarized by study intervention.

No statistical testing will be carried out for demographic or other baseline characteristics.

11. GENERAL MEDICAL/VACCINATION HISTORY AND EXAMINATIONS

Medical/Vaccination History information will be summarized for the ENR.

- Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 27.0 or higher.
- Data captured on the "Medical History" page of the eCRF will be presented by System Organ Class (SOC) and Preferred Term (PT). Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History section of the eCRF, not the AE section.
- Vaccine history will be checked for each participant with the participant's parent/LAR.

A listing of medical/vaccination history data will be provided.

12. PRIOR, CONCOMITANT AND CO-ADMINISTERED VACCINATIONS

Prior, concomitant and co-administered vaccination will be coded with the current version of the World Health Organization Drug Dictionary.

- Prior vaccinations are vaccinations per protocol given to participants prior to the dosing of study intervention and are recorded on the eCRF.
- Concomitant vaccinations are defined as any vaccine that the participant is receiving as of the time of enrolment

or receives during the study (other than study interventions) as recorded on the "Concomitant Vaccination" page of the eCRF.

13. MEDICATIONS

The percentage of participants who started medications after study intervention will be presented by study intervention for the ES. Medications will be presented by Anatomical Therapeutic Chemical (ATC) classification and preferred drug name and by study intervention.

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e., concomitant.

- 'Prior' medications are medications which started prior to the dose of study intervention.
- 'Concomitant' medications are medications which started on or after the day of the administration of study intervention.

Further details are in Section 6.8 of the Protocol. Concomitant medications which started from Day 1 to Visit 3 blood sample will be presented in table summaries (Any, antipyretic action) and in listings for all medications.

14. STUDY INTERVENTION EXPOSURE

Exposure to study intervention will be presented for the ES. The date and time of study intervention administration will be taken from the eCRF "Exposure-MMRVNS vaccine/ProQuad vaccine" form. For dosing instructions and route, refer to Table 8 of the Protocol.

Data will also be presented in listings.

CCI [redacted]

PPD [redacted] CCI [redacted]

15. IMMUNOGENICITY OUTCOMES

15.1. Primary Immunogenicity

15.1.1. Primary Immunogenicity Variable(s) & Derivation(s)

The primary objective is to evaluate the immune response to the MMRVNS vaccine (formulated with different potencies) and the MMRV vaccine (pooled group) in terms of GMC at Day 43 for antibodies to measles, mumps, rubella and varicella. For the derivation of GMC refer to section 6.6.

15.1.2. Intercurrent Event Handling and Data Imputation for Primary Immunogenicity Variable(s)

Missing data will not be replaced.

15.1.3. Primary Analysis of Primary Immunogenicity Variable(s)

The primary immunogenicity endpoints of anti-measles, anti-mumps, anti-rubella and anti-gE antibody GMCs at Day 43 will be summarized by study intervention with their 95% CI derived considering log10-transformed concentrations are normally distributed with unknown variance for antibodies against each antigen. The distribution of antibody concentration for each antigen will be graphically presented by reverse cumulative curves per study intervention. The concentration below the assay cut-off will be assigned to half the cut-off for the purpose of GMC computation. This analysis will be based on the PPS and the ES. The analysis, for PPS only, will also be repeated split by country.

Table E: Assay cut-off

Component	Assay cut-off	Method
Anti-measles Antibody immunoglobulin (IgG)	29.082 mIU/mL	Multiplex Luminex based Immuno Assay
Anti-mumps Antibody IgG	189.240 AU/mL	
Anti-rubella Antibody IgG	1.916 IU/mL	
Anti-gE Antibody IgG	97 mIU/mL	ELISA

Abbreviations: ELISA = Enzyme-linked immunosorbent assay

An adjusted GMC and GMC ratio with 2-sided 95% CI for study intervention which is derived from an ANOVA model on log10 transformed antibody concentration adjusted for log-transformed pre-dose antibody concentration for each antigen. The country will be added as a covariate. Study intervention will be included in the model and group contrasts with associated 2-sided 95% CI will be exponentiated to obtain study intervention GMC ratios for antibodies against each antigen and will be based on the PPS.

The GMC ratio will be estimated along with its corresponding 2-sided 95% CI by exponentiating the least-squares means for the difference.

For the interim analyses, an ANCOVA model on log-transformed anti-measles, anti-mumps, anti-rubella and anti-gE with MMRVNS dose level will be used as covariate in addition to the indicator of investigational vaccine.

15.2. Secondary Immunogenicity

15.2.1. Secondary Immunogenicity Variables & Derivations

The secondary objective is to evaluate the immune response of MMRVNS vaccine (formulated with different potencies) and the MMRV vaccine (pooled group) in terms of seroresponse rates for antibodies to measles, mumps, rubella and varicella viruses at Day 43 and will be based on the PPS and ES.

15.2.2. Intercurrent Event Handling and Data Imputation for Secondary Immunogenicity Variable(s)

Missing data will not be replaced.

15.2.3. Analysis of Secondary Immunogenicity Variables

The percentage of participants with a seroresponse will be summarized by study intervention and corresponding 2-sided 95% exact CI will be reported based on Clopper and Pearson method (Clopper CJ, 1934) for each antigen. The analysis will also be repeated split by country. These summaries will be produced for PPS and ES.

The number and percentage of participants with a seroresponse at Day 43 for each antigen and 2-sided 95% CI on group difference in the seroresponse rate (MMRV pooled group – MMRVNS group [different potencies])- will be computed based on Miettinen and Nurminen method (Miettinen O., 1985) for PPS.

For interim analyses, seroresponse for each antibody will be analyzed using a logistic regression with MMRVNS potencies used as a covariate for PPS. The dose effect will be constrained to be positive.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the ES.

There will be no statistical comparisons between the study interventions for safety data.

Secondary Safety Endpoints:

- Solicited events
  - 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 intervention
  - 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 intervention
  - 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 intervention

- Unsolicited adverse events
  - Percentage of participants reporting unsolicited AEs during the 43-day period (day of administration and 42 following days) after the dose of study intervention

- Serious adverse events

CCI [redacted]

PPD [redacted] CCI [redacted]

- Percentage of participants reporting SAEs after the dose of study intervention up to the end of study

16.1. Adverse Events

Adverse Events will be coded using MedDRA central coding dictionary, Version 27.0 or higher. Adverse events will be described using frequency and percentage.

Adverse Events will be grouped by SOC and PT and summarized by study intervention at time of onset of the AE. The summary tables will present the number and percentage of total participants and number of events, by SOC and by PT for each study intervention.

For the summaries of AEs, participants who experience the same AE (in terms of the MedDRA SOC and PT) more than once will only be counted once for that event in the number of participants but all occurrences of the same event will be counted in the number of events.

See APPENDIX 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as pre-treatment or treatment-emergent (TEAE) due to missing or partial dates, the AE will be classified by the worst case; i.e., TEAE. TEAE are defined as AEs which commence on or after the time of the study intervention through to the study end. All AE summaries will be restricted to TEAEs only.

Listings of all AEs and SAEs leading to discontinuation from the study will be provided.

16.1.1. Solicited Adverse Events

Solicited events are recorded in electronic diaries. Duplicate entries are defined as records with identical participant ID, category, object of the observation, date and time of collection, result or finding in original units and evaluator. In case of duplicate records, the first record will be kept for analysis. The first record is determined by sequence number assigned in the SDTM dataset. In the case of duplicate entries with differing result, the worst case record will be kept for analysis.

In the event the electronic diary was started later than the day of vaccination, it remained open to record solicited events beyond the end of the solicited periods. Data beyond the solicited period will remain in the datasets but will not be used in the statistical analysis, since the solicited period is based on Study Day for the statistical analyses, see section 6.1.

For each study intervention and each solicited event, the incidence rates (frequencies and percentages) of vaccinated participants with solicited administration site events collected within 4 days (Day 1 to Day 4), systemic events (drowsiness and loss of appetite) collected within 4 days (Day 1 to Day 4) and systemic events (fever, measles/rubella-like rash, varicella-like rash and other rash [not measles/rubella-like rash or varicella-like rash]) collected within 43 days (Day 1 to Day 43) will be summarized (percentage of vaccinated participants with each of any, grade 2 or 3, related, grade 3 leading to medical attention). The completeness defined as the percentage of vaccinated participants who documented presence/absence of each event as well as the daily prevalence of each symptom among vaccinated participants who documented presence /absence of the event on that day will be provided. These will also be summarized for each country.

The duration of each solicited event, in days, will be summarized using descriptive statistics (n, mean, standard

deviation, median and range) for each study intervention. The duration will be calculated from the first date that the symptom was reported up to the last date the symptom was reported ignoring any dates when the symptom was absent or was not recorded:

Last date symptom recorded – first date symptom recorded + 1

The number of solicited events still ongoing at the end of the solicited period will be summarized by study intervention by maximum intensity (any, grade 2-3 and grade 3).

Table F: Solicited events

Solicited administration site events	Solicited systemic events
Pain at Injection Site	Drowsiness
Redness at Injection Site	Loss of appetite
Swelling at Injection Site	Fever
	Measles/rubella-like rash
	Varicella-like rash
	Other rash (not measles/rubella-like rash or varicella-like rash)

Table G: Intensity Scales for Solicited Events in Children (4 to 6 years of Age)

Adverse Event	MedDRA Lower Level Term	Intensity Grade	Parameter
Pain at Injection Site	Administration site pain (10058049)	0	None
		1	Mild: Minor reaction to touch
		2	Moderate: Cries/protests on touch
		3	Severe: Cries when limb is moved/spontaneously painful

CCI [redacted]

PPD [redacted] CCI [redacted]

Adverse Event	MedDRA Lower Level Term	Intensity Grade	Parameter
Redness at Injection Site	Administration site erythema (10074796)	0	None
		1	> 0 - ≤ 5 mm
		2	> 5 - ≤ 20 mm
		3	> 20 mm
Swelling at Injection Site	Administration site swelling (10075107)	0	None
		1	> 0 - ≤ 5 mm
		2	> 5 - ≤ 20 mm
		3	> 20 mm
Fever*	Pyrexia (10037660)	0	<38.0°C (100.4°F)
		1	≥ 38.0°C (≥ 100.4°F) - ≤ 39.0°C (≥ 102.2°F)
		2	> 39.0°C (≥ 102.2°F) - ≤ 39.5°C (≥ 103.1°F)
		3	> 39.5°C (≥ 103.1°F)
Measles/rubella-like rash	Maculopapular rash (10037898)	0	None
		1	1-25 lesions
		2	26-50 lesions
		3	≥51 lesions
Varicella-like rash	Rash vesicular (10052566)	0	None
		1	1-25 lesions
		2	26-50 lesions
		3	≥51 lesions
Other rash (not measles/rubella-like rash or varicella-like)	Generalized rash (10049201)	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 care and would cause the parent(s)/LAR(s) to seek medical advice

CCI [redacted]

PPD [redacted] CCI [redacted]

Adverse Event	MedDRA Lower Level Term	Intensity Grade	Parameter
Drowsiness	Drowsiness (10013649)	0	Behaviour as usual
		1	Mild: Drowsiness easily tolerated
		2	Moderate: Drowsiness that interferes with normal activity
		3	Severe: Drowsiness that prevents normal activity which prevents normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at school/day
Loss of appetite	Decreased appetite (10061428)	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

* Temperature will be analyzed in 0.5°C increments from ≥ 38.0°C (≥ 100.4°F)

The number and percentage of participants per study intervention reporting unsolicited adverse events with MedDRA preferred terms that are synonymous with solicited adverse events, and starting after the end of each solicited period, will be summarized by severity (mild, moderate or severe). If a participant experiences an event on more than one occasion, the maximum intensity will be reported. The following table shows the corresponding MedDRA preferred terms or higher level terms that will be selected from the unsolicited adverse events for this analysis.

Table H: Unsolicted adverse events that are synonymous with soicted adverse events

Solicited Adverse Event	MedDRA PT/HLT

Pain at injection site	Administration site pain (PT)
Redness at injection site	Administration site erythema (PT)
Swelling at injection site	Administration site swelling (PT)
Drowsiness	Somnolence (PT)
Loss of appetite	Decreased appetite (PT)
Fever	Pyrexia (PT)
Rash (all types combined)	Rashes, eruptions and exanthems NEC (HLT)

16.1.1.1. eCOA Compliance

Overall electronic diary (eCOA) compliance (across all eCOAs and all participants) for the study is calculated as:

$$\frac{Total\ number\ of\ complete\ eCOAs}{(Expected\ number\ of\ complete\ eCOAs\ per\ participant\ \times\ Total\ number\ of\ particpants)}$$

Where the expected number of complete eCOAs per participant is defined as 43, the number of days in which the eCOA is expected to be completed. This definition will also apply to participants who discontinue the study early.

An eCOA is considered complete if there is no missing data within the assessment. Solicited event data reported by the investigator will not contribute to eCOA compliance. On days when the option to select "no symptoms to report" is available and there are no occurrences of the symptoms solicited for on that day, an eCOA will be considered

complete if the temperature result is available.

A participant is considered to be compliant with their eCOA if at least 80% of their eCOA are complete, i.e, a participant is compliant if they meet the following criteria:

$$\frac{Total\ number\ of\ complete\ eCOAs}{Expected\ number\ of\ complete\ eCOAs} \times 100 \geq 80\%$$

The overall compliance, and the number of participants who are 0 - <50% compliant, 50 - <80% compliant and ≥80% compliant with eCOA assessments will be summarized.

16.1.2. Unsolicited AEs, including SAEs

For each study intervention, the incidence rates (frequencies and percentages) of participants/events with unsolicited AEs (any, related, grade 3, leading to medical attention and related grade 3 respectively), including serious AE, occurring within 43-days (Days 1-43) post-dose of study interventions will be presented by SOC and PT. The incidence rates of participants/events with any unsolicited AEs will be repeated and summarized by country.

16.1.2.1. Relationship to Study intervention

Causality, as indicated by the Investigator is classed as "related" and "not related" to MMRVNS/MMRV. A "related" AE is defined as an AE with a relationship to study intervention as "related". If a participant reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study intervention will be used in the corresponding relationship summaries for each study intervention.

16.1.3. Unsolicited AEs, Excluding SAEs

For each study intervention, the incidence rates (frequencies and percentages) of participants/events with unsolicited

AEs, excluding serious AE, occurring within 43-days (Days 1-43) post-dose of study interventions will be presented by SOC and PT.

Immediate unsolicited AE is defined as an unsolicited AE that occurred within 30 minutes of vaccination. The immediate unsolicited AE flag is derived as follows: If the AE does not occur on the day of vaccination the flag is set to 'N'. Otherwise, if the AE occurs on the day of vaccination but happened before the vaccination then the flag is also set to 'N'. Otherwise, if the AE occurs on the day of vaccination and AE DATETIME minus Vaccination DATETIME is <= 30 minutes then set the flag to 'Y'. Otherwise, if the AE occurs on the day of vaccination and did not happen before the vaccination but either the time of vaccination or time of the AE is missing, then flag is set to 'U'. If the time of the AE is set to "00:00", then it will be assumed to be unknown and will be handled as missing. Immediate unsolicited AEs will be flagged in the listings.

16.1.4. Serious AEs

For each study intervention, the incidence rates (frequencies and percentages) of participants with SAE occurring post-dose of study interventions will be presented by SOC and PT. Similar tabulation will be done for SAE with causal relationship to vaccination as assessed by the investigator; for fatal SAE and for causally related fatal SAE. Serious AEs will be recorded on the "Expedited Adverse Events" page of the eCRF. The incidence rates of participants with serious AEs will be repeated and summarized by country.

Listings of AEs and SAEs leading to discontinuation of study will be provided.

17. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Physical Examination

CCI [redacted]

PPD [redacted] CCI [redacted]

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

18. REFERENCES

Clopper CJ, P. E. (1934). The use of confidential or fiducial limits illustrated in the case of the binomial.

Biometrika, 26:404-413.

Nauta, J. (2010). *Statistics in Clinical Vaccine Trials.* Heidelberg: Springer.

Miettinen O., N. M. (1985). Comparative analysis of 2 rates. . *Statistics in Medicine*, 213-226.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according to the following IQVIA Output Conventions

Document Headers
All TFL is to include the following header:

GSK Vaccines Vaccine: MMRVNS and MMRV Study 217715 (MMRVNS 20-001) - *DELIVERY DESIGNATION*

where delivery designation is the name of the current delivery, e.g., DRY-RUN, FINAL ANALYSIS REPORT, etc

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-dd Thh:mm:ss.

Spelling Format

English US

Presentation of Intervention Groups

For outputs, intervention groups will be represented as follows and in the given order:

Intervention Group	For Tables and Graphs	For Listings
MMRV(H)NS	MMRV(H)NS	MMRV(H)NS

CCI [redacted]

PPD [redacted] CCI [redacted]

Intervention Group	For Tables and Graphs	For Listings
MM(H)RVNS	MM(H)RVNS	MM(H)RVNS
M(L)M(L)R(L)V(L)NS	(MMRV)(L)NS	(MMRV)(L)NS
MMRV_Lot1	MMRV	MMRV Lot1
MMRV_Lot2		MMRV Lot2

Presentation of Visits

For outputs, visits will be represented as follows and in that order:

Short Name	Long Name
Visit 1	Visit 1 (Day 1)
Visit 2	Visit 2 (Day 15)
Visit 3	Visit 3 (Day 43)
Safety Follow-up	Safety Follow-up (Day 181)

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized study intervention (or intervention received if it's a safety output), first by active dose [by ascending dose group] and then control

- Center-participant ID,
- Date (where applicable).

Decimal places

Decimal places for categorical data

- For percentages one decimal will be displayed
- Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

- Decimal places for Demographic and baseline characteristics will be as follows:

The mean, median, and standard deviation for continuous baseline characteristics (age) will be presented with one decimal.

- Serological Summary Statistics

The number of decimals used when displaying geometric mean concentrations (GMC) and their confidence limits is shown in the following table:

GMC value	Number of decimals
<0.1	3

CCI [redacted]

PPD [redacted] CCI [redacted]

GMC value	Number of decimals
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

- When multiple categories of GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e. the one with the higher number of decimals). For example, if GMC values of <0.1 appear in the same table as values of >=0.1 and <10 3 decimals should be displayed for both.

- GMC ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

When partially completed dates (i.e. with missing day or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

The following exceptions apply:

CCI [redacted]

PPD [redacted] CCI [redacted]

- Adverse event start dates with missing day:

  - If the event starts in the same month as the study intervention, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match study dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the study intervention given during that month.

- Adverse event start dates with missing day and month:

  - If the event starts in the same year as study intervention, the contents of AE.AESTRTPT (the flag indicating if the event occurred before or after vaccination) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the study intervention given during that year. If 'before vaccination' is selected, the imputed date will be one day before the) study intervention given during that year.

If the imputed start date falls after the event end date, the imputed start date will be adjusted to be the end date minus 1 day.

All other cases of incomplete AE or concomitant medication/vaccination start date will follow the standard rules above.

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, assign as prior If start date >= study med start date and start date <= end of intervention, assign as concomitant
Partial	Known/Partial/ Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If start date < study med start date, assign as prior If start date >= study med start date and start date <= end of intervention, assign as concomitant
Missing	Known/Partial/ Missing	If start date < study med start date, assign as prior