# TITLE PAGE

**Protocol Title:** A phase II, observer-blind, randomized, controlled study to evaluate the immunogenicity and safety of a varicella vaccine at various potencies compared with *Varivax*, as a first dose, administered in healthy children in their second year of life

**Protocol Number:** 217212 (VNS 20-006)

**Amendment Number**: 3.0

**Product:** Investigational varicella vaccine

**Short Title:** A study on the immune response and safety of various potencies of an investigational chickenpox vaccine compared with a marketed chickenpox vaccine, given to healthy children 12 to 15 months of age

**Study Phase:** II

**Sponsor Name:** GlaxoSmithKline Biologicals SA (GSK)

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

**ClinicalTrials.gov Identifier:** NCT05084508

**EudraCT Number:** 2022-001910-21

**Date of Original Protocol:** Final Version 2: 12 July 2021

**Date of Protocol Amendment 1.0:** 08 October 2021

**Date of Protocol Amendment 2.0:** 15 November 2021

**Date of Protocol Amendment 3.0:** 18 May 2022

**Sponsor Signatory:**

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

PPD

**Md Ahsan Habib, MBBS, MIPH**
**Clinical and Epidemiology 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 | Date | Substantial | Region |
|---|---|---|---|
| Amendment 3.0 | 18-May-2022 | Yes | Global |
| Amendment 2.0 | 15-Nov-2021 | Yes | Global |
| Amendment 1.0 | 08-Oct-2021 | Yes | Global |
| Original Protocol (Final Version 2) | 12-Jul-2021 | - | - |

## Amendment 3.0 (18-May-2022)

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

## Overall Rationale for the Amendment:

The protocol was amended primarily to reflect the expansion of the study to the countries other than the United States of America (US). Outside of the US, participants will have the same vaccination schedule but will be co-administered *Prevnar 13* only if the pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule. Also, the storage conditions for *Varivax* were updated with the country-specific details, and corrections were made to the temperature excursions for study vaccines. Additionally, this amendment conditionally allowed administration of a second dose of *Varivax* and/or *Havrix* in non-US countries (not part of the study procedures).

**Table 2 Description of the Most Important Changes in Amendment 3.0**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1. Synopsis<br>1.3. Schedule of Activities<br>2.1. Study Rationale<br>5.1. Inclusion Criteria | Updated the text to reflect the following (in **bold**; in the exact or similar wording):<br>In this study, all participants recruited in the **US** will be co-administered with a measles, mumps and rubella vaccine (*M-M-R II*, also called ***M-M-RVaxPro* in countries outside the US,** and hereafter designated as MMR), a hepatitis A vaccine (*Havrix*) and a 13-valent pneumococcal conjugate vaccine (*Prevnar 13*).<br>**Participants recruited outside of the US will be co-administered with MMR, *Havrix*, and in some countries, with *Prevnar 13*. Outside the US, *Prevnar 13* will only be administered in countries where pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule.** | To reflect addition of non-US sites to the study and clarify the inclusion criteria applicable to the participants at non-US sites.<br>To note that in some countries, there can be a different name for the MMR vaccine. |
| 1.2. Synopsis<br>1.3. Schedule of | **At the end of the study or shortly after the study, depending on the vaccines' availability, GSK will provide a second dose of** | To allow administration of the |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Activities<br>2.1. Study Rationale | ***Varivax* and/or *Havrix* to participants enrolled in non-US countries if local health departments do not routinely provide varicella and/or hepatitis A vaccine. Study participants who do not achieve the pre-specified seroresponse threshold criteria will be re-vaccinated with a dose of *Varivax*.** | second dose of the varicella or hepatitis A vaccine (not part of study procedures). |
| 6.2. Preparation/Handling/Storage/Accountability | Added the text (in **bold**):<br>***Varivax* will be stored at −15°C to −30°C (+5°F to −22°F) in the US and other countries with frozen formulation and at +2°C to +8°C (+36°F to +46°F) in the rest of the world. (Note: refrigerated *Varivax* vaccine will be used at non-US sites, while frozen *Varivax* vaccine will be used at sites in the US and other countries with frozen formulation.)** | To specify the storage conditions for the study vaccine at the US and non-US sites. |
| Throughout the protocol where applicable | Removed the statements implying the study will be conducted in the US only; made updates regarding other countries to the scientific rationale for study design; mentioned Independent Ethics Committee(s) as entities overseeing the ethics conduct of the study besides Institutional Review Boards; mentioned the non-US-specific regulatory requirements the study will be performed in accordance with. | To reflect addition of non-US sites to the study and note applicable administrative changes to the conduct of the study. |

The detailed description of changes (i.e., added/removed text) and minor updates is provided in Appendix 5.

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# 1.0 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:** A phase II, observer-blind, randomized, controlled study to evaluate the immunogenicity and safety of a varicella vaccine at various potencies compared with *Varivax*, as a first dose, administered in healthy children in their second year of life.

**Short Title:** A study on the immune response and safety of various potencies of an investigational chickenpox vaccine compared with a marketed chickenpox vaccine, given to healthy children 12 to 15 months of age.

**Rationale:** Varicella (chickenpox) is an acute, highly contagious infectious disease caused by the varicella zoster virus. Safe and effective varicella vaccines have shown to have significant global and national public health impact when implanted in national immunization plans, e.g., as in the United States of America (US). GlaxoSmithKline Biologicals SA (GSK) is developing a candidate varicella vaccine (VNS vaccine). The main purpose of this study is to demonstrate the immunogenicity of the investigational VNS vaccine in 3 potencies compared with commercially available Merck's varicella vaccine, *Varivax* (hereafter designated as VV vaccine), when given as a first dose to children 12 to 15 months of age. In this study, all participants recruited in the US will be co-administered with a measles, mumps and rubella vaccine (M-M-R II, also called *M-M-RVaxPro* in countries outside the US, and hereafter designated as MMR), a hepatitis A vaccine (*Havrix*) and a 13-valent pneumococcal conjugate vaccine (*Prevnar 13*). Participants recruited outside of the US will be co-administered with MMR, *Havrix*, and in some countries, with *Prevnar 13.* Outside the US, *Prevnar 13* will only be administered in countries where pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule. At the end of the study or shortly after the study, depending on the vaccines'availability, GSK will provide a second dose of *Varivax* and/or *Havrix* to participants enrolled in non-US countries if local health departments do not routinely provide varicella and/or hepatitis A vaccine. Study participants who do not achieve the pre-specified seroresponse threshold criteria will be re-vaccinated with a dose of *Varivax*.

**Objectives, Endpoints, and Estimands:** The study will evaluate the immune response of the investigational VNS vaccine (formulated at 3 different potencies) and the VV vaccine in terms of geometric mean concentration (GMC) and in terms of seroresponse rate (percentage of participants for whom the post-dose anti-glycoprotein E [gE] antibody concentration is ≥300 mIU/mL) to gE. The study will also evaluate the safety and the reactogenicity (incidence of solicited adverse events [AEs], unsolicited AEs, and serious adverse events [SAEs]) following the administration of the VNS and VV vaccines.

**Overall Design:** This will be a phase II, observer-blind, randomized, multicenter controlled study with 5 parallel intervention groups of healthy children aged 12 to 15 months at the time of intervention. Participants will be randomized to receive a single dose of an investigational varicella vaccine (3 groups each receiving one of the 3 different vaccine potencies [a low, medium, and high potency of the VNS vaccine, respectively]) or a single dose of a comparator licensed varicella vaccine (2 groups each receiving one of the 2 different lots of the VV vaccine, which will be pooled for all analyses). All participants in the US will be co-administered with *MMR*, *Havrix,* and *Prevnar 13* vaccines. Participants recruited outside of the US will be co-administered with *MMR*, *Havrix*, and in some countries, with *Prevnar 13*. Outside the US,

*Prevnar 13* will only be administered in countries where pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule. If *Prevnar 13* is to be administered, participants are required to have previously received the primary series of pneumococcal conjugate vaccine in their first year of life with last dose at least 60 days prior to study entry.

Randomization to one of the 5 groups will be performed in a 2:2:2:1:1 ratio prior to intervention. There will be 3 study visits, at Day 1 (intervention), Day 15 (virtual or in-person), and Day 43, as well as 1 safety call and 1 safety follow-up contact, at Day 2-3 and Day 181, respectively.

**Number of Participants:** Approximately 800 participants will be randomly assigned to the 5 study groups to provide approximately 200 enrolled participants per each VNS group and 100 enrolled participants per each VV group. Approximately 90% of the enrolled participants are expected to be included in the Per Protocol Set (PPS) and evaluated for immunogenicity.

**Intervention Groups and Duration:**

**VNS_Low:** VNS low potency vaccine, MMR*, *Havrix,* and *Prevnar 13***

**VNS_Med:** VNS medium potency vaccine, MMR*, *Havrix,* and *Prevnar 13***

**VNS_High:** VNS high potency vaccine, MMR*, *Havrix,* and *Prevnar 13***

**VV_Lot1:** VV vaccine Lot 1, MMR*, *Havrix,* and *Prevnar 13***

**VV_Lot2:** VV vaccine Lot 2, MMR*, *Havrix,* and *Prevnar 13***

**M-M-R II* or *M-M-RVaxPro*, depending on the country.

***Prevnar 13* will only be administered to participants enrolled in the US and in countries where pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule.

**Statistical Methods:** Three analyses sets will be used in this study, the Enrolled Set, the Exposed Set (ES), and the PPS. The intercurrent medical conditions that may lead to elimination from the PPS will be confirmed immunodeficiency conditions, or development of varicella or herpes zoster in the interval between study intervention administration and the collection of the blood specimen for immunogenicity at Visit 3. The immunogenicity analyses will be based on the PPS. The statistical analyses in this study will be descriptive. The study includes 2 immunogenicity objectives (one primary and one secondary) and one safety objective. The GMCs will be summarized by group with their 95% confidence interval (CI) derived considering log-transformed anti-gE antibody concentrations are normally distributed with unknown variance. The seroresponse rates to gE will be summarized by group with their 95% CIs. The safety analyses will be based on the ES.

**Data Monitoring Committee:** An Independent Data Monitoring Committee comprising of clinical experts and an independent biostatistician will perform periodic safety reviews of the unblinded study data.

## 1.2 Schema

See Figure 1 in Section 4.1.

## 1.3 Schedule of Activities

### Table 3 Schedule of Activities

| **Age** | **12-15 months of age at the time of study intervention administration** | | | | | **Notes** |
|---|---|---|---|---|---|---|
| **Type of contact** | **Visit 1** | **Safety call** | **Visit 2*** | **Visit 3** | **Safety follow-up contact** | |
| **Time points** | **Day 1** | **Day 2-3** | **Day 15** | **Day 43** | **Day 181** | |
| Informed consent | ● | | | | | See Appendix 2 for details |
| Check inclusion/exclusion criteria | ● | | | | | See Section 5.1 and Section 5.2 for details |
| Collect demographic data | ● | | | | | See Section 8.2.1.1 for details |
| Medical history | ● | | | | | See Section 8.2.1.1 for details |
| Vaccination history (protocol-specific vaccines including pneumococcal conjugate vaccine **) | ● | | | | | See Section 8.2.1.1 for details<br>See Section 5.1 for details |
| Physical examination | ● | | | | | See Section 8.2.1.1 for details |
| Randomization | ○ | | | | | See Section 6.3.2 for details |
| **Study interventions** | | | | | | See Appendix 1 for the definition |
| Check contraindications, warnings and precautions to study intervention administration | ○ | | | | | See Section 8.2.1.2 for details |
| Check criteria for temporary delay for enrollment and study intervention administration | ● | | | | | See Section 5.5 for details |
| Study group and treatment 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 (VNS vaccine/VV vaccine, MMR, *Havrix*, and *Prevnar 13***) administration | ● | | | | | Study participants who do not achieve the pre-specified seroresponse threshold criteria will be re-vaccinated with a dose of *Varivax* |
| Recording of administered study treatment number | ● | | | | | |

| **Age** | **12-15 months of age at the time of study intervention administration** | | | | | **Notes** |
|---|---|---|---|---|---|---|
| **Type of contact** | **Visit 1** | **Safety call** | **Visit 2*** | **Visit 3** | **Safety follow-up contact** | |
| **Time points** | **Day 1** | **Day 2-3** | **Day 15** | **Day 43** | **Day 181** | |
| Distribute eDiaries/download the app | ○ | | | | | An eDiary/personal electronic device application (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. See Appendix 4 for details |
| Second dose of *Varivax* and/or *Havrix* | | | | | x | At the end of the study or shortly after the study, depending on the vaccines' availability, GSK will provide a second dose of *Havrix* and/or *Varivax* in countries where they are not routinely provided. The administration of the second dose of *Havrix* and *Varivax* is not part of the study procedures, however, the administration of the second dose (or the date of the planned visit for administration) should be recorded in the eCRF. |
| **Laboratory assessment** | | | | | | |
| Blood sampling for antibody determination (~3 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 9.3 for more information |
| Phone contact for safety follow-up | | ● | | | ● | Or any other convenient procedure |
| Recording of solicited administration site events from Day 1-4 post study intervention administration | ○ | ○ | | | | Only events following the administered dose of VNS vaccine or VV vaccine will be solicited |
| Safety follow-up with clinical staff to review post-vaccination safety data | | | ● | | | |
| Recording of solicited systemic events (drowsiness, loss of appetite and irritability) from Day 1-15 post study intervention administration | ○ | ○ | ○ | | | See Section 8.3 and Appendix 4 |

| **Age** | **12-15 months of age at the time of study intervention administration** | | | | | **Notes** |
|---|---|---|---|---|---|---|
| **Type of contact** | **Visit 1** | **Safety call** | **Visit 2*** | **Visit 3** | **Safety follow-up contact** | |
| **Time points** | **Day 1** | **Day 2-3** | **Day 15** | **Day 43** | **Day 181** | |
| Recording of solicited systemic events (fever, varicella-like rash [including injection site varicella-like rash] and general rash [not varicella-like]) from Day 1-43 post study intervention administration | ○ | ○ | ○ | ○ | | See Section 8.3 and Appendix 4 |
| Recording of non-serious AEs from Day 1-43 post study intervention administration | ● | ● | ● | ● | | See Section 8.3 and Appendix 4 |
| eDiary/app completion reminder | | ● | | | | |
| Review of eDiaries/app data | | ○ | ● | ● | | |
| Return of eDiaries/uninstall or disable the app | | | | ○ | | See Section 8.5 for details |
| Recording of SAEs | ● | ● | ● | ● | ● | See Section 8.3 for details and Appendix 4 for the definition |
| Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine | ● | ● | ● | ● | ● | The collection and reporting periods start once the participant's parent(s)/LAR(s)'s informed consent is obtained |
| Study conclusion | | | | | ● | See Section 4.3 for the definition. |

AE = adverse event; App = application; eDiary = Electronic Diary; gE = glycoprotein E; LAR = legally acceptable representative; MMR = *M-M-R II* or *M-M-RVaxPro*; SAE = serious adverse event;

VNS vaccine = investigational vaccine; VV vaccine = comparator vaccine (*Varivax*); MMR, *Havrix*, and *Prevnar 13* = co-administered vaccines.

Notes:

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

** *Prevnar 13* will only be administered to participants in the United States and in the countries where pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule.

● 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.

[x] is used to indicate a procedure (that is not part of the study) that requires documentation in the individual eCRF

Refer to Table 4 for allowed intervals between study visits.

Refer to the Study Reference Manual /pharmacy manual for the volume of the vaccine after reconstitution.

## Table 4 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 |
| Visit 1→Visit 3 | 42 days | 35 to 56 days |
| Visit 1→ Safety follow-up contact | 180 days | 180 to 201 days |

*Number of days between the visits.

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

Varicella (i.e., chickenpox) is an acute, highly contagious infectious disease caused by the varicella zoster virus, which typically affects children under 10 years of age. Safe and effective varicella vaccines to prevent varicella have shown to have significant global and national public health impact when implanted in national immunization plans, e.g., as in the United States of America (US) and many other countries worldwide.

GlaxoSmithKline Biologicals SA (hereafter designated as GSK) is developing a candidate varicella vaccine (VNS vaccine). The main purpose of this study is to demonstrate the immunogenicity of the investigational VNS vaccine in 3 potencies (designated as VNS_Low vaccine, VNS_Med vaccine, and VNS_High vaccine), when compared with the commercially available Merck's varicella vaccine, *Varivax* (designated as VV vaccine), when given as a first dose to children 12 to 15 months of age. In order to obtain more representative data on the comparator, participants enrolled in the VV group will be randomized to 2 different lots (designated as VV_Lot1 and VV_Lot2). Throughout the study, the VV lots will be analyzed as pooled lots.

In addition to assessing the immunogenicity of both varicella vaccines, this study intends to also generate safety data in the participants.

All participants recruited in the US will be co-administered with a measles, mumps, rubella vaccine (*M-M-R II*, hereafter designated as MMR), a hepatitis A vaccine (*Havrix*) and a 13-valent pneumococcal conjugate vaccine (*Prevnar 13*). Participants recruited outside of the US will be co-administered with an MMR vaccine (*M-M-R II* or *M-M-RVaxPro* depending on the country)**,** *Havrix*, and in some countries, with *Prevnar 13*. Outside the US, *Prevnar 13* will only be administered in countries where pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule.

At the end of the study or shortly after the study, depending on the vaccines' availability, GSK will provide a second dose of *Varivax* and/or *Havrix* to participants enrolled in non-US countries if local health departments do not routinely provide varicella and/or hepatitis A vaccine. Study participants who do not achieve the pre-specified seroresponse threshold criteria will be re-vaccinated with a dose of *Varivax.*

## 2.2 Background

Varicella is characterized by fever and a generalized, itchy, vesicular rash. It is commonly regarded as a mild childhood illness. However, serious complications such as secondary bacterial

infection and pneumonia from varicella infections can occur, leading to hospitalizations and in rare cases even to death [CDC, 2015].

Universal mass vaccination against varicella is implemented in several countries [WHO, 2014; CDC, 2015]. It has led to a decrease in varicella morbidity (cases and hospitalizations) and mortality (deaths) [Wagenpfeil, 2004; Siedler, 2010; CDC, 2018].

GSK's candidate VNS vaccine strain has been derived from an Oka varicella strain. Of the varicella strains investigated in preclinical studies, only the Oka strain was considered suitable for vaccine production by the World Health Organization (WHO). The vaccines containing this strain were developed and evaluated in healthy and immunocompromised adults, adolescents and children by several pharmaceutical companies. The VNS vaccine is intended for active immunization for the prevention of varicella in healthy individuals of 12 months of age and older. The VNS vaccine has never been administered to humans.

Whereas there are no safety and effectiveness data available for the candidate VNS vaccine, this vaccine is expected to have a similar safety and efficacy profile as the 2 most widely used varicella vaccines containing an Oka varicella strain (Merck's *Varivax* and GSK's *Varilrix* vaccines). The summaries of the currently available clinical data on these vaccines are provided in the current Investigator's Brochure (IB).

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

The investigational VNS vaccine is expected to have a benefit-risk profile similar to Merck's *Varivax* and GSK's *Varilrix* vaccines. Detailed information about the expected risks and reasonably expected adverse events (AEs) of these 2 licensed varicella vaccines are summarized in the current IB. No significant safety concerns have been identified in clinical trials and during post-marketing use of these vaccines.

The most common currently known AEs following administration of varicella vaccines are local reactions, such as pain, soreness, erythema, and swelling. Based on the information from the manufacturers' clinical trials of varicella vaccines, local reactions are reported by 19% of children. These local adverse reactions are generally mild and self-limited. A varicella-like rash at the injection site is reported by 3% of children. A median of 2 lesions have been present. These lesions generally occur within 2 weeks and may be maculopapular rather than vesicular. A generalized varicella-like rash is reported by 4% to 6% of recipients of the varicella vaccine, with an average of 5 lesions. Most of these generalized rashes occur within 3 weeks and may be mainly maculopapular. Systemic reactions are not common. Fever within 42 days of vaccination is reported by 15% of children. The majority of these episodes of fever have been attributed to concurrent illness rather than to the vaccine. Varicella vaccine is a live virus vaccine and may

result in a latent infection, similar to that caused by wild varicella virus. Consequently, zoster caused by the vaccine virus has been reported [CDC, 2015] but rarely so.

Additional risks may be associated with the co-administered vaccines, MMR, *Havrix*, and *Prevnar 13*. These vaccines are widely used in the US and some other countries per routine pediatric immunization schedule and may cause expected and reasonable AEs. Refer to the package inserts or prescribing information for information regarding the summary of adverse reactions of MMR, *Havrix*, and *Prevnar 13*.

During this study of the candidate VNS vaccine, there may also be risks related to the blood sampling (e.g., bruising and pain at the blood draw site).

### 2.3.2 Risk Mitigation Strategies

For the safety of the participants, the protocol has incorporated various risk mitigation measures, including 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.

All study activities at the study center will be performed by trained clinical staff authorized by the study investigator. The attendance of the study participants to in-person study visits is expected to pose risks that do not extend the risks associated with clinic visits for routine immunization of children 12 to 15 months of age.

After the vaccination, participants will be observed for at least 30 minutes, with medical attention available in case of anaphylaxis.

The burden of the study for the participant will be minimized as much as possible. For taking blood samples, 3 attempts at most should be performed. If the investigator/designee is not successful after the third attempt, the investigator/designee will make no further attempts. A local numbing cream or patch will also be offered at the discretion of the investigator prior to blood sampling, to minimize pain when blood samples are drawn.

The blinded monitoring of study data will be performed by the GSK's designee/Contract Research Organization (IQVIA) (see study administrative structure in Appendix 2 [Table 12]). Additional unblinded safety monitoring will be performed by an Independent Data Monitoring Committee (IDMC). 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 non-serious AEs) (see Section 8.2.3). In addition, for the first 200 study participants through their Day 43 follow-up, the following criteria would be applied, that would result in a pause in study activities, including dosing and enrollment:

a. Any death considered at least possibly related to vaccination (refer to Section 8.3.3 for expedited reporting)

b. ≥1 participant with SAE(s) considered at least possibly related to vaccination (refer to Section 8.3.3 for expedited reporting)

c. ≥2 participants with the same or similar Grade 3 unsolicited adverse events (AE) considered to be at least possibly related to vaccination, (refer to Section 8.3.1 for diligent reporting of Grade 3 unsolicited AEs at each contact/visit)
Note: "similarity" of the events will be based on medical judgment.

An enrollment pause is also foreseen for the first IDMC review after 200 participants (approximately 50 participants in each group, considering pooled VV groups) are enrolled and vaccinated. The analysis will take place once all 200 participants have returned for their Day 43 visit (Visit 3) or have withdrawn from the study, within the allowed interval for the visit. A positive outcome of the IDMC review will be a pre-requisite for the continuation of the study.

GSK/IQVIA will immediately notify the investigators if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), European Union (EU) CTR, and applicable regulatory requirements. Aspects of the study concerned with the investigational medicinal products will meet the requirements of EU – Good Manufacturing Practice, as applicable.

### 2.3.3 Benefit Assessment

By receiving the investigational VNS vaccine or the comparator vaccine *Varivax,* the participants are expected to be protected against varicella.

By receiving the co-administered vaccines MMR*, Havrix*, and *Prevnar 13* [if applicable] vaccines), the participants are expected to be protected against measles, mumps and rubella (*MMR*), hepatitis A (*Havrix*) and pneumococcal infections (*Prevnar 13*, if applicable).

All participants will undergo a physical examination at the first study visit; these evaluations, made by skilled and trained clinical staff, may potentially provide participants' parent(s)/legally acceptable representatives (LAR[s]; see the definition in Appendix 1) with valuable knowledge about the participant's health. In case the study staff discovers any medical condition, the participant may be referred to the local healthcare system.

### 2.3.4 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize possible risks to the participants in this study, the potential risks associated with the study intervention(s) and study assessments are balanced by the potential benefits that may be provided to the participants.

# 3.0 OBJECTIVES AND ENDPOINTS

## Table 5 Study Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the immune response of VNS vaccine (formulated with different potencies) and VV vaccine in terms of geometric mean concentration at Day 43 | • Anti-gE antibody concentration at Day 43 |
| **Secondary** | |
| • To evaluate the immune response of VNS vaccine (formulated with different potencies) and VV vaccine in terms of seroresponse rate* at Day 43 | • Seroresponse to gE at Day 43 |
| • To evaluate safety and reactogenicity following administration of VNS and VV vaccines | **Solicited events**<br>• Percentage of participants reporting each solicited administration site event in terms of injection site redness, pain and swelling within 4 days (Day 1 to Day 4) post-dose of VNS vaccine or VV vaccine<br>• Percentage of participants reporting each solicited systemic event in terms of fever, varicella-like rash†, and general rash (not varicella-like) within 43 days (Day 1 to Day 43) post-dose of study interventions**<br>• Percentage of participants reporting each solicited systemic event in terms of drowsiness, loss of appetite, and irritability within 15 days (Day 1 to Day 15) post-dose of study interventions**<br>**Unsolicited adverse events (AEs)*****<br>• Percentage of participants reporting unsolicited AEs within 43 days (Day 1 to Day 43) post-dose of study interventions**<br>**Serious adverse events (SAEs)**<br>• Percentage of participants reporting SAEs post-dose of study interventions** up to the end of study |

AE = adverse event; gE = glycoprotein E; SAE = serious adverse event; VNS vaccine = investigational vaccine, VV vaccine = comparator vaccine (*Varivax*).

*Seroresponse rate is defined as the percentage of participants for whom post-dose of the study interventions (Day 43), the anti-gE antibody concentration is ≥300 mIU/mL.

**Study interventions = VNS vaccine (investigational vaccine); VV vaccine (*Varivax*, comparator vaccine); MMR (*M-M-R II* or *M-M-RVaxPro*), *Havrix* and *Prevnar 13* (if applicable) vaccines (co-administered vaccines).
Note: *Prevnar 13* will only be administered to participants enrolled in the United States and in countries where pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule

*** Unsolicited AEs include non-serious and serious AEs.

† Includes injection site varicella-like rash.

# 4.0 STUDY DESIGN

## 4.1 Overall Design

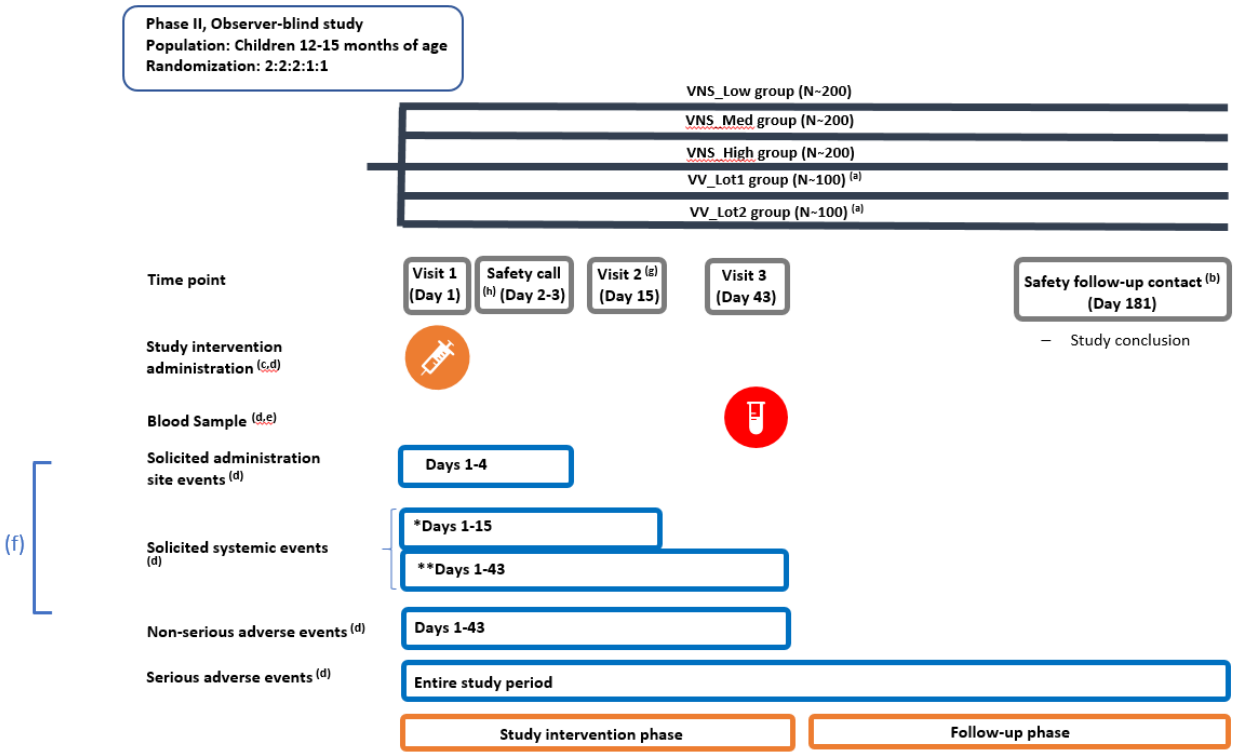
This will be a phase II, observer-blind (see the definition in Appendix 1), randomized, multicenter controlled study with 5 parallel intervention groups of healthy children aged 12 to 15 months at the time of intervention. Participants will be randomized to receive a single dose of an investigational varicella vaccine (3 groups of 200 participants each receiving one of the 3 different vaccine potencies [a low, a medium, and a high potency of the VNS vaccine, respectively]) or a single dose of a comparator licensed varicella vaccine (2 groups of 100 participants each receiving one of the 2 different lots of the VV vaccine, which will be pooled for all analyses).

All participants will be co-administered with an MMR vaccine, a hepatitis A vaccine (*Havri*x) and, if applicable, a 13-valent pneumococcal conjugate vaccine (*Prevnar 13*). *Prevnar 13* will only be administered to participants enrolled in the US and in countries where pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule.

At the end of the study or shortly after the study, depending on the vaccines' availability, GSK will provide a second dose of *Varivax* and/or *Havrix* to participants enrolled in non-US countries if local health departments do not routinely provide varicella and/or hepatitis A vaccine. Study participants who do not achieve the pre-specified seroresponse threshold criteria will be re-vaccinated with a dose of *Varivax*.

The study design diagram is provided in Figure 1.

**Figure 1 Study Design Overview**




VNS_Low, VNS_Med, and VNS_High vaccine = VNS vaccine in low, medium, and high potency; VV_Lot 1 and VV_Lot 2 = VV vaccine in 2 lots

[a] VV_Lot 1 and VV_Lot 2 groups will be analyzed as pooled groups

[b] Contact (by telephone call or any other convenient procedure) for the safety follow-up will take place 6 months post-dose of study interventions

[c] Study interventions: VNS vaccine (investigational vaccine) or VV vaccine (*Varivax*, comparator vaccine); MMR (*M-M-R II* or *M-M-RVaxPro*), *Havrix*, and *Prevnar 13* if applicable (co-administered vaccines). Note: *Prevnar 13* will only be administered to participants enrolled in the US and in countries where pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule

[d] Recording in the electronic Case Report Form

[e] Blood sampling for anti-glycoprotein E enzyme-linked immunosorbent assay

[f] Independent Data Monitoring Committee review details are provided in Section 8.2.3.

[g] Visit 2 for review of post-vaccination safety data may be a virtual visit

[h] Safety call to remind completion of the electronic Diary/smartphone application and address any potential early post-vaccination safety concerns

*Drowsiness, loss of appetite, irritability

**Fever, varicella-like rash (including injection site varicella-like rash) and general rash (not varicella-like)

Healthy children aged 12 to 15 months will be enrolled in this study according to the inclusion and exclusion criteria (see Section 5.0). The randomization to one of the 5 groups will be performed in a 2:2:2:1:1 ratio prior to intervention.

The study groups are shown in Table 6.

**Table 6 Study Groups**

| Study groups | Number of participants | Age (Min-Max) | Study interventions | Blinding |
|---|---|---|---|---|
| | | | | Visit 1 → Safety follow-up contact (observer-blind) |
| VNS_Low | 200 | 12 – 15 months | VNS_Low vaccine, MMR, *Havrix*, and *Prevnar 13** | × |
| VNS_Med | 200 | 12 – 15 months | VNS_Med vaccine, MMR, *Havrix*, and *Prevnar 13** | × |
| VNS_High | 200 | 12 – 15 months | VNS_High vaccine, MMR, *Havrix*, and *Prevnar 13** | × |
| VV_Lot 1 | 100 | 12 – 15 months | VV vaccine (*Varivax* Lot 1), MMR, *Havrix*, and *Prevnar 13** | × |
| VV_Lot 2 | 100 | 12 – 15 months | VV vaccine (*Varivax* Lot 2), MMR, *Havrix*, and *Prevnar 13** | × |

VNS_Low, VNS_Med, and VNS_High vaccine = VNS vaccine in low, medium, and high potency; VV_Lot 1 and VV_Lot 2 vaccines = VV vaccine in 2 lots; MMR = *M-M-R II* or *M-M-RVaxPro*; MMR, *Havrix*, and *Prevnar 13* = co-administered vaccines

**Prevnar 13* will only be administered to participants enrolled in the United States and in the countries where pneumococcal conjugate vaccine is recommended at 12 to 15 months as per national immunization schedule

There will be 3 in-person study visits: on Day 1, when the participants receive study intervention, on Day 15 (either in-person or virtually, for review of post-vaccination safety data), and on Day 43, when blood sampling for vaccine antibody testing will be performed. There will also be 1 safety call on Day 2-3 and 1 safety follow-up contact, on Day 181; these may be performed over the phone or by any other convenient means of communication. Refer to the Study Reference Manual which will contain a guide telephone script to be used for the Day 2-3 safety call, Day 15 (if the visit is conducted virtually) and for the Day 181 safety follow-up call.

The visits should occur within a pre-defined visit window (see Table 4).

The study will be performed in the observer-blind manner (see the definition in Appendix 1 and additional details in Section 4.2.3). An IDMC will perform periodic safety reviews of the study data. An enrollment pause is foreseen for the first IDMC review after 200 participants (approximately 50 participants in each group, considering pooled VV groups) are enrolled and vaccinated (See Section 8.2.3 for additional details).

The safety data will be collected through an Electronic Diary (eDiary)/personal electronic device application (app) for solicited events and at study visits/contacts for unsolicited events. The humoral immunogenicity testing of blood samples will be performed by enzyme-linked immunosorbent assay (ELISA) method at GSK's laboratory or in a laboratory designated by GSK.

## 4.2 Scientific Rationale for Study Design

### 4.2.1 Rationale for Clinical Study Population

Varicella (chickenpox) is common in children under 10 years of age. In many countries worldwide, vaccination against varicella in early years of life is recommended to prevent development of chickenpox in older age. According to the WHO, the countries which decide to introduce routine childhood varicella immunization, should administer the first dose at 12 to 18 months of age [WHO, 2014]. In the US, the incidence of varicella has decreased significantly since implementation of the national varicella vaccination program in 1996 [CDC, 2015]. In the US, as per the recommendation of the Advisory Committee on Immunization Practices (ACIP) children are routinely administered the first dose of the varicella vaccine at 12 to 15 months of age and the second dose at 4 to 6 years of age. However, the second dose may be administered at an earlier age provided that the interval between the first and second dose is at least 3 months [ACIP, 2007].

### 4.2.2 Choice of Comparator and Co-administered Vaccines

This will be an active-controlled study. The co-administered interventions will be included to maintain the standard of care.

#### *4.2.2.1 Comparator*

The varicella vaccine manufactured by Merck & Co, *Varivax*, similarly to the investigational VNS vaccine, contains an Oka varicella strain and is intended for the vaccination against varicella in healthy individuals from 12 months of age. *Varivax* has proven effectiveness. It is approved in more than 70 countries. It is the only varicella vaccine licensed in the US, where it is considered the standard of care.

#### *4.2.2.2 Co-administered Vaccines*

MMR, *Havrix*, and *Prevnar 13* vaccines are part of the routine pediatric vaccination schedules in the US [ACIP, 2007] and some other countries.

### 4.2.3 Rationale for Blinding

Because of the difference in the presentation of the investigational VNS vaccine and the commercial VV vaccine, i.e., the difference in the labeling of the vaccine vials and the difference in the appearance of the diluent presentation (a prefilled syringe for VNS vaccine *versus* a vial for the VV vaccine), double blinding is not possible. The study will be conducted in an observer-blind manner. See the definitions of double-blinding and observer-blind in Appendix 1 and refer to Section 6.3.4 for details.

### 4.2.4 Justification for Dose of Varicella Vaccine

In general, varicella dosing recommendations include 1 or 2 doses. In the US, it is recommended that the pediatric population receives 2 doses of varicella vaccine. In EU, vaccination with 2 doses of varicella vaccine is recommended in different countries according to local and regional public health guidelines.

The participants in this study will receive a single dose of investigational or comparator varicella vaccine. The second dose of varicella vaccine will not be offered in this study, as the study participants will not yet reach an appropriate age within the study time frame as per the ACIP recommended schedule [ACIP, 2007].

## 4.3 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

Participants shall be enrolled into the study according to inclusion criteria and if they meet none of the exclusion criteria. Prospective approval of protocol deviations to enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 Inclusion Criteria

- Healthy participants as established by medical history and clinical examination before entering into the study.
- A male or female between, and including, 12 and 15 months of age (i.e., from his/her 1-year birthday until the day before age of 16 months) at the time of the administration of the study interventions.
- Written informed consent obtained from the parent(s)/LAR(s) of the participant prior to performance of any study-specific procedure.
- 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 eDiaries, return for follow-up visits).
- Only for US participants and participants in countries where pneumococcal conjugate vaccine is recommended at 12-15 months of life as per national immunization schedule: Participants who previously received the primary series of pneumococcal conjugate vaccine in their first year of life with the last dose at least 60 days prior to study entry.

## 5.2 Exclusion Criteria

### 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 varicella.
- Recurrent history of or uncontrolled neurological disorders or seizures.
- Participant with history of SARS-CoV-2 infection 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.

Refer to Section 5.5 for criteria for temporary delay or enrollment and/or intervention.

### 5.2.2 Prior and 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 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 interventions 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, or equivalent. 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 against measles, mumps, rubella, hepatitis A, and/or varicella virus.
- Previous administration of a booster dose of any pneumococcal conjugate vaccine.
- Planned administration/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.

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

  *In case of 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 governmental recommendations and that the Sponsor/designee 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 1]).

### 5.2.4 Other Exclusions

- Child in care (see the definition in Appendix 1).
- Any study personnel's immediate dependents, family, or household members.
- Participants with the following high-risk individuals in their household:
    - Immunocompromised individuals.
    - 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, Activity, and Dietary Restrictions

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 Temporary Delay for Enrollment and/or Intervention Administration

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

- Acute disease and/or fever at the time of enrollment and/or study intervention administration. Fever is defined as temperature ≥ 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

For the definition of study intervention, refer to Appendix 1.

## 6.1 Study Interventions Administered

The study interventions that will be administered in the study are provided in Table 7.

## Table 7 Study Intervention Administered

| **Study intervention** | **VNS_Low vaccine** | | **VNS_Med vaccine** | | **VNS_High vaccine** | | ***Varivax*** | |
|---|---|---|---|---|---|---|---|---|
| **Study intervention formulation:** | Live attenuated varicella virus (OKA strain) ($\geq 1\times10^{3.0}$ pfu/dose) | Water for injections | Live attenuated varicella virus (Oka strain) ($\geq 1\times10^{3.0}$ pfu/dose) | Water for injections | Live attenuated varicella virus (Oka strain) ($\geq 1\times10^{3.0}$ pfu/dose) | Water for injections | Varicella virus Oka/Merck strain (live, attenuated) ($\geq$ 1350 pfu/dose) | 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:** | 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:** | | | | | | | | |
| Location | Arm | | Arm | | Arm | | Arm | |
| Directionality | Upper | | Upper | | Upper | | Upper | |
| Laterality | Left | | Left | | Left | | Left | |
| **Number of doses to be administered:** | 1 | | 1 | | 1 | | 2*** | |
| **Volume to be administered*:** | At least 0.28 mL | | At least 0.5 mL | | At least 0.5 mL | | 0.5 mL | |
| **Packaging and labeling** | Refer to SRM for more details | | Refer to SRM for more details | | Refer to SRM for more details | | Refer to SRM for more details | |
| **Manufacturer:** | GSK | | GSK | | GSK | | Merck & Co. | |

| **Study intervention (co-administered)** | **MMR** | | ***Havrix*** | ***Prevnar 13**** |
|---|---|---|---|---|
| **Study intervention formulation:** | Live attenuated measles virus Enders' Edmonston strain (≥ 3.0 $log_{10}$ $TCID_{50}$); Live attenuated mumps virus Jeryl Lynn™ [Level B] strain (≥ 4.1 $log_{10}$ $TCID_{50}$); Live attenuated rubella virus Wistar RA 27/3 strain (≥ 3.0 $log_{10}$ $TCID_{50}$) | Water for injections q.s. 0.5 mL | Hepatitis A virus antigen (HM175 strain) (720 ELISA Units) adsorbed on aluminum hydroxide; Aluminum hydroxide (0.25 mg $Al^{3+}$); Water for injections q.s. 0.5 mL | PS1(2.2 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; PS3(2.2 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; PS4(2.2 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; PS5(2.2 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; PS6A(2.2 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; PS6B(4.4 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; PS7F(2.2 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; PS9V(2.2 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; PS14(2.2 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; PS18C(2.2 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; PS19A(2.2 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; PS19F(2.2 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; PS23F(2.2 µg)-$CRM_{197}$ adsorbed on aluminum phosphate; Aluminum phosphate (0.125 mg $Al^{3+}$); Water for injections q.s. 0.5 mL |
| **Presentation:** | Powder for suspension for injection (vial) | Solution for suspension for injection | Suspension for injection (syringe) | Suspension for injection (syringe) |
| **Type:** | Biologic/Combination Product | | Biologic/Combination Product | Biologic/Combination Product |
| **Route of administration:** | Subcutaneous injection | | Intramuscular injection | Intramuscular injection |
| **Administration site:** | | | | |
| Location | Arm | | Thigh | Thigh |
| Directionality | Upper | | Anterolateral | Anterolateral |
| Laterality | Right | | Right | Left |
| **Number of doses to be administered:** | 1 | | 2*** | 1 |
| **Volume to be administered*:** | 0.5 mL | | 0.5 mL | 0.5 mL |
| **Packaging and labeling** | Refer to SRM for more details | | Refer to SRM for more details | Refer to SRM for more details |
| **Manufacturer:** | Merck & Co | | GSK | Pfizer |

$TCID_{50}$ = tissue cell culture infectious doses 50%; PS = polysaccharide; $CRM_{197}$ = non-toxic cross-reacting mutant of diphtheria toxin; ELISA = enzyme-linked immunosorbent assay; GSK = GlaxoSmithKline Biologicals SA; pfu = plaque-forming units; SRM = Study Reference Manual; VNS_Low, VNS_Med, and VNS_High = VNS vaccine in low, medium, and high potency; MMR = measles, mumps, rubella vaccine (*M-M-R II* or *M-M-RVaxPro*)

* Refer to the Study Reference Manual/pharmacy manual for the volume after reconstitution

****Prevnar 13** will only be administered to participants enrolled in the United States and in countries where pneumococcal conjugate vaccine is recommended at 12 to 15 months as per national immunization schedule

*** For non-US participants only. At the end of the study or shortly after the study, depending on the vaccines' availability, GSK will provide a second dose of *Havrix* and/or *Varivax* in countries where they are not routinely provided. The administration of the second dose of *Havrix* and *Varivax* is not part of the study procedures.

## 6.2 Preparation/Handling/Storage/Accountability

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

*Varivax* will be stored at −15°C to −30°C (+5°F to −22°F) in the US and other countries with frozen formulation and at +2°C to +8°C (+36°F to +46°F) in the rest of the world. (Note: refrigerated *Varivax* vaccine will be used at non-US sites, while frozen *Varivax* vaccine will be used at sites in the US and other countries with frozen formulation.)

Temperature excursions must be reported in degree Celsius, as described below:

- **For VNS Diluent**

Any temperature excursion outside the range of +1.5°C to +8.4°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate (electronic) temperature excursion decision form ([e]TDF). The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor. The impacted IMPs may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the SRM/pharmacy manual for more details on actions to take.

- **For VNS Antigen**

Any temperature excursion above −15.0°C (for −20°C/−4°F label storage condition) impacting IMPs must be reported in the appropriate (electronic) Temperature Excursion Decision Form (e)TDF. The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor. In case of temperature excursion above −20.0°C up to −15.0°C impacting IMPs, there is no need to report in (e)TDF, but adequate actions must be taken to restore the −20°C/−4°F or below label storage temperature. The impacted IMPs may still be used, but the site should avoid re-occurrence of such temperature excursion. Refer to the SRM/pharmacy manual for more details on actions to take.

- **For *Varivax* Diluent, *Varivax* antigen with refrigerated formulation and all other products (*Prevnar 13*, *Havrix*, MMR)**

Any temperature excursion outside the range of 2.0°C to +8.0°C (for +2°C to +8°C/+36°F to +46°F label storage condition) impacting study interventions must be reported in the appropriate

(e)TDF. The impacted study interventions must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

- **For *Varivax* Antigen in the US and other countries with frozen formulation**

Any temperature excursion above −15.0°C impacting study interventions must be reported in the appropriate (e)TDF. The impacted study interventions must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

All study interventions that are impacted by a temperature excursion may not be used and must be quarantined at label storage conditions until usage approval has been obtained from/via the local study contact (e.g., Site Monitor). Refer to the SRM/pharmacy manual for details and instructions on the temperature excursion reporting and usage decision process, packaging, and accountability of the study interventions.

### 6.2.1 Minimizing Environmental Contamination with Genetically Modified Organisms

Not applicable.

## 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

The 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 1 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 1 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 an observer-blind manner. To do so, study interventions will be prepared and administered by qualified study personnel who will not participate in data collection, evaluation, review, or the entry of any study endpoint.

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

#### *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 will have unrestricted, immediate, and direct access to the participant's individual study intervention through IVRS/IWRS. At activation, the study centers will be provided instructions and/or other applicable information for emergency unblinding. 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 1) 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 1) 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 1)/family member may also request emergency unblinding. Instructions for this will be provided to the participants' parent(s)/LAR(s) at enrollment.

#### *6.3.4.2 Emergency Unblinding Prior to Regulatory Reporting of Serious Adverse Events*

GSK policy (which incorporates ICH E2A guideline, EU Clinical Study Directive, and US Federal Regulations) is to unblind the report of any unexpected SAE that is attributable/suspected to be attributable to the investigational vaccine prior to regulatory reporting.

IQVIA will follow these policies along with IQVIA's standard procedures and will be responsible for unblinding the intervention assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to Appendix 4 for details).

In addition, IQVIA may unblind the intervention assignment for any participant with a suspected unexpected serious adverse reaction (SUSAR) or an SAE that is fatal or life-threatening. If the SAE requires an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or the sponsor's policy.

## 6.4 Study Intervention Compliance

When the study intervention is administered at the study center, participants will receive it from the authorized study center staff. The date of administration of each study intervention dose in the clinic will be recorded in the source documents and in the eCRF.

## 6.5 Dose Modification

Not applicable.

## 6.6 Continuing Access to Study Intervention after the End of the Study

At the end of the study or shortly after the study, depending on the vaccines' availability, GSK will provide a second dose of *Varivax* and/or *Havrix* to participants enrolled in non-US countries if local health departments do not routinely provide varicella and/or hepatitis A vaccine.

## 6.7 Treatment of Overdose

Any dose of any study vaccine greater than the recommended dose per protocol is considered an overdose. All cases of vaccine overdose should be reported as AEs (or SAEs, if SAE criteria are met) and followed accordingly. Sponsor does not recommend specific treatment for an overdose.

## 6.8 Concomitant Therapy

At each study visit/contact, the investigator or designee should question the participant's parent(s)/LAR(s) about any medications/products/supplements taken and vaccinations received by the participant, whether prescribed or over the counter.

The following concomitant therapies must be recorded in the eCRF:

- All concomitant medication associated with AE, including vaccines/products, except vitamins and dietary supplements, 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. These must also be recorded in the Expedited Adverse Event 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 TREATMENT 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 4 for the details regarding such events)
- Unsolicited non-serious 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 4 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 the scheduled visit and cannot be contacted by the study center.

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

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

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

Study procedures and their timing are summarized in the Schedule of Activities (SoA; Section 1.3).

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

The investigator will maintain a log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log.

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

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 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) or 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 8 at GSK laboratory or in a laboratory designated by GSK.

**Table 8 Laboratory Assay**

| Assay type | System | Component | Method |
|---|---|---|---|
| Humoral Immunity (Antibody determination) | Serum | Anti-gE antibodies | ELISA |

gE = glycoprotein E; ELISA = enzyme-linked immunosorbent assay

### 8.1.3 Immunological Correlates of Protection

There is no established correlate of protection (see the definition in Appendix 1) with the assay to be used in this study for the varicella vaccines administered in the frame of this study.

The investigator, even though remaining blinded with respect to each child's group attribution, will be provided with the list of children who fail to serorespond to varicella virus (i.e., achieve a post-vaccination anti-gE antibody concentration ≥300 mIU/mL) in a timely manner (no later than 12 months after the last sampling date of the last child enrolled).

Upon receiving the result, the investigator will assess if any step needs to be taken regarding the individual child. Study participants who do not achieve the pre-specified seroresponse threshold criteria will be re-vaccinated with a dose of *Varivax*.

## 8.2 Safety Assessments

### 8.2.1 Pre-intervention Administration Procedures

#### *8.2.1.1 Collection of Demographic Data, Medical/vaccination history, Physical Examination*

Demographic data such as age in months, sex, race, and ethnicity will be collected from each participant. Medical history should be collected and it should be verified that none of exclusion criteria related to medical and vaccination history (Section 5.2) are met. Prior vaccination history with respect to pneumococcal conjugate vaccine should be obtained and recorded in the eCRF. Physical examination will be performed for each participant. 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.

#### *8.2.1.2 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 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.

### 8.2.3 Safety Monitoring and Study Holding Rules

Besides safety monitoring by blinded Study/Center Monitors (see the definition in Appendix 1), 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.

Up to the completion of enrollment and vaccination of the first 200 participants through their Day 43 follow-up, enrollment will be paused for an ad hoc IDMC review of the cumulative safety data if any of the holding rules are met (See Section 8.2.3.1).

An enrollment pause is foreseen for the first IDMC review after 200 participants (50 in each group, considering pooled VV groups) are enrolled and vaccinated. The analysis will take place once all 200 participants have returned for their Day 43 visit (Visit 3) or have withdrawn from the study, within the allowed interval for the visit. A positive outcome of the IDMC review will be a pre-requisite for the continuation of the study.

Monthly SRT review 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 200 participants are enrolled and vaccinated. During the study, as per the IDMC charter, ad hoc IDMC meetings may be convened when a safety concern has been observed. In this case, enrollment shall be paused.

A subsequent IDMC review meeting is planned during the study, after Day 43 safety follow-up of 400 participants is completed, no enrollment pause is foreseen for this review. The details of the review will be described in an IDMC charter. The analysis will take place once all 400 participants have returned for their Day 43 visit (Visit 3) or have withdrawn from the study, within the allowed interval for the visit.

#### *8.2.3.1 Study Holding Rules*

The safety holding rules defined in Table 9 only apply to the first 200 study participants enrolled. Holding rules 1-3 will be assessed by the investigator on a continuous basis. Holding rules 1-3 will be assessed by the IDMC during the safety evaluations on unblinded data.

**Table 9 Study Holding Rules**

| Holding Rule | Event | Number of participants to pause vaccination in all groups, pending further evaluation by IDMC |
|---|---|---|
| 1 | Any death considered at least possibly related to study vaccination | ≥ 1 |
| 2 | Any SAE(s) considered at least possibly related to vaccination | ≥ 1 |
| 3 | Same or similar* Grade 3 unsolicited AE considered to be at least possibly related to vaccination | ≥ 2 |

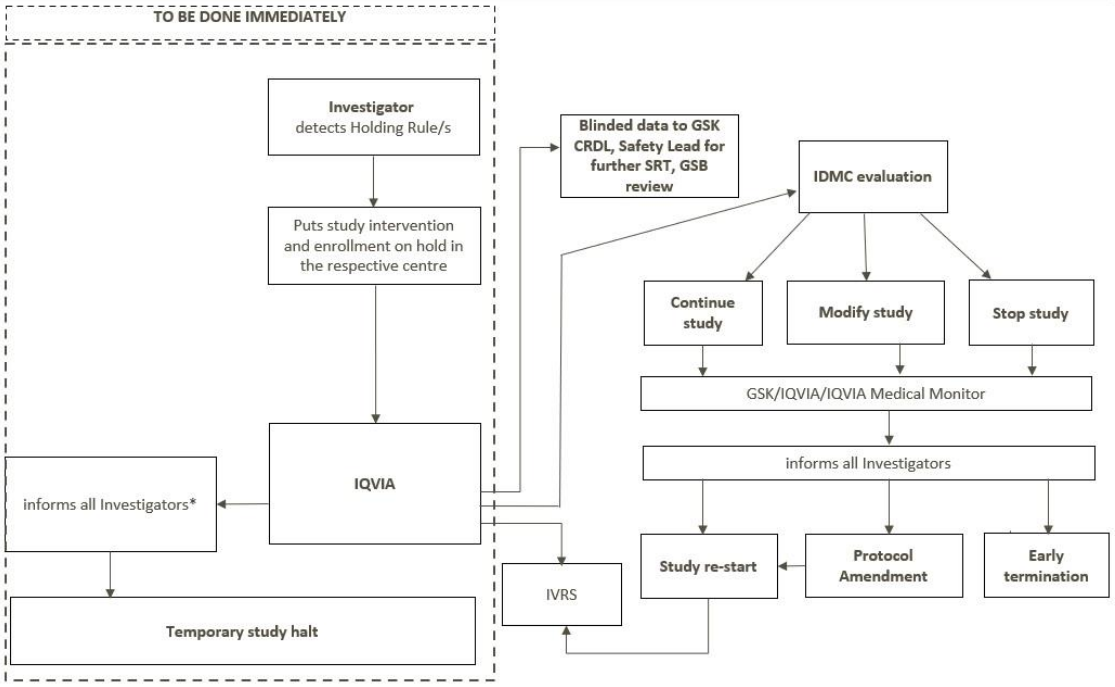
AE = adverse event; IDMC = Independent Data Monitoring Committee; SAE = serious adverse event
*based on medical judgment

If the investigator becomes aware of a holding rule being met, he/she must suspend administration of the study intervention, pause enrollment, and inform IQVIA immediately (e.g., holding rules 1-3). Refer to Appendix 4 for contact information.

GSK via IQVIA will inform all study investigators to suspend the study intervention and enrollment if any of the holding rules are met.

The following communication sequence for the identification of holding rules by the investigator must be followed (Figure 2).

**Figure 2 Communication Flow: Identification of Holding Rules by the Investigator**




CRDL = Clinical Research and Development Lead; GSB = Global Safety Board; IDMC = Independent Data Monitoring Committee; IVRS = Interactive Voice Response System; SRT = Safety Review Team
*Investigators are responsible to inform the Institutional Review Board/Independent Ethics Committee if a holding rule has been met.

#### *8.2.3.2 Outcome of Safety Evaluation*

If a safety signal is observed during the safety evaluations, or if any of the holding rules is met for the first 200 participants, the IDMC Chair (or his/her representative) is responsible for the urgent communication to GSK, including the rationale for the decision to put the study intervention administration on hold or not.

If no safety signal is observed in the first 200 participants, the favorable outcome of the safety evaluations will be documented and provided in writing, authorizing the investigator to start enrollment and dosing of the remaining participants in the study.

GSK via IQVIA will be accountable for notifying all investigators of the decision whether to suspend, modify or continue the conduct of the study on all groups or on selected groups.

Refer to Section 8.2.3.1 for a flow chart for escalation of safety signal.

## 8.3 Adverse Events

### 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 4.

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 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).

Provided that GSK marketed study interventions registered in the US are combination products (see Table 7, and the definition of a combination product in Appendix 1), associated AEs meeting pre-specified definitions will be classified as medical device AEs and SAEs, as well as adverse device effects (ADEs), serious adverse device effects (SADEs), and unanticipated serious adverse device effects (USADEs). Definitions of these events are provided in Appendix 4. Details on recording, follow-up and reporting of medical device deficiencies are provided in Section 8.3.6.

### 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 4.

The study center staff should instruct participants' parent(s)/LAR(s) on how to report signs and symptoms (e.g., crying and 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 you 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, have you 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 4.

### 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 4. 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 legal obligations and ethical responsibilities for the participant's safety and the safety of a study intervention under clinical investigation.

For coronavirus disease 2019 (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 suspected 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 Treatment of AEs

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

### 8.3.5 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.

### 8.3.6 Medical Device Deficiencies

This clinical study will collect information of any device deficiencies associated with the study interventions that are combination products (GSK marketed combination products registered in the US). Refer to Appendix 1 for the definition of a combination product and a medical device deficiency.

#### *8.3.6.1 Detection, Follow-up, and Reporting of Medical Device Deficiencies*

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

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

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

#### *8.3.6.2 Regulatory Reporting of Medical Device Deficiency When Used as Combination Product*

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

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

## 8.4 Pharmacokinetics and Pharmacodynamics

Pharmacokinetic and pharmacodynamic parameters are not evaluated in this study.

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

# 9.0 STATISTICAL CONSIDERATIONS

## 9.1 Statistical Hypotheses

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

## 9.2 Sample Size Determination

The target enrollment will be of 800 participants randomly assigned to 5 study groups (VNS_Low, VNS_Med, VNS_High, VV_Lot1, and VV_Lot2 groups) in a 2:2:2:1:1 ratio. Table 10 demonstrates the accuracy which can be achieved in terms of percentage of participants with AE based on the ES (200 participants per group considering pooled VV_Lot1 and VV_Lot2 groups), and in terms of percentage of participants with seroresponse based on the PPS (10% unevaluable participants out of the 200 enrolled participants is considered leading to about 180 participants in the PPS per group).

**Table 10 Exact 95% Confidence Interval for the Percentage of Participants with Adverse Event Based on the Exposed Set and for the Percentage of Participants with Seroresponse Based on the Per Protocol Set**

| Endpoint | n | N | % | Exact 95% CI |
|---|---|---|---|---|
| % of participants with an AE | 0 | 200 | 0.0 | [0.00%; 1.83%] |
| | 10 | 200 | 5.0 | [2.42%; 9.00%] |
| | 20 | 200 | 10.0 | [6.22%; 15.02%] |
| | 40 | 200 | 20.0 | [14.69%; 26.22%] |
| Seroresponse rate | 144 | 180 | 80.0 | [73.40%; 85.58%] |
| | 153 | 180 | 85.0 | [78.93%; 89.885%] |
| | 162 | 180 | 90.0 | [84.66%; 93.96%] |
| | 171 | 180 | 95.0 | [90.72%; 97.69%] |

AE = adverse event; CI = confidence interval; n/N = number of participants with an observation/total number of participants

See the analysis sets definitions in Section 9.3. Refer to Appendix 1 for the definitions of eligible, enrolled, and evaluable participants.

## 9.3 Populations for Analyses

For purposes of analysis, the analysis sets are defined in Table 11.

**Table 11 Analysis Sets**

| Analysis set | Description |
|---|---|
| Enrolled Set | Participants who received a study intervention or were randomized. Note that as per GCP enrolled participants' parent(s)/LAR(s) should have completed the informed consent process and participants should be eligible before initiating any study procedure. |
| Exposed Set (ES) | All participants who received a study intervention. Analysis per group is based on the varicella intervention administered. |
| Per Protocol Set (PPS) | All eligible participants who received all study interventions as per protocol, were not unblinded, had immunogenicity results post-dose, complied with blood draw intervals (refer to Table 3), without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination (see the footnote). |

GCP = good clinical practice; 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 varicella or herpes zoster in the interval between study intervention administration and the collection of the blood specimen for immunogenicity at Visit 3.

## 9.4 Statistical Analyses

### 9.4.1 Statistical Analysis Plan

The statistical analysis plan (SAP) will be developed and finalized before the First Participant First Visit (FPFV). This section is a summary of the planned statistical analyses of the primary and secondary immunogenicity endpoints.

Descriptive analyses of safety and demography summaries will be described in the SAP.

There is no intention to conduct specific analyses investigating the relationship between the gender of the participants and the immunogenicity and safety of the study vaccine. The ratio of male to female participants recruited into this study is expected to be in line with the demographics of the population aged 12 to 15 months of age.

### 9.4.2 Primary Endpoint Analyses

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

The geometric mean concentrations (GMCs) will be summarized by group with their 95% CI derived considering log-transformed anti-gE antibody concentrations are normally distributed with unknown variance. The concentration below the assay cut-off will be assigned half the cut-off for the purpose of GMC computation.

The group GMC ratio with nominal 95% CI will also be provided. This will be obtained using an analysis of variance (ANOVA) model on log-transformed concentrations. The model based on the data from all groups will include group and country as a fixed effect.

### 9.4.3 Secondary Endpoints Analyses

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

Seroresponse rate is defined as the percentage of participants for whom the post-dose anti-gE antibody concentration (Day 43) is ≥ 300 mIU/mL.

The seroresponse rates will be summarized by group with their 95% exact CI based on Clopper-Pearson method [Clopper and Pearson, 1934].

The 2-sided 95% CI on group difference in seroresponse rate (pooled VV group minus each VNS group [Low, Med, High]) will be computed based on the method of Miettinen and Nurminen [Miettinen and Nurminen, 1985].

## 9.5 Interim Analysis

### 9.5.1 Sequence of Analyses

Apart from the analyses to be performed in support to the IDMC, a statistical analysis and a report including safety and final immunogenicity data for all participants up to Day 43 time point are planned. Following unblinding for the analysis up to Day 43, accessibility to group attribution will be limited so that the study center blinding is maintained until the 6-month safety follow-up is completed for all participants.

One integrated CSR containing all data including the safety follow-up beyond Day 43 will then be generated upon study completion. This report will be made available to the investigators. 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 1 statistical analysis including all immunogenicity and safety data will be performed.

### 9.5.2 Statistical Considerations for Interim Analysis

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

# 10.0 REFERENCES

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# 11.0 APPENDICES

# Appendix 1 Abbreviations and the Glossary of Terms

| | |
|---|---|
| ACIP | Advisory Committee on Immunization Practices |
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| ANOVA | Analysis of variance |
| App | Application |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| COVID-19 | Coronavirus Disease 2019 |
| $CRM_{197}$ | Non-toxic Cross-Reacting Mutant of Diphtheria Toxin |
| CSR | Clinical Study Report |
| eCRF | electronic Case Report Form |
| EDC | Electronic Data Capture Tool |
| eDiary | Electronic Diary |
| ELISA | Enzyme-linked immunosorbent assay |
| EoS | End of Study |
| ES | Exposed Set |
| EU | European Union |
| FPFV | First Participant First Visit |
| GCP | Good Clinical Practice |
| gE | Glycoprotein E |
| GMC | Geometric Mean Concentration |
| HRP | Horseradish Peroxidase |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| ID | Identification |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IgG | Immunoglobulin G |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | Interactive Response Tool |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| LAR | Legally Acceptable Representative |
| LPLV | Last Participant Last Visit |
| MMR | Measles, mumps, and rubella vaccine |
| PPS | Per Protocol Set |
| PS | Polysaccharide |
| SADE | Serious Adverse Device Effect |

| | |
|---|---|
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SoA | Schedule of Activities |
| SRM | Study Reference Manual |
| SRT | Safety Review Team |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| (e)TDF | (electronic) Temperature Excursion Decision Form |
| US | United States of America |
| USADE | Unanticipated Serious Adverse Device Effect |
| VNS | Varicella vaccine (investigational vaccine) |
| VV | Varicella vaccine (comparator vaccine) |
| WHO | World Health Organization |

**Glossary of Terms**

| | |
|---|---|
| Adverse event: | Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.<br>An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse. |
| Blinding: | A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the participant's parent(s)/LAR(s), the study center and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment.<br>In a double-blind study, the participant's parent(s)/LAR(s), the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment. |

| | |
|---|---|
| Caregiver: | A caregiver is someone who<br>• lives in the close surroundings of a participant and has a continuous caring role or<br>• 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<br>• drug<br>• device<br>• biological product<br><br>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. |
| Invasive medical device: | A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body |
| Investigational vaccine/product: | A pharmaceutical form of an active ingredient being tested in a clinical study, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. |
| Investigator: | A person responsible for the conduct of the clinical study at a study center. If a study is conducted by a team of individuals at a study center, the investigator is the responsible leader of the team and may be called the principal investigator.<br>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 device deficiency: | A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer. |

| | |
|---|---|
| Medical Monitor | IQVIA's delegate providing significant scientific contribution to the conduct of the study. 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 GSK/IQVIA (see the study administrative structure in Appendix 2 [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 events: | 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. |

# Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

## Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments (see the definition in Appendix 1), ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Furthermore, any substantial amendments to the protocol may require regulatory authority approval before implementation per local legislation.
- IQVIA will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the 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), and all other applicable local regulations.
- After reading the protocol, all principal investigators will sign the protocol signature page and send a copy of the signed page to IQVIA (Appendix 6).

## Financial Disclosure

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

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

**Informed Consent Process**

- The investigator or his/her representative must fully explain the nature of the study to the participant's parent(s)/LAR(s) and answer all questions regarding the study.
- Participants' parent(s)/LAR(s) must be informed that their participation is voluntary.
- Freely given and written/witnessed/thumb printed informed consent must be obtained from each participant's parent(s)/LAR(s)/witness, as appropriate, prior to participation in the study.
- The content of the ICF must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written or witnessed/thumb printed informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants' parent(s)/LAR(s) must be re-consented to the most current version of the ICF(s) or an ICF addendum during their participation in the study.
- A copy of the ICF(s) must be provided to the participants' parent(s)/LAR(s).

**Data Protection**

- Any participant records or datasets that are transferred to IQVIA/GSK will contain the participant ID only; participant names or any information which would make the participant identifiable will not be transferred.
- The participants' parents/LARs must be informed that:
  - Their child's study-related data will be used by GSK in accordance with local data protection law.
  - Their child's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by GSK/IQVIA, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
  - GSK will ensure protection of the personal data of the investigator and study center staff which is collected within the framework of and for the purpose of the study, in accordance with the Data Privacy Notice that will be sent to the site staff.

The participants' parent(s)/LAR(s) must be notified about their rights regarding the use of their personal data in accordance with the data privacy section of the ICF.

### 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 |

### Medical Monitor

Refer to the SRM.

### Dissemination of Clinical Study Data

The key design elements of this protocol and results summaries will be posted on ClinicalTrials.gov, EudraCT, and/or GSK Clinical Study Register 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.

**Data Quality Assurance**

- The investigator should maintain a record of the location(s) of their respective essential documents, including source documents (see Appendix 1 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 1 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 1 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 1 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.
- Quality tolerance limits will be pre-defined 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 CSR/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.

**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 1.

**Study and Study Center Start and Closure**

The first act of recruitment is the date of the first participant enrollment and is considered the study start date.

GSK/IQVIA reserves the right to close the study center or terminate the study at any time for any reason. Study centers will be closed upon study completion. A study center is considered closed when all required 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 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 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, GSK/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.

# Appendix 3 Clinical Laboratory Tests

**Enzyme-linked immunosorbent assay**

Anti-gE ELISA is a two-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 sulphuric 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 titre is expressed in mIU/mL.

# Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## Adverse Events

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a patient or clinical study participant that is temporally associated with the use of study intervention, whether or not considered related to the study intervention.<br>An AE can, therefore, be any unfavorable and unintended sign, symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. |

| **Events <u>Meeting</u> the AE Definition** |
|---|
| • Significant or unexpected worsening or exacerbation of the condition/indication under study.<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study intervention administration even though they may have been present prior to the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention.<br>• Signs or symptoms temporally associated with study intervention administration.<br>• Signs, symptoms that require medical attention (e.g., hospital stays, physician visits, and emergency department visits).<br>• Pre- or post-intervention events that occur as a result of protocol-mandated procedures (i.e., invasive procedures).<br>• Clinically significant abnormal laboratory findings following the start of the study. |

| **Events <u>NOT</u> 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).<br>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.<br>• Pre-existing conditions or signs and/or symptoms present in a participant prior to the first/the study vaccination. These events will be recorded in the medical history section of the eCRF.<br>• Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline.<br>• Clinically significant abnormal laboratory findings or other abnormal assessments, unless judged by the investigator as more severe than expected for the participant's condition, or that are present or detected at the start of the study and do not worsen.<br>• However, if 1 or both of the following conditions apply, then the event should be reported promptly to IQVIA as an SAE:<br>– The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or<br>– The investigator considers that there is a reasonable possibility that the event was related to the administration of the study intervention. |

## Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study).

**An SAE is defined as any untoward medical occurrence that, at any dose:**

**a) Results in death**

**b) Is life-threatening**

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 that hypothetically might have caused death had it been more severe.

**c) Requires inpatient hospitalization or prolongation of existing hospitalization**

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

**d) Results in disability/incapacity**

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

**e) Other situations**

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

## Solicited Events

**Solicited Events will include the following:**

**a) Solicited administration site events**

The following administration site events will be solicited for toddlers 12 to 15 months of age at the time of the study intervention:

- Pain
- Redness
- Swelling

**b) Solicited systemic events**

The following systemic events will be solicited for toddlers 12 to 15 months of age at the time of the study intervention:

| **Solicited Events will include the following:** |
|---|
| • Fever<br>• Varicella-like rash (including injection site varicella-like rash)<br>• General rash (not varicella-like)<br>• Drowsiness<br>• Loss of appetite<br>• Irritability<br>Note: participants' parent(s)/LAR(s) will be instructed to measure and record body temperature in the evening using the temperature measuring device provided by GSK. The recommended route of temperature measurement will be the axilla. Should additional temperature measurements be performed at other times of day, participants' parent(s)/LAR(s) will be instructed to record the highest temperature in the eDiary/personal electronic device app. |

## Unsolicited Events

| **Definition of an Unsolicited Adverse Event:** |
|---|
| An unsolicited AE is an AE that was not included in a list of solicited events using an eDiary/personal electronic device app. Unsolicited events must have been spontaneously communicated by a participant's parent(s)/LAR(s) who have signed the informed consent. Unsolicited AEs include both serious and non-serious AEs.<br><br>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/parental/LAR(s)' concern. Detailed information about reported unsolicited AEs will be collected by qualified study center personnel and documented in the participant's records.<br><br>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. |

## COVID-19 Cases

Diagnosis of COVID-19 should be made in accordance with the WHO 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.

## Assessment of Intensity and Toxicity

The intensity of the following solicited AEs will be assessed as described in Table 13.

## Table 13 Intensity Scales for Solicited Symptoms in Toddlers (12 to 15 Months of Age)

| Toddler (12 to 15 months 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 |
| Varicella-like rash** | | Number of lesions |
| General rash (not varicella-like) | 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 AE would, for example, prevent attendance at school/day care and would cause the parent(s)/LAR(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 |
| Irritability | 0 | Behavior as usual |
| | 1 | Mild: Crying more than usual/no effect on normal activity |
| | 2 | Moderate: Crying more than usual/interferes with normal activity |
| | 3 | Severe: Crying that cannot be comforted/prevents normal activity |

*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 typical varicella-like rash manifests as a rash/lesions that may appear within 2 weeks (or sometimes later) after the varicella vaccination. Lesions may contain spots, bumps, blisters, or crusts. Refer to the Study Reference Manual for detailed varicella-like rash guidelines.

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

| | **Redness/swelling** | **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 | > 20 mm | ≥ 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 pre-defined outcomes as described above.

**Assessment of Causality**

All solicited administration site and systemic events will be considered causally related to administration of the study intervention. The complete list of these events is provided in Table 13.

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”, 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.

**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 CRF/paper Expedited Adverse Events Report as applicable/in the eCRF.

**Assessment of Outcomes**

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

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.

## 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. |
| **AE and SAE Recording** |
| • 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.<br>• 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.<br>• 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.<br><br>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 15 days (Day 1 to Day 15) or 43 days (Day 1 to Day 43), 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 non-serious AEs must be followed until the last contact or until the participant is lost to follow-up.

**Follow-up During the Study**

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

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

**Follow-up After the Participant is Discharged from the Study**

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

**Updating of SAE 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 become 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.

**Grade 3 unsolicited AE(s) at least possibly related to vaccination for the first 200 study participants through their Day 43 follow-up:**

- Once the investigator or designee become aware that study participant(s) have experienced a Grade 3 unsolicited AE considered to be at least possibly related to vaccination, the investigator or designated study staff must complete information in the AE form in the eCRF WITHIN 24 HOURS. The AE form 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 a Grade 3 unsolicited AE considered to be at least possibly related to vaccination, the AE form should still be completed within 24 hours. Once additional relevant information is received, the AE form should be updated WITHIN 24 HOURS. The investigator will always provide an assessment of causality at the time of the initial completion of the AE form.
- Refer to Section 8.3.1 for the details on timeframes for reporting of AE(s).

**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 become available.
- After the study is completed at a given site, the EDC will be taken offline to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE 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.

## Definitions of Medical Device Adverse Events and Adverse Device Effects

**A Medical Device AE is:**

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

**An Adverse Device Effect (ADE) is:**

Any AE related to the use of a medical device. This definition includes any AE resulting from:

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

## Definitions of a Medical Device SAE, Serious Adverse Device Effect, and Unexpected Serious Adverse Device Effect

**A Medical Device SAE is Any SAE that:**

a. Led to death

b. Led to serious deterioration in the health of the participant, that either resulted in:

- A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- A permanent impairment of a body structure or a body function.
- Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

c. Is a suspected transmission of any infectious agent via a medicinal product

**A Serious Adverse Device Effect (SADE) is:**

- A SADE is defined as an ADE that has resulted in any of the consequences characteristic of a serious adverse event.
- Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

**An Unanticipated SADE (USADE) is:**

- An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a SADE that by its nature, incidence, severity or outcome has not been identified in the current version of the IB.

**Recording and Reporting of Device Deficiencies**

- Device deficiencies must be reported to IQVIA within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- Fax transmission of the paper "Medical device or combination product with device deficiency/incident report form" is the preferred method to transmit this information to IQVIA.
- In rare circumstances and in the absence of Fax equipment, notification by phone is acceptable with a copy of "Medical device or combination product with device deficiency/incident report form" sent by overnight mail or courier service.
- IQVIA will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

# Appendix 5 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment (Amendment 3) is located directly before the Table of Contents (TOC).

**Detailed description of the changes in Protocol Amendment 3:**
(additional text in **bold** and *italic*; deletions in strikethrough)

**General Changes:**

- Throughout the protocol, the reference that the study will be conducted in the US, was removed. Rationale: the study will be expanded to the countries outside the US.
- A note, "***if applicable***" is added to *Prevnar 13* vaccination where necessary.
- ***M-M-RVaxPro*** was mentioned as a name for the MMR vaccine in some countries.
- Added "***approximately***" to "50 participants in each group", whenever mentioned.
- Through the protocol, it is noted that the ***IEC***, besides IRB, will also be an entity overseeing the ethical conduct of the study. The text regarding EU-specific regulations was also added as applicable.
- "Study as a whole" was replaced with "***country***" as a minimization factor for analysis.
- Added the note/footnote, ***Participants recruited outside of the US will be co-administered with MMR, Havrix, and in some countries, with Prevnar 13. Prevnar 13 will only be administered to participants enrolled in the United States and in countries where pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule***, when applicable (throughout the protocol and in the Schedule of Activities).
- Added the note, ***At the end of the study or shortly after the study, depending on the vaccines' availability, GSK will provide a second dose of Varivax and/or Havrix to participants enrolled in non-US countries if local health departments do not routinely provide varicella and/or hepatitis A vaccine. Study participants who do not achieve the pre-specified seroresponse threshold criteria will be re-vaccinated with a dose of Varivax*** (throughout the protocol and in the Schedule of Activities).
- Title Page, Sponsor's Signature Page, Header: updated the number of the protocol amendment from 2.0 to ***3.0***. Added the date of the amendment as applicable.
- Title Page: added the clinical trial registry numbers.

Note: In various sections, the repeated changes with the same or similar wording are not detailed if they have been made clear earlier.

Note: The minor changes such as for grammar/readability/correction of typos are not listed.

**1.0, Protocol Summary**

**Rationale:** ***Participants recruited outside of the US will be co-administered with MMR, Havrix, and in some countries, with Prevnar 13. Outside the US, Prevnar 13 will only be***

***administered in countries where pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule. At the end of the study or shortly after the study, depending on the vaccines' availability, GSK will provide a second dose of Varivax and/or Havrix to participants enrolled in non-US countries if local health departments do not routinely provide varicella and/or hepatitis A vaccine. Study participants who do not achieve the pre-specified seroresponse threshold criteria will be re-vaccinated with a dose of Varivax.***

**Overall Design:** ***Participants recruited outside of the US will be co administered with MMR, Havrix, and in some countries, with Prevnar 13. Outside the US, Prevnar 13 will only be administered in countries where pneumococcal conjugate vaccine is recommended at 12-15 months as per national immunization schedule. If Prevnar 13 is to be administered, participants are required to have previously received the primary series of pneumococcal conjugate vaccine in their first year of life with last dose at least 60 days prior to study entry.***

**1.3, Schedule of Activities**

Added the information about *Prevnar 13* administration at non-US sites.

Added the row with about the conditional administration of the second dose of *Varivax* and/or *Havrix*. Noted that, ***The administration of the second dose of Havrix and Varivax is not part of the study procedures, however, the administration of the second dose (or the date of the planned visit for administration) should be recorded in the eCRF.***

**2.1, Study Rationale**

Same changes as in **Protocol Summary**.

**2.3.2, Risk Mitigation Strategies**

***The burden of the study for the participant will be minimized as much as possible. For taking blood samples, 3 attempts at most should be performed. If the investigator/designee is not successful after the third attempt, the investigator/designee will make no further attempts. A local numbing cream or patch will also be offered at the discretion of the investigator prior to blood sampling, to minimize pain when blood samples are drawn.***

***GSK/IQVIA will immediately notify the investigators if any additional safety or toxicology information becomes available during the study.***

***This study will be performed in compliance with the protocol, ICH GCP, EU CTR, and applicable regulatory requirements. Aspects of the study concerned with the investigational medicinal products will meet the requirements of European Union – Good Manufacturing Practice, as applicable.***

**4.1, Overall Design**

Same changes as in **Protocol Summary** and **Study Rationale**.

**4.2.1, Rationale for Clinical Study Population**

***In many countries worldwide, vaccination against varicella in early years of life is recommended to prevent development of chickenpox in older age.***

~~The incidence of varicella has decreased significantly since implementation of the national varicella vaccination program in 1996 in the US [CDC, 2015].~~

***In the US, the incidence of varicella has decreased significantly since implementation of the national varicella vaccination program in 1996 [CDC, 2015].***

~~Adolescents (≥13 years) and adults should receive 2 doses of the single-antigen varicella vaccine 4 to 8 weeks apart.~~

**4.2.2.1, Comparator**

*Varivax* has proven effectiveness. ***It is approved in more than 70 countries.***

**4.2.2.2, Co-administered vaccines**

MMR, *Havrix*, and *Prevnar 13* vaccines are part of the routine pediatric vaccination schedules in the US ***and some other countries.***

**4.2.4, Justification for Dose of Varicella Vaccine**

In general, varicella dosing recommendations include 1 or 2 doses. In the US, it is recommended that the pediatric population receives 2 doses of varicella vaccine, ~~with the first dose administered at 12 to 15 months of age and the second dose administered between 4 and 6 years of age.~~ ***In EU, vaccination with 2 doses of varicella vaccine is recommended in different countries according to local and regional public health guidelines.***

**5.1, Inclusion Criteria**

- ***Only for US participants and participants in countries where pneumococcal conjugate vaccine is recommended at 12-15 months of life as per national immunization schedule***: Participants who previously received the primary series of pneumococcal conjugate vaccine in their first year of life with the last dose at least 60 days prior to study entry.

**6.1, Study Interventions Administered**

**Table 7, Study Intervention Administered**

Changed the number of doses for *Varivax* and *Havrix* from 1 to 2.

Added the footnotes:

*****Prevnar 13 will only be administered to participants enrolled in the United States and in countries where pneumococcal conjugate vaccine is recommended at 12 to 15 months as per national immunization schedule***

****** For non-US participants only. At the end of the study or shortly after the study, depending on the vaccines' availability, GSK will provide a second dose of Havrix and/or Varivax in***

***countries where they are not routinely provided. The administration of the second dose of Havrix and Varivax is not part of the study procedures.***

**6.2, Preparation/Handling/Storage/Accountability**

***Varivax will be stored at −15°C to −30°C (+5°F to −22°F) in the US and at +2°C to +8°C (+36°F to +46°F) in the rest of the world. (Note: Refrigerated Varivax vaccine will be used at non-US sites, while frozen Varivax vaccine will be used at sites in the US and other countries with frozen formulation).***

**Temperature excursions, For VNS Diluent:**

Any temperature excursion outside the range of ~~0~~***+1.5***°C to ~~+8.0~~***+8.4***°C (for +2 to +8°C/+36 to +46°F label storage condition).

~~In case of temperature excursion below +2.0°C down to 0.0°C impacting IMPs, there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature~~

- **For *Varivax* Diluent, *Varivax antigen with refrigerated formulation and all other products* (*Prevnar 13*, *Havrix*, MMR)**
- **For *Varivax* antigen in the US *and other countries with frozen formulation***

Any temperature excursion above −~~20~~***15.0***°C ~~(for −20°C/−4°F label storage condition)~~ impacting study interventions must be reported in the appropriate (e)TDF.

**6.3.2, Randomization to Study Intervention, 6.3.3, Intervention Allocation to Participants**

The ~~study as a whole~~ ***country*** and center will be used as minimization factors for randomization.

**6.6, Continuing 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.~~ ***At the end of the study or shortly after the study, depending on the vaccines' availability, GSK will provide a second dose of Varivax and/or Havrix to participants enrolled in non-US countries if local health departments do not routinely provide varicella and/or hepatitis A vaccine.***

**8.1.3, Immunological Correlates of Protection**

~~..while all children are expected to receive a second dose of the varicella vaccine as per ACIP recommended schedule at 4 to 6 years of age [ACIP, 2007].~~

**9.4.1, Statistical Analysis Plan**

***There is no intention to conduct specific analyses investigating the relationship between the gender of the participants and the immunogenicity and safety of the study vaccine. The ratio***

***of male to female participants recruited into this study is expected to be in line with the demographics of the population aged 12 to 15 months of age.***

## Appendix 1 Abbreviations and the Glossary of Terms

***IEC Independent Ethics Committee***

MMR Measles, mumps, and rubella vaccine

## Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

- The investigator will be responsible for the following:
  - Providing oversight of the conduct of the study at the 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)***, and all other applicable local regulations.

## Amendment 2.0 (15-November-2021)

### Overall Rationale for the Amendment:

This protocol was amended at the request of CBER to add drowsiness, loss of appetite, irritability, and general rash (not varicella-like) to the list of solicited systemic events. In addition, the reporting instructions for the Grade 3 unsolicited events (at least possibly related to vaccination for the first 200 study participants through their Day 43 follow-up) were updated.

### Description of the Most Important Changes in Amendment 2

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3 Schedule of Activities | Added the recording of solicited systemic events of drowsiness, loss of appetite and irritability from Day 1 to Day 15 post study intervention. | These adverse reactions are commonly described in the setting of vaccine trials in children over 12 months of age. |
| | Added the additional solicited systemic event to be collected from Day 1 to Day 43 post study intervention: general rash (not varicella-like). | |
| 3.0 Objectives and Endpoints | Included general rash (not varicella-like) in the endpoint related to solicited systemic event collected from Day 1 to Day 43. | |
| | Added the endpoint of the percentage of participants reporting each solicited systemic event in terms of drowsiness, loss of appetite, and irritability from Day 1 to Day 15. | |
| 4.0 Overall Design | Added the collection of solicited systemic events of drowsiness, loss of appetite, and irritability from Day 1 to Day 15 and clarified that fever, varicella-like rash (including injection site varicella-like rash) and general rash (not varicella-like) will be collected from Day 1 to Day 43. | |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.2 Preparation/Handling/ Storage/Accountability | Removed the mention of *Varivax* antigen from the products to be stored between 2.0°C to +8.0°C. | The *Varivax* antigen used in the study is a frozen one and not a refrigerated one. |
| Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting | Added general rash (not varicella-like), drowsiness, loss of appetite, irritability to the list of solicited systemic events. | These adverse reactions are commonly described in the setting of vaccine trials in children over 12 months of age. |
| | Added intensity scales grades for drowsiness, loss of appetite, irritability and general rash (not varicella-like). | To provide the instructions for assessment of intensity of the newly added events. |
| | Removed the requirement for the investigator to confirm the review of an SAE/Grade 3 unsolicited AE at least possibly related to vaccination for the first 200 study participants through their Day 43 follow-up by ticking the "reviewed" box in the electronic report. | For the alignment with the electronic case report form. |
| | Updated the reporting of Grade 3 unsolicited adverse events at least possibly related to vaccination for the first 200 study participants through their Day 43 follow-up. | |

**Detailed description of the changes in Protocol Amendment 2:**

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

### 1.3, Schedule of Activities

### Table 3 Schedule of Activities

The added cells and text:

| | | | | | | |
|---|---|---|---|---|---|---|
| ***Recording of solicited systemic events (drowsiness, loss of appetite and irritability) from Day 1-15 post study intervention administration*** | ○ | ○ | ○ | | | ***See Section 8.3 and Appendix 4*** |
| Recording of solicited systemic events ***(fever, varicella-like rash [including injection site varicella-like rash] and general rash [not varicella-like])*** from Day 1-43 post study intervention administration | ○ | ○ | ○ | ○ | | See Section 8.3 ~~for details~~ and Appendix 4 ~~for definitions~~ |
| Recording of non-serious AEs from Day 1-43 post study intervention administration | ● | ● | ● | ● | | See Section 8.3 ~~for details~~ and Appendix 4 ~~for definitions~~ |

### 3.0, Objectives and Endpoints

## Table 5, Study Objectives and Endpoints

The following change was made:

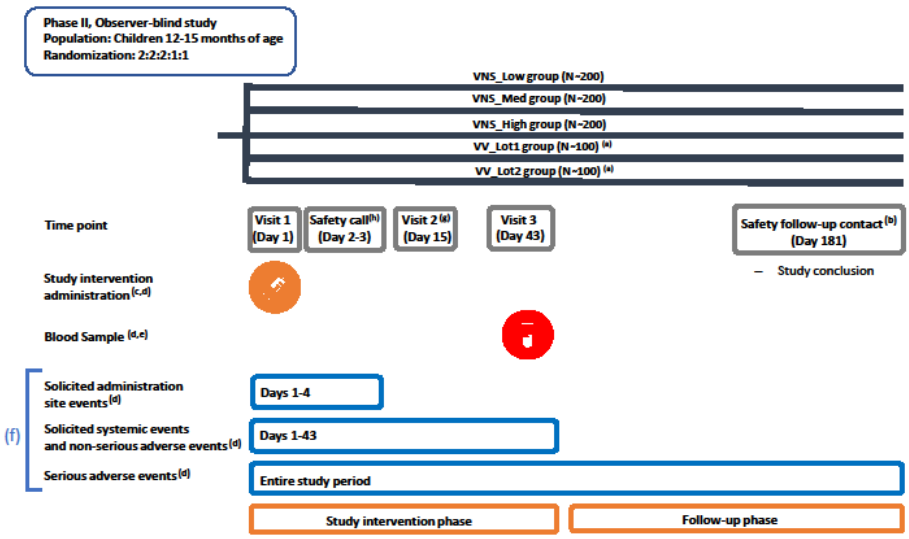
| | |
|---|---|
| • To evaluate safety and reactogenicity following administration of VNS and VV vaccines | **Solicited events**<br>• Percentage of participants reporting each solicited administration site event in terms of injection site redness, pain and swelling within 4 days (Day 1 to Day 4) post-dose of VNS vaccine or VV vaccine<br>• Percentage of participants reporting each solicited systemic event in terms of fever, ~~and~~ varicella-like rash[†]***, and general rash (not varicella-like)*** within 43 days (Day 1 to Day 43) post-dose of study interventions<br>• ***Percentage of participants reporting each solicited systemic event in terms of drowsiness, loss of appetite, and irritability within 15 days (Day 1 to Day 15) post-dose of study interventions***[**]<br>**Unsolicited adverse events (AEs)**[***]<br>• Percentage of participants reporting unsolicited AEs within 43 days (Day 1 to Day 43) post-dose of study interventions[**]<br>**Serious adverse events (SAEs)**<br>• Percentage of participants reporting SAEs post-dose of study interventions[**] up to the end of study |

## 4.1, Overall Design

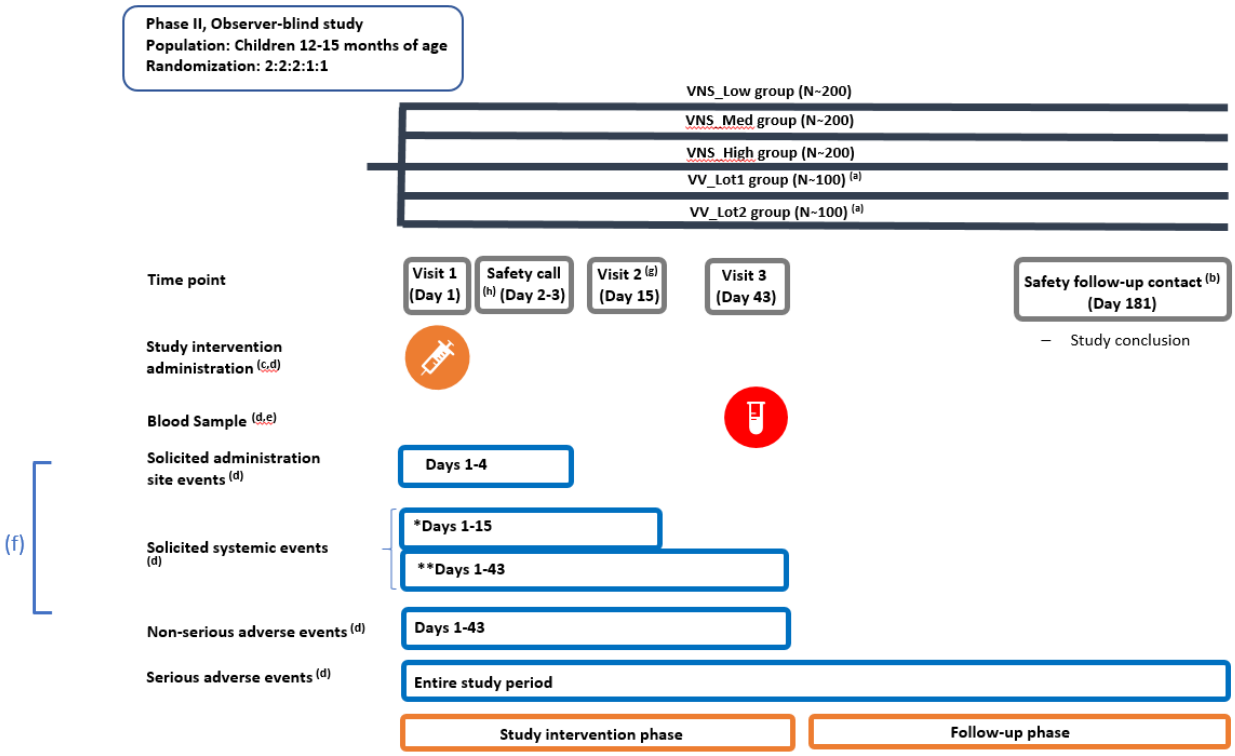
## Figure 1, Study Design Overview

The obsolete figure was replaced with the new one. The footnote was updated.

The obsolete figure:




The new figure:




VNS_Low, VNS_Med, and VNS_High vaccine = VNS vaccine in low, medium, and high potency; VV_Lot 1 and VV_Lot 2 = VV vaccine in 2 lots

[a] VV_Lot 1 and VV_Lot 2 groups will be analyzed as pooled groups

[b] Contact (by telephone call or any other convenient procedure) for the safety follow-up will take place 6 months post-dose of study interventions
[c] Study interventions: VNS vaccine (investigational vaccine) or VV vaccine (Varivax, comparator vaccine); M-M-R II, *Havrix*, and *Prevnar 13* (co-administered vaccines)
[d] Recording in the electronic Case Report Form
[e] Blood sampling for anti-glycoprotein E enzyme-linked immunosorbent assay
[f] Independent Data Monitoring Committee review details are provided in Section 8.2.3.
[g] Visit 2 for review of post-vaccination safety data may be a virtual visit
[h] Safety call to remind completion of the eDiary/app and address any potential early post-vaccination safety concerns
***Drowsiness, loss of appetite, irritability***
****Fever, varicella-like rash (including injection site varicella-like rash) and general rash (not varicella-like)***

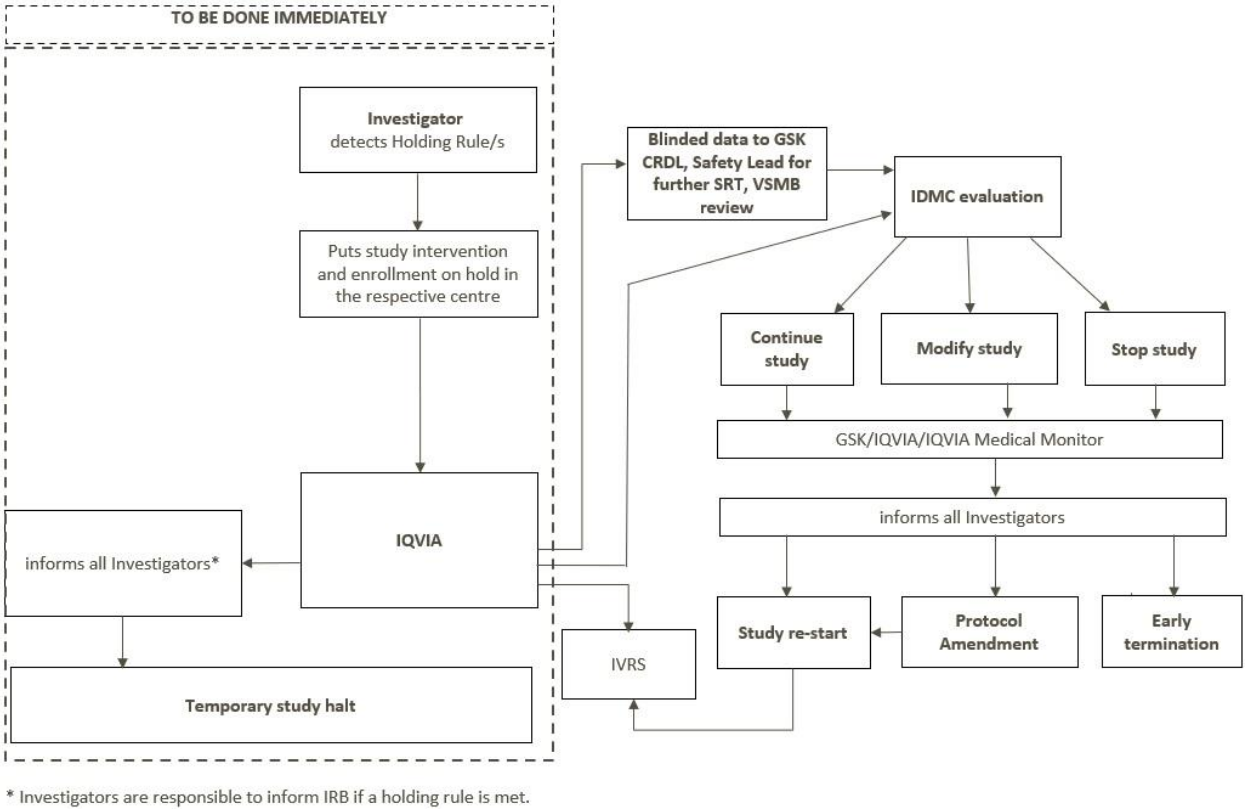
## 6.2, Preparation/Handling/Storage/Accountability

- **For ~~*Varivax Antigen*~~ *Diluent* and All Other Products (*Prevnar 13*, *Havrix*, *M-M-R II*)**

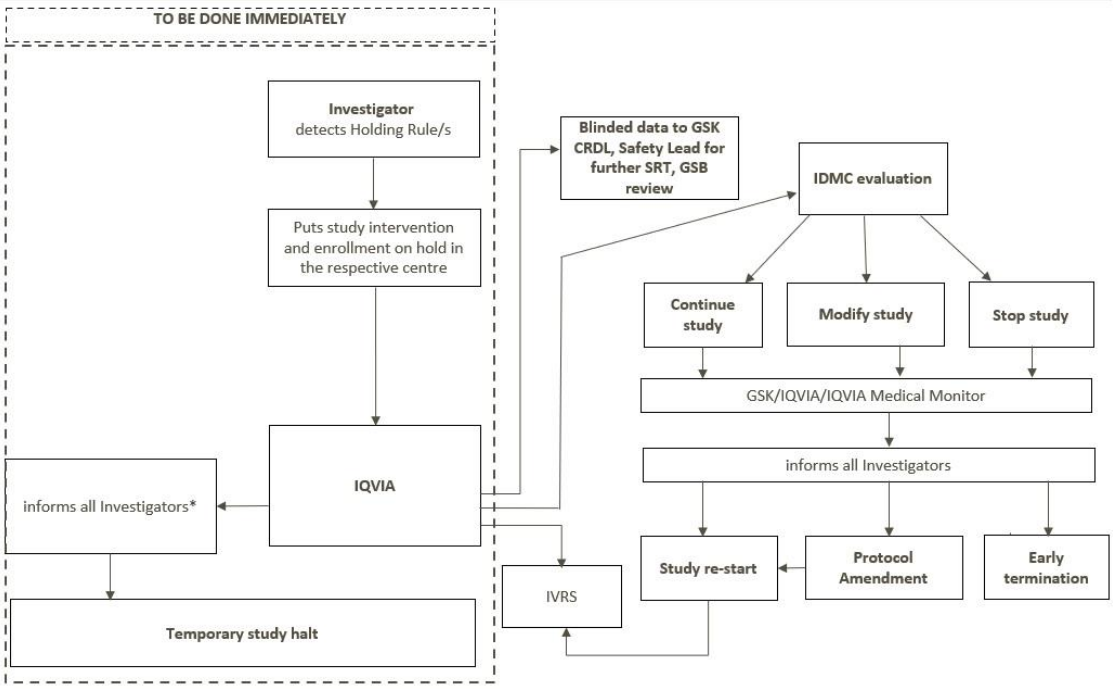
## 8.2.3.1, Study Holding Rules

**Figure 2 Communication Flow: Identification of Holding Rules by the Investigator**

Obsolete figure:




New figure:




***CRDL = Clinical Research and Development Lead; GSB = Global Safety Board; IDMC = Independent Data Monitoring Committee; IVRS = Interactive Voice Response System; SRT = Safety Review Team***

****Investigators are responsible to inform the Institutional Review Board if a holding rule is met.***

### 9.5.1, Sequence of Analyses

Apart from the analyses to be performed in support to the IDMC, a statistical analysis ***and a report*** including safety and final immunogenicity data for all participants up to Day 43 time point is planned. Following unblinding for the analysis up to Day 43, accessibility to group attribution will be limited so that the study center blinding is maintained until the 6-month safety follow-up is completed for all participants.

## Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

| **Solicited Events will include the following:** |
|---|
| **c) Solicited administration site events**<br>The following administration site events will be solicited for toddlers 12 to 15 months of age at the time of the study intervention:<br>• Pain<br>• Redness<br>• Swelling |
| **d) Solicited systemic events**<br>The following systemic events will be solicited for toddlers 12 to 15 months of age at the time of the study intervention: |

- Fever
- Varicella-like rash (including injection site varicella-like rash)
- General rash (not varicella-like)
- Drowsiness
- Loss of appetite
- Irritability

Note: participants' parent(s)/LAR(s) will be instructed to measure and record body temperature in the evening using the temperature measuring device provided by GSK. The recommended route of temperature measurement will be the axilla. Should additional temperature measurements be performed at other times of day, participants' parent(s)/LAR(s) will be instructed to record the highest temperature in the eDiary/personal electronic device app.

**b) Solicited systemic events**

The following systemic events will be solicited for ~~children~~***toddlers*** 12 to 15 months of age ***at the time of the study intervention***:

- Fever
- Varicella-like rash (including injection site varicella-like rash)
- ***General rash (not varicella-like)***
- ***Drowsiness***
- ***Loss of appetite***
- ***Irritability***

## Table 15 Intensity Scales for Solicited Symptoms in Toddlers (12 to 15 Months of Age)

| Toddler (12 to 15 months 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 |
| Varicella-like rash[**] | | Number of lesions |
| ***General rash (not varicella-like)*** | ***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 AE would, for example, prevent attendance at school/day care and would cause the parent(s)/LAR(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*** |
| ***Irritability*** | ***0*** | ***Behavior as usual*** |
| | ***1*** | ***Mild: Crying more than usual/no effect on normal activity*** |
| | ***2*** | ***Moderate: Crying more than usual/interferes with normal activity*** |
| | ***3*** | ***Severe: Crying that cannot be comforted/prevents normal activity*** |

[*]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 typical varicella-like rash manifests as a rash/lesions that may appear within 2 weeks (or sometimes later) after the varicella vaccination. Lesions may contain spots, bumps, blisters, or crusts. Refer to the Study Reference Manual for detailed varicella-like rash guidelines.

| **Time Period for Collecting and Recording of AEs and SAEs** |
|---|
| All solicited ***administration site*** ~~and solicited systemic events~~ that occur during 4 days (Day 1 to Day 4), ***and solicited systemic events that occur during*** 14***5 days (Day 1 to Day 15)*** ~~and~~***or*** 43 days (Day 1 to Day 43), ~~respectively~~, following administration of the study intervention must be recorded into the eDiary/personal electronic device app, irrespective of intensity ~~or whether or not they are considered intervention-related~~. 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. |

| **Events Requiring Expedited Reporting to IQVIA:** |
|---|
| **SAE(s) throughout the study** |

| |
|---|
| • Once the investigator or designee become 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.<br>• 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.<br>~~• The investigator will be required to confirm the review of the SAE causality by ticking the "reviewed" box in the electronic Expedited AE Report within 72 hours of submission of the SAE.~~<br>• Refer to Section 8.3.1 for the details on timeframes for reporting of SAEs. |
| **Grade 3 unsolicited AE(s) *at least possibly related to vaccination* for the first 200 study participants through their Day 43 follow-up:** |
| • Once the investigator or designee become aware that study participant(s) have experienced a Grade 3 unsolicited AE considered to be at least possibly related to vaccination, the investigator or designated study staff must complete information in the ~~electronic Expedited AE Report~~ ***AE form*** in the eCRF WITHIN 24 HOURS. The ~~report~~ ***AE form*** will always be completed as thoroughly as possible with all available details of the event.<br>• Even if the investigator does not have all information regarding a Grade 3 unsolicited AE considered to be at least possibly related to vaccination, the ~~report~~***AE form*** should still be completed within 24 hours. Once additional relevant information is received, the ~~report~~***AE form*** should be updated WITHIN 24 HOURS. The investigator will always provide an assessment of causality at the time of the initial ~~report~~***completion of the AE form*.**<br>~~• The investigator will be required to confirm the review of the Grade 3 unsolicited AE(s) causality by ticking the "reviewed" box in the electronic Expedited AE Report within 72 hours of submission of the Grade 3 unsolicited AE(s).~~<br>• Refer to Section 8.3.1 for the details on timeframes for reporting of AE(s). |

## Amendment 1.0 (08-October-2021)

## Overall Rationale for the Amendment:

This protocol was amended at the request of CBER to add early safety time point checks, to exclude participants with a history of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection who remain symptomatic, to exclude susceptible high-risk individual members of the potential participant's household, to clarify that varicella-like-rash includes injection site varicella-like rash, to include holding rules for the first 200 study participants enrolled and to revise the grading to assess the severity of the varicella-like rash.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis | Added 1 safety call and 1 new study visit | To address any potential safety concerns that may have arisen during the early post-vaccination time period and review post-vaccination safety data, respectively. |
| 1.3 Schedule of Activities | Added 1 safety call and 1 new study visit | To address any potential safety concerns that may have arisen during the early post-vaccination time period and review post-vaccination safety data, respectively. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Table 4 Intervals Between Study Visits | Added 1 safety call and 1 new study visit with accompanying intervals | To address any potential safety concerns that may have arisen during the early post-vaccination time period and review post-vaccination safety data, respectively. |
| 2.3.2 Risk Mitigation Strategies | Inserted holding rules | To ensure participant safety |
| 3 Objectives and endpoints | Added clarification that injection site varicella-like rash is included as solicited systemic event | To clarify AE information |
| 4.1 Overall Design, Figure 1 Study Design Overview | Added 1 safety call and 1 new study visit to study Schema | To address any potential safety concerns that may have arisen during the early post-vaccination time period and review post-vaccination safety data, respectively. |
| 4.1 Overall Design | Added 1 safety call and 1 new study visit in the footnote | To address any potential safety concerns that may have arisen during the early post-vaccination time period and review post-vaccination safety data, respectively. |
| 5.2 Exclusion Criteria | Inserted new criterion | To exclude participants with susceptible high-risk individuals in their household, in case of varicella transmission |
| 5.2 Exclusion Criteria | Inserted new criterion | To exclude participants with a history of SARS-CoV-2 infection who remain symptomatic |
| 8.1.3 Immunological Correlates of Protection | Added sentence “Study participants who do not achieve the pre-specified seroresponse threshold criteria will be re-vaccinated with a dose of *Varivax*.” | To specify when re-vaccination should take place. |
| 8.2.3 Study Holding Rules and Safety Monitoring | Adapted text to reflect the inclusion of holding rules | To further clarify procedures for safety monitoring by the IDMC and the SRT |
| 8.2.3 Study Holding Rules and Safety Monitoring | Added Section 8.2.3.1 and Table 9, both titled Study Holding Rules | To include holding rules as this is considered as a first time in human study |
| 8.2.3 Study Holding Rules and Safety Monitoring | Added Section 8.2.3.2, Outcome of Safety Evaluation | To explain what will happen following the outcome of the review by the IDMC of the safety data of the first 200 participants |
| Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting | Updated reporting requirements to include events listed in Holding Rules, clarification that injection site varicella-like rash is included as solicited systemic event, update of grading for varicella-like rash and fever | To include holding rules as this is considered a first time in human study, clarify AE information |
| Appendix 5 Protocol | Inserted new appendix | To track protocol amendment history |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Amendment History | | |

Non-substantial changes such as editorial changes and administrative changes are not included in this list.

**Detailed description of the changes in Protocol Amendment 1:**
(additional text in **bold** and *italic*; deletions in strikethrough)

**1.1, Synopsis (Overall Design):**

Randomization to one of the 5 groups will be performed in a 2:2:2:1:1 ratio prior to intervention. There will be ~~2~~***3*** study visits, at Day 1 (intervention), ***Day 15 (virtual or in-person),*** and Day 43, as well as ~~a~~ ***1 safety call and 1 safety*** follow-up contact, at Day ***2-3 and*** Day 181***, respectively***.

**1.2, Schema:** Third visit and safety call added to schema.

Added the following to Schema footnotes:

***[g] Visit 2 for review of post-vaccination safety data may be a virtual visit.***
***[h] Safety call to remind completion of the eDiary/app and check on potential early post-vaccination safety events***

**1.3, Schedule of Activities:** Third visit and safety call added.

| **Age** | **12-15 months of age at the time of study intervention administration** | | | | | **Notes** |
|---|---|---|---|---|---|---|
| | | | | | | |
| **Type of contact** | **Visit 1** | ***Safety call*** | **Visit 2[†]** | **Visit ~~2~~*3*** | **Safety follow-up contact** | |
| **Time points** | **Day 1** | ***Day 2-3*** | ***Day 15*** | **Day 43** | **Day 181** | |
| Informed consent | ● | | | | | See Appendix 2 for details |
| Check inclusion/exclusion criteria | ● | | | | | See Section 5.1 and Section 5.2 for details |
| Collect demographic data | ● | | | | | See Section 8.2.1.1 for details |
| Medical history | ● | | | | | See Section 8.2.1.1 for details |
| Vaccination history (protocol-specific vaccines including PCV) | ● | | | | | See Section 8.2.1.1 for details<br>See Section 5.1 for details |
| Physical examination | ● | | | | | See Section 8.2.1.1 for details |
| Randomization | ○ | | | | | See Section 6.3.2 for details |
| **Study interventions** | | | | | | See Appendix 1 for the definition |

| **Age** | **12-15 months of age at the time of study intervention administration** | | | | | **Notes** |
|---|---|---|---|---|---|---|
| | | | | | | |
| **Type of contact** | **Visit 1** | ***Safety call*** | **Visit 2†** | **Visit ~~2~~*3*** | **Safety follow-up contact** | |
| **Time points** | **Day 1** | ***Day 2-3*** | ***Day 15*** | **Day 43** | **Day 181** | |
| Check contraindications, warnings and precautions to study intervention administration | ○ | | | | | See Section 8.2.1.2 for details |
| Check criteria for temporary delay for enrollment and study intervention administration | ● | | | | | See Section 5.5 for details |
| Study group and treatment 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 (VNS vaccine/VV vaccine, and *M-M-R II, Havrix*, and *Prevnar 13*) administration | ● | | | | | ***Study participants who do not achieve the pre-specified seroresponse threshold criteria will be re-vaccinated with a dose of Varivax*** ~~The investigator will assess if re-vaccination with *Varivax* is needed for the children who fail to serorespond to varicella virus (i.e., post-vaccination anti-gE antibody concentration is <300 mIU/mL at Day 43) after the Day 43 immunogenicity results are available.~~ |
| Recording of administered study treatment number | ● | | | | | |

| **Age** | **12-15 months of age at the time of study intervention administration** | | | | | **Notes** |
|---|---|---|---|---|---|---|
| | | | | | | |
| **Type of contact** | **Visit 1** | ***Safety call*** | **Visit 2†** | **Visit ~~2~~3** | **Safety follow-up contact** | |
| **Time points** | **Day 1** | ***Day 2-3*** | ***Day 15*** | **Day 43** | **Day 181** | |
| Distribute eDiaries/download the app | ○ | | | | | An eDiary/personal electronic device application (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. See Appendix 4 for details |
| **Laboratory assessment** | | | | | | |
| Blood sampling for antibody determination (~3 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 9.3 for more information |
| Phone contact for safety follow-up | | ● | | | ● | Or any other convenient procedure |
| Recording of solicited administration site events from Day 1-4 post study intervention administration | ○ | ○ | | | | Only events following the administered dose of VNS vaccine or VV vaccine will be solicited |
| ***Safety follow-up with clinical staff to review post-vaccination safety data*** | | | ● | | | |
| Recording of solicited systemic events from Day 1-43 post study intervention administration | ○ | ○ | ○ | ○ | | See Section 8.3 for details and Appendix 4 for definitions |
| Recording of non-serious AEs from Day 1-43 post study intervention administration | ● | ● | ● | ● | | See Section 8.3 for details and Appendix 4 for definitions |
| ***eDiary/app completion reminder*** | | ● | | | | |
| Review of eDiaries/app data | | ○ | ● | ● | | |

| **Age** | **12-15 months of age at the time of study intervention administration** | | | | | **Notes** |
|---|---|---|---|---|---|---|
| | | | | | | |
| **Type of contact** | **Visit 1** | ***Safety call*** | **Visit 2†** | **Visit ~~2~~*3*** | **Safety follow-up contact** | |
| **Time points** | **Day 1** | ***Day 2-3*** | ***Day 15*** | **Day 43** | **Day 181** | |
| Return of eDiaries/uninstall or disable the app | | | | ○ | | See Section 8.5 for details |
| Recording of SAEs | • | • | • | • | • | See Section 8.3 for details and Appendix 4 for the definition |
| Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine | • | • | • | • | • | The collection and reporting periods start once the participant's parent(s)/LAR(s)'s informed consent is obtained |
| Study Conclusion | | | | | • | See Section 4.3 for the definition. |

***†Visit 2 (Day 15) may be conducted in-person or virtually.***
Refer to the Study Reference Manual (SRM)***/Pharmacy Manual*** for the volume of the vaccine after reconstitution.

**Table 4 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*** |
| Visit 1→Visit ***3~~2~~*** | 42 days | 35 to 56 days |
| Visit 1→ Safety follow-up contact | 180 days | 180 to 201 days |

Note: Whenever possible, the investigator should arrange study visits following the planned visit interval. Deviation from allowed interval between Visit 1 and Visit ***~~2~~3*** will lead to elimination from the Per Protocol Set.

## 2.3.2, Risk Mitigation Strategies:

The blinded monitoring of study data will be performed by the GSK's designee/Contract Research Organization (IQVIA) (see study administrative structure in Appendix 2 [Table 12]). Additional unblinded safety monitoring will be performed by an Independent Data Monitoring Committee (IDMC). ~~composed of clinical experts, independent of the study protocol and external to GSK and IQVIA, and an independent biostatistician. Frequent~~ ***Monthly*** Safety Review Team (SRT) review will occur up to the completion of enrollment and vaccination of the first 200 participants, to monitor cumulative, blinded safety data (including serious and non-serious AEs) (see Section 8.2.3). ***In addition, for the first 200 study participants through their***

***Day 43 follow-up, the following criteria would be applied, that would result in a pause in study activities, including dosing and enrollment:***

a. ***Any death at least possibly related to vaccination (refer to Section 8.3.3 for expedited reporting)***

b. ***≥1 participant with SAE/s at least possibly related to vaccination (refer to Section 8.3.3 for expedited reporting)***

c. ***≥2 participants with the same or similar Grade 3 unsolicited AE at least possibly related to vaccination, (refer to Section 8.3.1 for diligent reporting of Grade 3 unsolicited AEs at each contact/visit)***
***Note: "similarity" of the events will be based on medical judgment.***

An enrollment pause is ***also*** foreseen for the first IDMC review after 200 participants (50 in each group, considering pooled VV groups) are enrolled and vaccinated. The analysis will take place once all 200 participants have returned for their Day 43 visit (Visit ~~2~~***3***) or have withdrawn from the study, within the allowed interval for the visit. A positive outcome of the IDMC review ~~of the Day 43 safety follow-up data of the 200 participants~~ will be a pre-requisite for the continuation of the study.

**Section 3, Objectives and Endpoints:**

[†] ***Includes injection site varicella-like rash.***

**Section 4.1, Overall Design:**

There will be ~~2~~***3*** in-person study visits: on Day 1, when the participants receive study intervention, ***on Day 15 (either in-person or virtually, for review of post-vaccination safety data),*** and on Day 43, when blood sampling for vaccine antibody testing will be performed. ~~The third visit~~ ***There will also be 1***~~2 call~~ ***safety*** ~~follow-up~~ ***call on*** Day ***2-3 and 1 safety follow-up contact,*** on Day 181***;*** ~~will be a safety follow-up contact and it~~ ***these*** may be performed over the phone or by any other convenient means of communication. The visits should occur within a pre-defined visit window (see Table ~~2~~***4***).

**Section 5.2.1, Medical Conditions:**

- ***Participant with history of SARS-CoV-2 infection who is still symptomatic***.

**Section 5.2.2, Prior and Concomitant Therapy:**

- Planned administration/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 ~~2~~***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.

Any other age-appropriate vaccine may be given starting at Visit ~~2~~*3* and anytime thereafter.

**Section 5.2.4, Other Exclusions:**

- ***Participants with the following high-risk individuals in their household:***
    - ***Immunocompromised individuals.***
    - ***Pregnant women without documented history of varicella.***
    - ***Newborn infants of mothers without documented history of varicella.***
    - ***Newborn infants born <28 weeks of gestation.***

**Section 6.0, Study Intervention, Table 7, Study Interventions Administered:**

*Refer to the SRM***/*pharmacy manual*** for the volume after reconstitution

**Section 8.1.3, Immunological Correlates of Protection:**

Upon receiving the result, the investigator will assess if any step needs to be taken regarding the individual child, while all children are expected to receive a second dose of the varicella vaccine as per ACIP recommended schedule at 4 to 6 years of age ~~(~~[ACIP, 2007]~~)~~. ***Study participants who do not achieve the pre-specified seroresponse threshold criteria will be re-vaccinated with a dose of Varivax.***

**Section 8.2.3, Safety Monitoring *and Study Holding Rules***

Besides safety monitoring by blinded Study/Center Monitors (see the definition in Appendix 1), 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.

***Up to the completion of enrollment and vaccination of the first 200 participants through their Day 43 follow-up, enrollment will be paused for an ad hoc IDMC review of the cumulative safety data if any of the holding rules are met (See Section 8.2.3.1).***

An enrollment pause is foreseen for the first IDMC review after 200 participants (50 in each group, considering pooled VV groups) are enrolled and vaccinated. ~~A positive outcome of the IDMC review of the Day 43 safety follow-up data of the 200 participants will be a pre-requisite for the continuation of the study.~~ The analysis will take place once all 200 participants have returned for their Day 43 visit (Visit ~~2~~*3*) or have withdrawn from the study, within the allowed interval for the visit. ***A positive outcome of the IDMC review will be a pre-requisite for the continuation of the study.***

~~In addition to the planned IDMC meetings, frequent~~ ***Monthly***-SRT review 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 200 participants are enrolled and vaccinated. During the study, as per the IDMC charter, ad hoc IDMC meetings may be convened when a safety concern has been observed. In this case, enrollment shall be paused.

A subsequent IDMC review meeting is planned during the study, after Day 43 safety follow-up of 400 participants is completed, no enrollment pause is foreseen for this review. The details of the review will be described in an IDMC charter. The analysis will take place once all 400 participants have returned for their Day 43 visit (Visit ***3***~~2~~) or have withdrawn from the study, within the allowed interval for the visit.

***Section 8.2.3.1, Study Holding Rules***

***The safety holding rules defined in Table 9 only apply to the first 200 study participants enrolled. Holding rules 1-3 will be assessed by the investigator on a continuous basis. Holding rules 1-3 will be assessed by the IDMC during the safety evaluations on unblinded data.***

***Table 9 Study Holding Rules***

| ***Holding Rule*** | ***Event*** | ***Number of participants to pause vaccination in all groups, pending further evaluation by IDMC*** |
|---|---|---|
| ***1*** | ***Any death considered at least possibly related to study vaccination*** | ***≥ 1*** |
| ***2*** | ***Any SAE(s) considered at least possibly related to vaccination*** | ***≥ 1*** |
| ***3*** | ***Same or similar* Grade 3 unsolicited AE considered to be at least possibly related to vaccination*** | ***≥ 2*** |

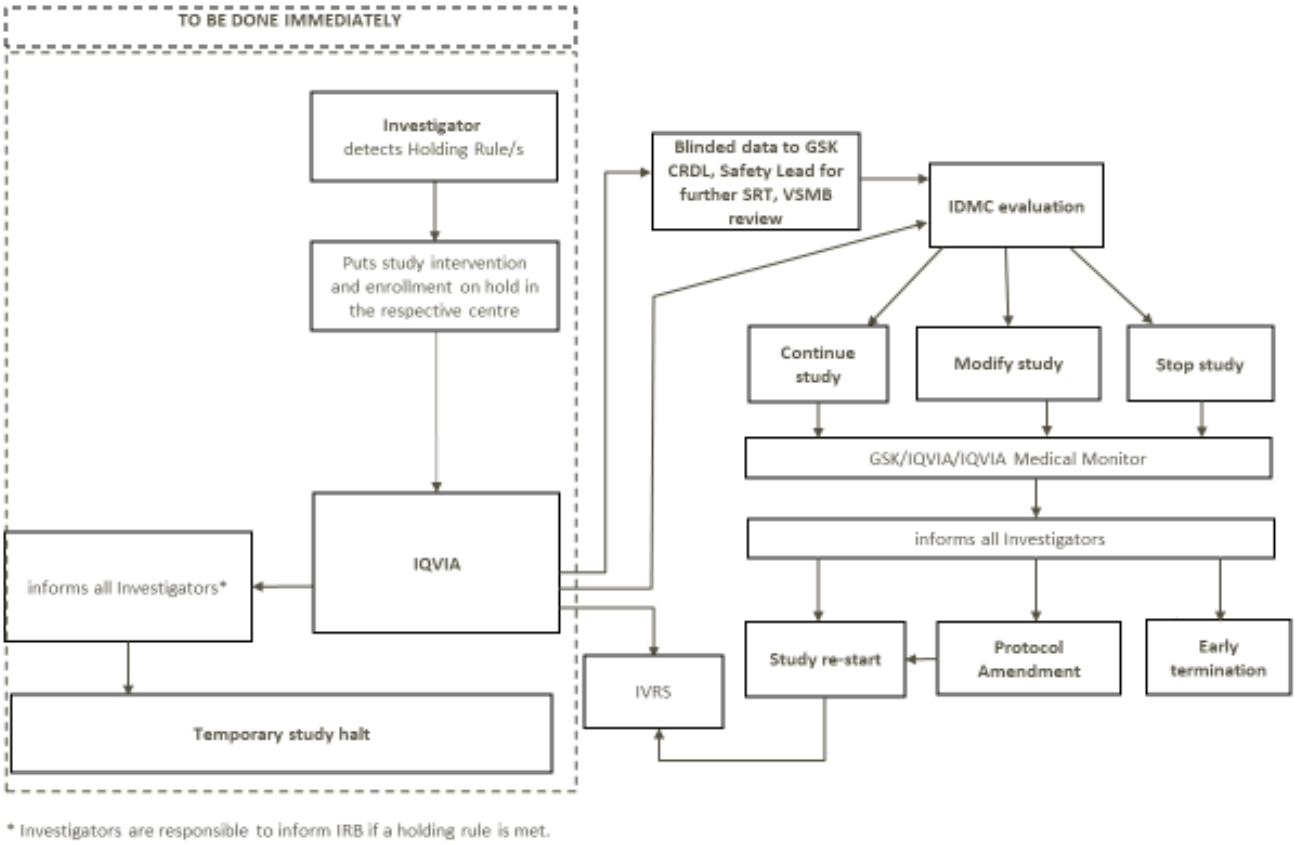
***AE = adverse event; IDMC = Independent Data Monitoring Committee; SAE = serious adverse event***
****based on medical judgment***

***If the investigator becomes aware of a holding rule being met, he/she must suspend administration of the study intervention, pause enrollment, and inform IQVIA immediately (e.g., holding rules 1-3). Refer to Appendix 4 for contact information.***

***GSK via IQVIA will inform all study investigators to suspend the study intervention and enrollment if any of the holding rules are met.***

***The following communication sequence for the identification of holding rules by the investigator must be followed (Figure 2).***

***Figure 2 Communication Flow: Identification of Holding Rules by the Investigator***




***Section 8.2.3.2 Outcome of Safety Evaluation***

***If a safety signal is observed during the safety evaluations, or if any of the holding rules is met for the first 200 participants, the IDMC Chair (or his/her representative) is responsible for the urgent communication to GSK, including the rationale for the decision to put the study intervention administration on hold or not.***

***If no safety signal is observed in the first 200 participants, the favorable outcome of the safety evaluations will be documented and provided in writing, authorizing the investigator to start enrollment and dosing of the remaining participants in the study.***

***GSK via IQVIA will be accountable for notifying all investigators of the decision whether to suspend, modify or continue the conduct of the study on all groups or on selected groups.***

***Refer to Section 8.2.3.1 for a flow chart for escalation of safety signal.***

## Section 9.3, Populations for Analyses, Table 11, Analysis Sets:

Note: Intercurrent medical conditions that may lead to elimination from the PPS are defined as confirmed immunodeficiency condition, or development of varicella or herpes zoster in the interval between study intervention administration and the collection of the blood specimen for immunogenicity at Visit ~~3~~***2***.

## Appendix 1, Abbreviations and the Glossary of Terms:

***SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2***

## Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting:

**b) Solicited systemic events**

The following systemic events will be solicited for children 12 to 15 months of age:

- Fever
- Varicella-like rash ***(including injection site varicella-like rash)***

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

| | Redness/swelling | Varicella-like rash* | Fever† |
|---|---|---|---|
| 0 | None | None | ***< 38.0°C (100.4°F)*** ~~Temperature will be analyzed in 0.5°C~~ ***≥ 38.0°C (100.4°F) - ≤ 39.0°C (102.2°F)*** ~~increments from ≥~~ ***> 39.0°C (102.2°F) - ≤ 39.5°C (103.1°F)*** ~~38°C (≥ 100.4°F)~~. ~~Grade 3 fever is defined as~~ > 39.5°C. (103.1°F) |
| 1 | > 0 - ≤ 5 mm | 1-~~50~~***25*** lesions | |
| 2 | > 5 - ≤ 20 mm | ~~51~~***26***-~~150~~***50*** lesions | |
| 3 | > 20 mm | ~~>~~≥ ~~150~~***51*** lesions | |

* ***Including injection site varicella-like rash***

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

| **Events Requiring Expedited Reporting to IQVIA:** |
|---|
| **SAE(s) throughout the study** |
| • Once ~~an~~ t***he*** investigator ***or designee become aware that study participant(s) have experienced an*** SAE ~~has occurred in a study participant~~, the investigator or ~~investigator's designee~~ 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. ~~The report allows to specify that the event is serious or non-serious.~~<br>• 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.<br>• The investigator will be required to confirm the review of the SAE causality by ticking the "reviewed" box in the electronic Expedited AE Report within 72 hours of submission of the SAE.<br>• Refer to Section 8.3.1 for the details on timeframes for reporting of SAEs. |

| ***Grade 3 unsolicited AE(s) for the first 200 study participants through their Day 43 follow-up:*** |
|---|
| • ***Once the investigator or designee become aware that study participant(s) have experienced a Grade 3 unsolicited AE considered to be at least possibly related to vaccination, 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.***<br>• ***Even if the investigator does not have all information regarding a Grade 3 unsolicited AE considered to be at least possibly related to vaccination, 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.***<br>• ***The investigator will be required to confirm the review of the Grade 3 unsolicited AE(s) causality by ticking the "reviewed" box in the electronic Expedited AE Report within 72 hours of submission of the Grade 3 unsolicited AE(s).***<br>• ***Refer to Section 8.3.1 for the details on timeframes for reporting of AE(s).*** |

# Appendix 6 Signature of Investigator

PROTOCOL TITLE: A phase II, observer-blind, randomized, controlled study to evaluate immunogenicity and safety of a varicella vaccine at various potencies compared with *Varivax,* as a first dose, administered in healthy children in their second year of life.

PROTOCOL NO: 217212 (VNS 20-006)

VERSION: Protocol Amendment 3.0

This protocol is a confidential communication of GSK. I confirm that I have read this protocol, I understand it, I will work according to this protocol and ensure that all persons assisting me with the study are adequately informed about the study interventions and other study-related duties as described in the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from GSK.

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____