# TITLE PAGE

**Protocol Title:**

A Phase III, Open-label, Randomized, Controlled, Multi-country Study to Evaluate the Immune Response, Safety and Reactogenicity of RSVPreF3 OA Investigational Vaccine When Co-administered with 20-Valent Pneumococcal Conjugate Vaccine (PCV20) in Adults Aged 60 Years and Older.

**Protocol Number:** 219276

**Compound:** RSVPreF3 OA

**Study Phase:** III

**Sponsor Name:** GlaxoSmithKline Biologicals S.A.

**Legal Registered Address:** Rue De L'institut 89, 1330 Rixensart, Belgium

**EU CT Number**: 2022-501988-40-00

**Date of Original Protocol:** 06 January 2023

**Date of Original Protocol v2.0:** 27 February 2023

**Date of Protocol Amendment v1.0:** 23 June 2023

**Approval Date:** 23-June-2023

Sponsor Signatory

PPD

Nadia Meyer, MD

Clinical Project Lead

RSV Older Adults

Date

Medical Monitor name and contact information will be provided separately.

# Protocol Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals SA.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To ensure that all individuals assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including blood and serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the participant.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of GSK in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational intervention(s), and more generally about his/her financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.

- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

**Investigator name:** _____

**Signature:** _____

**Date:** _____

# PROTOCOL SUMMARY OF CHANGES TABLE

| **DOCUMENT HISTORY** | | | |
|---|---|---|---|
| **Document** | **Date** | **Substantial** | **Region** |
| Amendment 1.0 | 23-June-2023 | Yes | Global |
| Original Protocol v2.0 | 27-February-2023 | No | Global |
| Original Protocol | 06-January-2023 | - | - |

Amendment v1.0 (23-June-2023)

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

Overall Rationale for Protocol Update:

The protocol has been amended to include the definition of Serious Adverse Reaction (SAR)/Suspected Unexpected Serious Adverse Reactions (SUSAR), and to clarify time period for collecting AE, SAE, and pIMD information as required in Request for Information from Belgium member state of the European Medicines Agency dated 14-June-2023.

(Added text is ***bold italic***, deleted text is ~~strikethrough~~)

| **Section # and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| 8.3.1 Time Period and Frequency for Collecting AE, SAE, and pIMD Information | Edited text:<br>***All AEs (regardless of the assessment of relatedness to the study vaccines), including all SAEs and all pIMDs will be collected from the first study intervention administration. All SAEs and all pIMDs will be collected until 6 months after the last study intervention administration at the timepoints specified in the SoA (Section 1.3).***<br>***AEs (including SAEs and pIMDs) leading to withdrawal from the study will be collected from the time of the first study intervention administration until the participant is discharged from the study.***<br>***In addition, SAEs assessed as related to study participation (e.g.,*** | Clarification |

| | | |
|---|---|---|
| | ***protocol-mandated invasive procedures) or related to any other GSK product (non-IMP) will be recorded from the time a participant consents to participate in the study until the participant is discharged from the study.***<br><br>Deleted text:<br>~~All SAEs and pIMDs will be collected from the start of study intervention until 6 months after the last administration of study interventions at the time points specified in the SoA (Section 1.3).~~<br>~~SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product (non-IMP) will be recorded from the time a participant consents to participate in the study until the participant is discharged from the study.~~<br>~~All AEs/SAEs/pIMDs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study intervention until the participant is discharged from the study.~~ | |
| 10.4 Appendix 4: Abbreviations and Glossary of Terms | Added to Abbreviations and Glossary of Terms list:<br>Serious Adverse Reaction:<br>Suspected Unexpected Serious Adverse Reactions: All noxious and unintended responses to an investigational medicinal product (IMP) related to any dose administered that result in death, are life-threatening, require patient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, or are a congenital anomaly or birth defect.<br>Suspected Unexpected Serious Adverse Reactions: A Suspected Unexpected Serious Adverse | Required in Request for Information from Belgium, EMA |

| | | |
|---|---|---|
| | Reaction is a Serious Adverse Reaction whose nature, severity or outcome is not consistent with the reference safety information. | |

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# 1.0 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase III, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with 20-valent pneumococcal conjugate vaccine (PCV20) in adults aged 60 years and older.

**Rationale:**

GlaxoSmithKline Biologicals SA (GSK) is developing a new respiratory syncytial virus (RSV) PreFusion protein 3 Older Adult (OA) investigational vaccine (RSVPreF3 OA) against RSV-associated (subtypes A and B) disease in adults ≥60 years of age (YOA). The vaccine development is currently in Phase III, and immunogenicity, safety, and reactogenicity of the candidate vaccine when co-administered with other vaccines are being investigated.

Like RSV, pneumococcal disease also presents high disease burden among older adults and the seasonality of RSV disease and invasive pneumococcal disease is similar.

The present study will assess the immunogenicity, safety and reactogenicity of the RSVPreF3 OA investigational vaccine when co-administered with the 20 valent pneumococcal conjugate vaccine (referred to as *Prevnar 20* in USA or *Apexxnar* in Europe [hereafter referred to as PCV20]) in adults ≥60 YOA.

**Objectives, Endpoints, and Estimands:**

| Objectives | Endpoints and Estimands |
|---|---|
| **Primary*** | |
| • To demonstrate the non-inferiority of PCV20 when co-administered with the RSVPreF3 OA investigational vaccine compared to PCV20 administered alone | • Opsonophagocytic (OP) antibody (Ab) titers for each of the pneumococcal vaccine serotype (ST) expressed as between groups geometric mean titer (GMT) ratio, 1 month after the PCV20 dose |
| • To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine in terms on RSV-A neutralization antibodies when co-administered with PCV20 compared to RSVPreF3 OA investigational vaccine administered alone | • RSV-A neutralizing Ab titers expressed as between groups GMT ratio, 1 month after the RSVPreF3 OA investigational vaccine dose |
| • To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine in terms of RSV-B neutralization antibodies when co-administered with the PCV20 vaccine compared to RSVPreF3 OA investigational vaccine administered alone. | • RSV-B neutralizing Ab titers expressed as between groups GMT ratio, 1 month after the RSVPreF3 OA investigational vaccine dose |

| Objectives | Endpoints and Estimands |
|---|---|
| **Secondary** | |
| • To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with the PCV20 or administered alone | • RSV-A neutralizing Ab titers expressed as mean geometric increase (MGI) over baseline at 1 month after the RSVPreF3 OA investigational vaccine dose<br>• RSV-B neutralizing Ab titers expressed as MGI over baseline at 1 month after the RSVPreF3 OA investigational vaccine dose |
| • To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and PCV20, co-administered or administered alone. | • Percentage of participants reporting each solicited event with onset within 7 days after vaccine administration (i.e., the day of vaccination and 6 subsequent days)<br>• Percentage of participants reporting unsolicited AE within 30 days after vaccine administration (i.e., the day of vaccination and 29 subsequent days)<br>• Percentage of participants reporting SAEs after vaccine administration (Day 1) up to EoS (6 months after last vaccination)<br>• Percentage of participants reporting pIMDs after vaccine administration (Day 1) up to EoS (6 months after last vaccination) |

Abbreviations: Ab=antibody; AE=adverse event; EoS=end of study; GMT=geometric mean titer; MGI=mean geometric increase; OA=older adult; OP=opsonophagocytic; PCV20=20-valent pneumococcal vaccine; pIMD=potential immune-mediated disease; RSV=respiratory syncytial virus; RSVPreF3 OA=respiratory syncytial virus PreFusion protein 3 older adult investigational vaccine; SAE=serious adverse event; ST=serotype.

* PCV and RSV-A endpoint will be assessed as co-primary and following the current success RSV-B will be demonstrated as sequential. Refer to Section 9.3.1.1 for the testing sequence of primary objectives.

**Overall Design:**

**Experimental design**: Phase III, open-label, randomized, controlled, multi-country study with 2 parallel groups.

**Study groups and Randomization**: Approximately 1090 eligible participants will be randomly (1:1) assigned to 2 study groups using a centralized randomization system on internet at Visit 1 (Day 1). The randomization algorithm will use a minimization procedure accounting for age (60 to 69, 70 to 79 or ≥80 years) and center. Minimization factors will have equal weight in the minimization algorithm.

Overall, participants will be enrolled in 3 age categories with a balance between males and females. It is intended to enroll:

- Approximately 40% of participants 60 to 69 YOA, approximately 30% of participants 70 to 79 YOA and approximately 10% of participants ≥80 YOA. The remaining 20% can be distributed freely across the 3 age categories.
- Approximately 40% of participants from each sex; the remaining 20% can be distributed freely between the 2 sexes.

**Duration of study**: The total duration of the study, per participant, will be approximately 6 months for the co-ad group, and 7 months for the control group.

**Co-administration (Co-ad) group**: Study intervention administration RSVPreF3 OA investigational vaccine and PCV20 vaccine on Visit 1 (Day 1) and follow-up for 6 months, until end of study (EoS). Two site visits (Visit 1 [Day 1] and Visit 2 [Day 31]) and a phone contact 6 months post-last dose.

**Control group**: Study intervention administrations of PCV20 vaccine on Visit 1 (Day 1) and RSVPreF3 OA investigational vaccine on Visit 2 (Day 31) and -follow-up for 6 months, until EoS. Three site visits (Visit 1 [Day 1], Visit 2 [Day 31], and Visit 3 [Day 61]) and a phone contact 6 months post-last dose.

**Number of Participants:**

Approximately 1090 participants aged ≥60 years will be randomly (1:1) assigned to 2 study groups (i.e., co-ad group or the control group).

**Safety monitoring:** the study will be conducted with oversight by the project Safety Review Team.

## 1.2 Schema

**Figure 1 Study Design Overview**

AE=Adverse Event; Co-Ad group=Co-Administration group; D=Day; N=Number of participants; PCV=20-valent pneumococcal conjugate vaccine; pIMD=potential Immune-Mediated Disease; RSV=RSVPreF3 OA; SAE=Serious Adverse Event.

## 1.3 Schedule of Activities

**Table 1 Schedule of Activities for the Co-ad Group**

| Type of contact | Visit 1 | Visit 2[a] | Phone Contact[b] |
|---|---|---|---|
| **Timepoints Co-ad Group** | **Day 1** | **Day 31[c]** | **6-months post-last dose** |
| Obtain informed consent | ● | | |
| Distribution of participant card | ○ | | |
| Check inclusion/exclusion criteria for screening | ● | | |
| Screening conclusion | ● | | |
| Check with participant if he/she will appoint a caregiver and distribute caregiver information letter, when applicable | ○ | ○ | |
| **Baseline and demographic assessments** | | | |
| Collect demographic data | ● | | |
| Record relevant vaccination and medical history | ● | | |
| Perform targeted physical examination | ○ | | |
| **Laboratory assessment** | | | |
| Blood sampling for antibody determination (~15 mL) | ●[d] | ●[e] | |
| **Study interventions** | | | |
| Check contraindications, warnings, and precautions to study intervention administration | ○ | | |
| Check criteria for temporary delay for enrollment and study intervention administration | ○ | | |
| Randomization and study group allocation | ● | | |
| Intervention numbers allocation | ○ | | |
| Record body temperature before study interventions administration[f] | ● | | |

| Type of contact | Visit 1 | Visit 2[a] | Phone Contact[b] |
|---|---|---|---|
| **Timepoints Co-ad Group** | **Day 1** | **Day 31[c]** | **6-months post-last dose** |
| Study interventions administration (PCV20 + RSVPreF3 OA investigational vaccine) (including 30-minute post-dosing observation) | ● | | |
| Recording of administered study interventions numbers | ● | | |
| **Safety assessments** | | | |
| Setup of eDiary | ○ | | |
| Training on use of eDiary | ○ | | |
| Recording of solicited events in eDiary (Days 1 – 7 post-dosing) | Δ | | |
| Recording of ongoing solicited events in eDiary if applicable (Days 8 – 30 post-dosing) | Δ | Δ | |
| Review eDiary | | ○[g] | |
| Collect eDiary or assist participant to delete application | | ○ | |
| Recording of unsolicited AEs (Days 1 - 30 post-dosing) | ● | ● | |
| Recording of concomitant medications/vaccinations | ● | ● | ● |
| Recording of intercurrent medical conditions | ● | ● | ● |
| Recording of SAEs and pIMDs | ● | ● | ● |
| Recording of AEs/SAEs leading to withdrawal from the study | ● | ● | ● |
| Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[h] | ● | ● | ● |
| Contact for safety follow-up | | | ● |
| Study conclusion | | | ● |

Abbreviations; AE=adverse event; COVID-19=coronavirus disease 2019; eCRF=electronic case report form; eDiary=electronic diary; OA=older adult; SAE=serious adverse event; PCV20=20-valent pneumococcal conjugate vaccine; pIMD=potential immune-mediated disease; RSV=respiratory syncytial virus.

Note: The double-line borders indicate the analyses which will be performed on all data obtained up to these timepoints (refer to Section 9.4.1).

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
[Δ] is used to indicate a study procedure that requires documentation in the eDiary.
[a] Visit 2 should preferably be done on site but if deemed necessary (during special circumstances such as the COVID-19 pandemic), this study visit can be replaced by a home visit conducted by authorized staff. Any information from the participant required according to study procedures and not collected during the home visit can be obtained by means of a phone call conducted by the site staff.
[b] Six months after last vaccination. For this contact, multiple formats (e.g., email, text message, fax, or phone call) can be proposed by the study site.
[c] Visit window shown in Table 3.
[d] Sample collected at Day 1 will be used as baseline for RSV and PCV20 antibody titers.
[e] Sample collected at Day 31 will be used for the post-vaccination RSV vaccine- and PCV20 vaccine-related testing.
[f] The route for measuring body temperature can be oral or axillary. Fever is defined as temperature ≥38.0 °C/100.4 °F, regardless of the location of measurement.
[g] Designated site staff should review the eDiary frequently during the active event collection period to assess participant/caregiver compliance and monitor reported events.
[h] SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to study vaccine administration) up to end of study (EoS).

**Table 2 Schedule of Activities for the Control Group**

| Type of contact | Visit 1 | Visit 2 | Visit 3[a] | Phone Contact[b] |
|---|---|---|---|---|
| **Timepoints Control Group** | **Day 1** | **Day 31[c]** | **Day 61[c]** | **6-months post-last dose** |
| Obtain informed consent | ● | | | |
| Distribution of participant card | ○ | | | |
| Check inclusion/exclusion criteria for screening | ● | | | |
| Screening conclusion | ● | | | |
| Check with participant if he/she will appoint a caregiver and distribute caregiver information letter, when applicable | ○ | ○ | ○ | |
| **Baseline and demographic assessments** | | | | |
| Collect demographic data | ● | | | |
| Record relevant vaccine and medical history | ● | ● | ● | |
| Perform targeted physical examination | ○ | | | |
| **Laboratory assessment** | | | | |
| Blood sampling for antibody determination (~15 mL) | ●[d] | ●[e] | ●[f] | |
| **Study intervention** | | | | |
| Check contraindications, warnings, and precautions to study intervention administration | ○ | ○ | | |
| Check criteria for temporary delay for enrollment and study intervention administration | ○ | ○ | | |
| Randomization and study group allocation | ● | | | |
| Intervention number allocation (PCV20) | ○ | | | |
| Intervention number allocation (RSVPreF3 OA investigational vaccine) | | ○ | | |
| Record body temperature before study intervention administration[g] | ● | ● | | |
| Study intervention administration (PCV20) (including 30-minute post-dosing observation) | ● | | | |

| Type of contact | Visit 1 | Visit 2 | Visit 3[a] | Phone Contact[b] |
|---|---|---|---|---|
| **Timepoints Control Group** | **Day 1** | **Day 31[c]** | **Day 61[c]** | **6-months post-last dose** |
| Study intervention administration (RSVPreF3 OA investigational vaccine) (including 30-minute post-dosing observation) | | ● | | |
| Recording of administered study intervention number | ● | ● | | |
| **Safety assessments** | | | | |
| Setup of eDiary | ○ | | | |
| Training on use of eDiary | ○ | | | |
| Recording of solicited events in eDiary (Days 1 - 7 post-dosing) | Δ | Δ | | |
| Recording of ongoing solicited events in eDiary if applicable (Days 8 – 30 post-dosing) | Δ | Δ | Δ | |
| Review eDiary | | ○[h] | ○[h] | |
| Collect eDiary or assist participant to delete application | | | ○ | |
| Recording of unsolicited AEs (Days 1 - 30 post-dosing) | ● | ● | ● | |
| Recording of concomitant medications/vaccinations | ● | ● | ● | ● |
| Recording of intercurrent medical conditions | ● | ● | ● | ● |
| Recording of SAEs and pIMDs | ● | ● | ● | ● |
| Recording of AEs/SAEs leading to withdrawal from the study | ● | ● | ● | ● |
| Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[i] | ● | ● | ● | ● |
| Contact for safety follow-up | | | | ● |
| Study conclusion | | | | ● |

Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; eCRF=electronic case report form; eDiary=electronic diary; SAE=serious adverse event; PCV20=20-valent pneumococcal conjugate vaccine; pIMD=potential immune-mediated disease; RSV=respiratory syncytial virus.

Note: The double-line borders indicate the analyses which will be performed on all data obtained up to these timepoints (refer to Section 9.4.1).

● is used to indicate a study procedure that requires documentation in the individual eCRF.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

[Δ] is used to indicate a study procedure that requires documentation in the individual eDiary.

[a] Visit 3 should preferably be done on site but if deemed necessary (during special circumstances such as the COVID-19 pandemic), this study visit can be replaced by a home visit conducted by authorized staff. Any information from the participant required according to study procedures and not collected during the home visit can be obtained by means of a phone call conducted by the site staff.

[b] Six months after last vaccination. For this contact, multiple formats (e.g., email, text message, fax, or phone call) can be proposed by the study site.

[c] Visit window shown in Table 4

[d] Sample collected at Day 1 will be used as baseline for PCV20 antibody titers.

[e] Sample collected at Day 31 will be used for the post-vaccination PCV20 vaccine-related testing. This sample will also be used as baseline for the RSV vaccination in the Control group.

[f] Sample collected at Day 61 will be used for the post-vaccination RSV vaccine-related testing.

[g] The route for measuring body temperature can be oral or axillary. Fever is defined as temperature ≥38.0°C/100.4°F, regardless of the location of measurement.

[h] Designated site staff should review the eDiary frequently during the active event collection period to assess participant/caregiver compliance and monitor reported events.

[i] SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to study vaccine administration) up to EoS.

**Table 3 Interval Between Study Visits (Co-ad Group)**

| Interval | Planned visit interval | Allowed interval (Visit window) |
|---|---|---|
| Visit 1 (Day 1/study intervention administration) → Visit 2 (Day 31) | 30 days | 30-42 days |
| Visit 1 → phone contact | 180 days | 180-210 days |

**Table 4 Interval Between Study Visits (Control Group)**

| Interval | Planned visit interval | Allowed interval (Visit window) |
|---|---|---|
| Visit 1 (Day 1/study intervention administration) → Visit 2 (Day 31) | 30 days | 30-42 days |
| Visit 2 (Day 31/study intervention administration) → Visit 3 (Day 61) | 30 days | 30-42 days |
| Visit 2 → phone contact | 180 days | 180-210 days |

# 2.0 INTRODUCTION

## 2.1 Study Rationale

GlaxoSmithKline Biologicals SA (GSK) is developing a new respiratory syncytial virus (RSV) PreFusion protein 3 Older Adult (OA) investigational vaccine (RSVPreF3 OA) against RSV-associated (subtypes A and B) disease in adults ≥60 years of age (YOA). The vaccine development is currently in Phase III, and immunogenicity, safety, and reactogenicity of the candidate vaccine when co-administered with other vaccines are being investigated.

The present study will assess the immunogenicity, safety, and reactogenicity of the RSVPreF3 OA investigational vaccine when co-administered with the 20-valent pneumococcal conjugate vaccine (referred to as Prevnar 20 in USA or Apexxnar in Europe [hereafter referred to as PCV20]) in adults ≥60 YOA.

## 2.2 Background

Respiratory syncytial virus can cause severe lower respiratory tract infection in older adults and adults with chronic medical conditions including cardiopulmonary and immunocompromising conditions.

Based on epidemiological data collected prospectively in 2008-2010 in 14 countries worldwide (including North America, Europe, and East Asia), the average percentage of documented RSV infection in older adults with influenza-like illness is 7.4%, with values between 0% and 17.1% across countries[1]. In 2015, an estimated 1.5 million episodes of RSV-related acute respiratory illness occurred in older adults in industrialized countries; approximately 14.5% of these episodes involved a hospital admission.[2] Further information on RSV incidence and disease burden can be found in the Investigator's Brochure (IB).

There are 2 subtypes of RSV virus- RSV-A and RSV-B. RSV virus circulates with other respiratory viruses, and infections peak during winter period. To date, no licensed vaccine or prophylactic treatment is available for RSV. Currently available treatment for RSV infection is limited to supportive care. Like RSV, pneumococcal disease also presents high disease burden among older adults and the seasonality of RSV disease and invasive pneumococcal disease is similar.[3,4]

Pneumococcal vaccines for adults are available in both conjugated and polysaccharide formulations. A PPSV23 is licensed, along with conjugated pneumococcal vaccines including, PCV15 and PCV20. Currently the recommendations for pneumococcal vaccination vary from country to country. Some countries recommend polysaccharide vaccine, other recommend conjugate vaccine, while some recommend the use of both.

## 2.3 Benefit/Risk Assessment

### 2.3.1 Risk Assessment

Detailed information about the known and expected benefits and potential risks and reasonably expected adverse events (AEs) of the RSVPreF3 OA investigational vaccine can be found in the Investigator's Brochure (IB) and Development Safety Update Report (DSUR).

Study participants must be observed closely for at least 30 minutes after the administration of the study interventions. Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis and/or syncope.

| Important Potential/Identified Risk | Mitigation Strategy |
|---|---|
| **RSV investigational vaccine** | |
| Potential immune-mediated diseases (pIMDs) are considered a potential risk, as for all vaccines containing an adjuvant system. | Refer to Section 10.3.3 for details. |
| Syncope and hypersensitivity reactions (including anaphylaxis). | All participants will remain under observation at the clinical center for at least 30 minutes after vaccination.<br>Participants with a history of hypersensitivity or severe allergic reaction to any component of the vaccine are excluded from study enrollment. |
| **Study procedures** | |
| Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, erythema/redness, and swelling. | As a mitigation strategy, physicians can implement the measures that they consider necessary. |
| Pain and bruising may occur at the site where blood is drawn. | As a mitigation strategy, physicians can implement the measures that they consider necessary. |
| Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle insertion. | Participants who mention experiencing previous episodes of fainting or dizziness before, during or after a blood draw, will remain under observation at the clinical center until deemed necessary by site personnel. Appropriate medical treatment must be readily available during this period. |

Abbreviations: PCV20=20 pneumococcal serotypes vaccine; pIMD=potential immune-mediated disease; RSV=respiratory syncytial virus.

For expected adverse reactions associated with Pfizer's PCV20 vaccine, please refer to the Prescribing Information.

### 2.3.2 Benefit Assessment

The participants may have the benefit of being protected against RSV infection during the active season. In a large Phase III vaccine clinical trial in adults aged 60 years and above, the RSVPreF3 investigational vaccine candidate demonstrated overall vaccine efficacy of 82.6% (96.95% confidence interval [CI], 57.9 to 94.1) against RSV lower respiratory tract disease (RSV-LRTD).[5] The vaccine was well tolerated with a favorable safety profile.

All participants in this study will also receive PCV20 vaccine as part of this study, which is one of the most recently developed pneumococcal vaccines and is recommended in US for adults ≥65 years of age for the prevention of pneumococcal disease.

An indirect benefit is that the information obtained in this study will generate more knowledge about the RSV vaccine and the possibility to be co-administered with pneumococcal vaccine. Another benefit for all study participants may include gaining information about their general health status through the recurrent medical evaluations/assessments associated with this study (i.e., physical examination).

### 2.3.3 Overall Benefit-Risk Conclusion

The RSVPreF3 OA investigational vaccine is in clinical development. Considering the recent data on the vaccine efficacy, and measures taken to minimize the risk to participants in this study the potential risks are justified by the potential benefits linked to the development of this vaccine.

*Prevnar 20*™ is a vaccine indicated for active immunization for the prevention of pneumonia and invasive disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults 18 years of age and older.

# 3.0 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

| Objectives | Endpoints and Estimands |
|---|---|
| **Primary*** | |
| • To demonstrate the non-inferiority of PCV20 when co-administered with the RSVPreF3 OA investigational vaccine compared to PCV20 administered alone | • Opsonophagocytic (OP) antibody (Ab) titers for each of the pneumococcal vaccine serotype (ST) expressed as between groups geometric mean titer (GMT) ratio, 1 month after the PCV20 dose |
| • To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine in terms of RSV-A neutralization antibodies when co-administered with PCV20 compared to RSVPreF3 OA investigational vaccine administered alone | • RSV-A neutralizing Ab titers expressed as between groups GMT ratio, 1 month after the RSVPreF3 OA investigational vaccine dose |
| • To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine in terms of RSV-B neutralization antibodies when co-administered with the PCV20 vaccine compared to RSVPreF3 OA investigational vaccine administered alone | • RSV-B neutralizing Ab titers expressed as between groups GMT ratio, 1 month after the RSVPreF3 OA investigational vaccine dose |
| **Secondary** | |
| • To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with the PCV20 or administered alone | • RSV-A neutralizing Ab titers expressed as mean geometric increase (MGI) over baseline at 1 month after the RSVPreF3 OA investigational vaccine dose<br>• RSV-B neutralizing Ab titers expressed as MGI over baseline at 1 month after the RSVPreF3 OA investigational vaccine dose |
| • To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and PCV20, co-administered or administered alone. | • Percentage of participants reporting each solicited event with onset within 7 days after vaccine administration (i.e., the day of vaccination and 6 subsequent days)<br>• Percentage of participants reporting unsolicited AE within 30 days after vaccine administration (i.e., the day of vaccination and 29 subsequent days)<br>• Percentage of participants reporting SAEs after vaccine administration (Day 1) up to EoS (6 months after last vaccination)<br>• Percentage of participants reporting pIMDs after vaccine administration (Day 1) up to EoS (6 months after last vaccination) |

Footnotes for the Objectives, Endpoints, and Estimands table.
Abbreviations: Ab=antibody; AE=adverse event; EoS=end of study; GMT=geometric mean titer; MGI=mean geometric increase; OA=older adult; OP=opsonophagocytic; PCV20=20-valent pneumococcal vaccine; pIMD=potential immune-mediated disease; RSV=respiratory syncytial virus; RSVPreF3 OA=respiratory syncytial virus PreFusion protein 3 older adult investigational vaccine; SAE=serious adverse event; ST=serotype.
* PCV and RSV-A endpoint will be assessed as co-primary and following the current success RSV-B will be demonstrated as sequential. Refer to Section 9.3.1.1 for the testing sequence of primary objectives.

Details related to attributes of estimand covering intercurrent events, population and treatment definition are provided in the Section 9.0.

# 4.0 STUDY DESIGN

## 4.1 Overall Design

The Study Design Overview is provided in Figure 1.

**Experimental design**: Phase III, open-label, randomized, controlled, multi-country study with 2 parallel groups.

**Study groups and Randomization**: Approximately 1090 eligible participants will be randomly (1:1) assigned to 2 study groups using a centralized randomization system on internet at Visit 1 (Day 1). The randomization algorithm will use a minimization procedure accounting for age (60 to 69, 70 to 79 or ≥80 years) and center. Minimization factors will have equal weight in the minimization algorithm.

Overall, participants will be enrolled in 3 age categories with a balance between males and females. It is intended to enroll:

- Approximately 40% of participants 60 to 69 YOA, approximately 30% of participants 70 to 79 YOA, and approximately 10% of participants ≥80 YOA. The remaining 20% can be distributed freely across the 3 age categories.
- Approximately 40% of participants from each sex; the remaining 20% can be distributed freely between the 2 sexes.

**Duration of study**: The total duration of the study, per participant, will be approximately 6 months for the co-ad group, and 7 months for the control.

**Safety monitoring:** the study will be conducted with oversight by the project Safety Review Team (SRT). See Section 10.1.6 for SRT structure.

**Co-administration (Co-ad) group**: Study intervention administration RSVPreF3 OA investigational vaccine and PCV20 vaccine on Visit 1 (Day 1) and follow-up for 6 months, until end of study (EoS). Two site visits (Visit 1 [Day 1] and Visit 2 [Day 31]) and a phone contact 6 months post-last dose.

**Control group**: Study intervention administrations of PCV20 vaccine on Visit 1 (Day 1) and RSVPreF3 OA investigational vaccine on Visit 2 (Day 31) and follow-up for 6 months, until EoS. Three site visits (Visit 1 [Day 1], Visit 2 [Day 31] and Visit 3 [Day 61]) and a phone contact 6 months post-last dose.

See Table 5 for study interventions administered.

### 4.1.1 Overview of the Recruitment Plan

No separate screening visit is planned for this study. The study is planned to be conducted at sites in multiple countries. The recruitment plan will be defined by each participating site.

The recruitment plan may be adapted based on the actual number of participants enrolled in each country. In case a site would fall behind in participant recruitment, a redistribution of the enrollment target per site in the participating countries may be made. This would allow the other participating sites to enroll additional participants to ensure full and timely enrollment of the overall targeted number of participants specified in this protocol.

The procedures for participants identification/recruitment must be approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) together with the material intended for participants identification/recruitment and participants use.

### 4.1.2 Enrollment Rules

Overall, participants will be enrolled in 3 age categories reflecting an approximate age distribution in the general population with a balance between males and females. It is therefore intended to enroll:

- Approximately 40% of participants 60 to 69 YOA, approximately 30% of participants 70 to 79 YOA, and approximately 10% of participants ≥80 YOA. The remaining 20% can be distributed freely across the 3 age categories.
- Approximately 40% of participants from each sex; the remaining 20% can be distributed freely between the 2 sexes.

## 4.2 Scientific Rationale for Study Design

GlaxoSmithKline Biologicals SA (GSK) is developing a new respiratory syncytial virus (RSV) PreFusion protein 3 Older Adult (OA) investigational vaccine (RSVPreF3 OA) against RSV-associated (subtypes A and B) disease in adults ≥60 years of age (YOA). The vaccine development is currently in Phase III, and immunogenicity, safety, and reactogenicity of the candidate vaccine when co-administered with other vaccines are being investigated.

Like RSV, pneumococcal disease also presents high disease burden among older adults. Moreover, the seasonality of RSV disease and invasive pneumococcal disease is similar.

The present study will assess the immunogenicity, safety, and reactogenicity of the RSVPreF3 OA investigational vaccine when co-administered with the pneumococcal conjugate vaccine (referred to as *Prevnar 20* in USA or *Apexxnar* in Europe [hereafter referred to as PCV20]) in adults ≥60 YOA.

## 4.3 Justification for Dose

Based on the results up to 1-month post-Dose 2 from study RSV OA=ADJ-002, a single dose regimen (0.5 mL) and the 120 µg RSVPreF3/AS01$_E$ formulation were selected for further evaluation in the Phase 3 clinical program. The RSV OA=ADJ-002 study was designed to assess the immunogenicity of a 2-dose AS01-adjuvanted or unadjuvanted vaccine administered according to a 0-, 2-month schedule with the aim to maximize the immune response against RSV and vaccine efficacy over several seasons. Based on the data from clinical development programs for AS01-adjuvanted protein antigen vaccines in OA, such as Shingrix and the chronic obstructive pulmonary disease (COPD) investigational vaccine, it was expected that immunological responses would reach higher levels 1 month post-Dose 2 as compared with 1-month post-Dose 1. However, the RSV OA=ADJ-002 results demonstrated that the second dose given 2 months after the first dose had no added value in terms of humoral and/or cellular immune responses. The humoral response, both in terms of RSV-A neutralizing antibody GMTs and RSVPreF3 IgG geometric mean concentrations (GMCs), peaked 1 month after the first dose, and the second dose did not increase the level observed after first dose.

The results from study RSV OA=ADJ-002 demonstrated statistically significant superiority of the 120 µg formulations in terms of RSV-A neutralizing titers over at least one of the 30 µg and 60 µg formulations with the same adjuvant content or unadjuvanted. The data demonstrated an immunologic benefit of any AS01$_E$ or AS01$_B$ formulations over unadjuvanted formulations in terms of frequency of RSVPreF3-specific CD4+ T cells expressing at least 2 markers. Importantly, despite lower baseline observed in OA, the AS01-containing formulations induced CD4+ T cells frequencies at a close or similar level as in young adults, that is not observed with the unadjuvanted formulations.

There was no safety concern detected in unadjuvanted groups to be linked to the RSVPreF3 antigen assessed for the first time in OA. The acceptable safety/reactogenicity profile in all 120 µg groups, together with the immunological benefit demonstrated for the 120 µg antigen dose, supports the selection of a 120 µg based formulation. The results also showed that all the AS01-adjuvanted formulations evaluated are considered to have a clinically acceptable safety profile. The AS01-adjuvanted formulation with the lowest reactogenicity profile, i.e., the AS01$_E$-based formulation, was selected. The immunological response observed after 1 vaccine dose of the AS01$_E$-based formulation is considered adequate for a RSVPreF3 OA candidate vaccine.

In the current study, the PCV20 vaccine will be administered as a 0.5 mL single-dose pre-filled syringe as per Prescribing Information.

## 4.4 End of Study Definition

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

End of Study is the last subject last visit (LSLV) (contact at 6 months post-last dose).

## 4.5 Study Stopping Criteria

Not applicable for this study.

## 4.6 Participant Input into Design

Not applicable for this study.

# 5.0 STUDY POPULATION

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

## 5.1 Inclusion Criteria

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

- A male or female ≥60 YOA at the time of the first study intervention administration.
- Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the eDiary, return for follow-up visits, ability to access and utilize a phone or other electronic communications).
    - *Note: In case of physical incapacity that would preclude the self-completion of the eDiary, either site staff can assist the participant (for activities performed during site visits) or the participant may assign a caregiver* to assist him/her with this activity (for activities performed at home). However, at no time will the site staff or caregiver* evaluate the participant's health status while answering diaries or make decisions on behalf of the participant.*
      **A 'caregiver' is a person who has a continuous caring role for a participant or may be a person having substantial periods of contact with a participant and/or is engaged in his/her daily health care (e.g., a relative of the participant including family members or friends).*
- Written or witnessed informed consent obtained from the participant prior to any study-specific procedure being performed.
- Participants living in the general community or in an assisted-living facility that provides minimal assistance, such that the participant is primarily responsible for self-care and activities of daily living.
- Participants who are medically stable in the opinion of the investigator at the time of first study intervention administration. Participants with chronic stable medical conditions with or without specific treatment, such as diabetes mellitus, hypertension, or cardiac disease, are allowed to participate in this study if considered by the investigator as medically stable.

## 5.2 Exclusion Criteria

**The following criteria should be checked at the time of study entry. The potential participant MAY NOT be included in the study if ANY exclusion criterion applies:**

### 5.2.1 Medical Conditions

- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., current malignancy, human immunodeficiency virus) or

immunosuppressive/cytotoxic therapy (e.g., medication used during cancer chemotherapy, organ transplantation, or to treat autoimmune disorders), based on medical history and physical examination (no laboratory testing required).

- History of any reaction or hypersensitivity (e.g., anaphylaxis) likely to be exacerbated by the study interventions, in particular any history of severe allergic reaction to any vaccine containing diphtheria toxoid (for example, diphtheria-tetanus-pertussis [DTaP]), or PPSV23.
- Participants considered by investigator as suffering from serious or unstable chronic illness.
- Any history of dementia or any medical condition that moderately or severely impairs cognition.
    - *Note: If deemed necessary for clinical evaluation, the investigator can use tools such as Mini-Mental State Examination (MMSE), Mini-Cog or Montreal Cognitive Assessment (MoCA) to determine cognition levels of the participant.*
- Recurrent or uncontrolled neurological disorders or seizures. Participants with medically -controlled chronic neurological diseases can be enrolled in the study as per investigator assessment, provided that their condition will allow them to comply with the requirements of the protocol (e.g., completion of the eDiary, attend regular phone calls/study site visits).
- Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival up to EoS).
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.

### 5.2.2 Prior and Concomitant Therapy

- History of previous vaccination with any licensed or investigational pneumococcal conjugate vaccine, or planned receipt through study participation.
- History of previous vaccination with any licensed or investigational pneumococcal polysaccharide vaccine in the last 5 years from enrollment, or planned receipt through study participation.
- Previous vaccination with any licensed or investigational RSV vaccine
- 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 first dose of study interventions and ending 30 days after the last study intervention administration, or their planned use during the study period.
- Planned or actual administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first study intervention administration and ending 30 days after the last study intervention administration.

- Planned or actual administration of adjuvanted quadrivalent influenza vaccine or live influenza vaccine not foreseen by the study protocol in the period starting 30 days before the first study intervention administration and ending 30 days after the last study intervention administration.
  *Note: In case an emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organized by the 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 or designee is notified accordingly.*

- Administration of long-acting immune-modifying drugs during the period starting 180 days before the administration of first dose of study interventions or planned administration at any time during the study period (e.g., infliximab).
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 90 days before the administration of first dose of study interventions or planned administration during the study period.
- Chronic administration (defined as more than 14 consecutive days in total) of immunosuppressants or other immune-modifying drugs during the period starting 90 days prior to the first study intervention dose or planned administration during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent. Inhaled and topical steroids are allowed.

### 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 vaccine/product (drug or invasive medical device).

  *Note: European Economic Community (EEC) directive 93/42/EEC defines an invasive medical device as 'A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.'*

### 5.2.4 Other Exclusions

- History of chronic alcohol consumption and/or drug abuse as deemed by the investigator to render the potential participant unable/unlikely to provide accurate safety reports or comply with study procedures.
- Bedridden participants.
- Planned move during the study conduct that prohibits participation until study end.
- Participation of any study personnel or their immediate dependents, family, or household members.

## 5.3 Caregiver Support

Study participants may decide to assign a caregiver to help them fulfill the study procedures. Please refer to the Glossary of Terms for the definition of a caregiver.

A caregiver can be appointed by the participant at any time during the study, when the participant feels it is necessary. Each caregiver should receive the caregiver information letter before providing support to the study participant. Ideally, a single caregiver should be appointed by the participant but, in some situations, it may happen that several caregivers will support a study participant throughout the conduct of the study. This should be recorded in the source documents. However, every effort should be made to ensure that only one caregiver enters the data into the eDiary to allow for timely completion.

Caregivers may help the study participants with performing some practical study procedures such as receiving or making phone calls to site staff, planning study visits, transcribing responses to diaries, transportation to and from the study site etc. However, at no time, the caregiver should evaluate the participant's health status while answering diaries or make decisions on behalf of the participant. At the first study visit (Visit 1 [Day 1]) the site staff should inform the participant of the possibility to appoint a caregiver. Then at subsequent study visit(s), the site staff should check again with the participant if he/she wishes to appoint a caregiver or if there were or will be changes of caregiver.

## 5.4 Lifestyle Considerations

Not applicable for this study.

## 5.5 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized to study intervention/entered in the study.

Limited data for screening failures (including reason for screening failure and any SAEs related to study participation, or to a concurrent GSK medication/vaccine from the time of consent obtained) will be collected and reported in the eCRF.

Individuals who do not meet the criteria for participation in this study (screen failure) but at some point, in the future are expected to meet the eligibility criteria may be rescreened. Individuals who are rescreened will be assigned a new participant number and will undergo the informed consent process, and then restart a new screening phase.

## 5.6 Criteria for Temporarily Delaying

Study intervention administration may be postponed within the permitted time interval as deemed appropriate by the investigator until transient conditions cited below are resolved and prior to the EoS enrollment period:

- Acute disease and/or fever at the time of study intervention administration. Refer to Section 1.3 (Schedule of Activities [SoA]) for definition of fever and location for measuring body temperature in this study.
- Participants with a minor illness (such as mild diarrhea) without fever may be dosed at the discretion of the investigator.
- Participants with symptoms suggestive of active Coronavirus Disease 2019 (COVID-19) infection (e.g., fever, cough, etc.). The return of the participant to the site will follow the specific guidance from local public health and other competent authorities (e.g., free of symptoms, COVID-19 negative testing, etc.).
- Participants with known contact with COVID-19 positive individual may be vaccinated at least 14 days after the exposure, provided that the participant remains symptom-free, and at the discretion of the investigator.
- In case of administration of inactivated and subunit influenza vaccines or COVID-19 vaccines (fully licensed or with EUA): postponement of study intervention administration within given protocol timelines and prior to the end of the study enrollment period, to allow respect of at least 14 days interval between flu/COVID-19 vaccination and study intervention administration.
- Use of antipyretics and/or analgesics and/or antibiotics within 3 days prior to study intervention administration.
- Other issues (e.g., technical, or administrative) preventing dose administration on day of visit.
- In case of delayed enrollment, all visit activities will be repeated when the participant is able to return for the visit.

For Visit 1, if the planned study intervention administration is delayed, blood sampling does not need to be repeated if it was obtained during enrollment visit. The following procedures must be repeated prior to the delayed study intervention administration:

- Body temperature
- Re-check contraindications, warnings, precautions to study intervention
- Re-check inclusion/exclusion criteria

Visit window for Visit 2 starts from day of first study intervention administration.

For delay in the study intervention administration during Visit 2 of the control group, the following procedures must be repeated:

- Body temperature
- Re-check contraindications, warnings, precautions to study intervention
- Re-check inclusion/exclusion criteria

# 6.0 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. Refer to the Glossary of Terms for the definition of study intervention.

## 6.1 Study Interventions Administered

**Table 5 Study Interventions Administered**

| **Study Intervention Name:** | **RSVPreF3 OA Investigational Vaccine** | | ***Prevnar 20/Apexxnar*** |
|---|---|---|---|
| **Study intervention formulation** | RSVPreF3 (120 µg) | $AS01_E$: QS-21* (25 µg), MPL (25µg), liposomes; Water for injection | PS1(2.2 µg)[1,2]; PS3(2.2 µg)[1,2]; PS4(2.2 µg)[1,2]; PS5(2.2 µg)[1,2]; PS6A(2.2 µg)[1,2]; PS6B(4.4 µg)[1,2]; PS7F(2.2 µg)[1,2]; PS8(2.2 µg)[1,2]; PS9V(2.2 µg)[1,2]; PS10A(2.2 µg)[1,2]; PS11A(2.2 µg)[1,2]; PS12F(2.2 µg)[1,2]; PS14(2.2 µg)[1,2]; PS15B(2.2 µg)[1,2]; PS18C(2.2 µg)[1,2]; PS19A(2.2 µg)[1,2]; PS19F(2.2 µg)[1,2]; PS22F(2.2 µg)[1,2]; PS23F(2.2 µg)[1,2]; PS33F(2.2 µg)[1,2]; [1]conjugated to $CRM_{197}$ (51 µg); [2]adsorbed on $AlPO_4$ (0.125 mg $Al^{3+}$); Water for injections |
| **Presentation** | Vial; powder for suspension for injection | Vial; suspension for suspension for injection | Suspension for injection |
| **Route of Administration** | Intramuscular use | | Intramuscular use |
| **Product category** | Biologic | | Biologic |
| **Type** | Study | | Study |
| **Administration site** | | | |
| **Location** | Deltoid | | Deltoid |
| **Laterality** | Non-dominant | | Co-ad group: Dominant<br>Control group: Non-dominant |
| **Number of doses to be administered** | 1 | | 1 |
| **Dose Volume**** | 0.5 mL | | 0.5 mL |
| **Packaging, labeling***** | Refer to Pharmacy Manual for details | | Refer to Pharmacy Manual for details |
| **Manufacturer** | GSK | | Pfizer |

Abbreviations: Al=aluminum; $AlPO_4$=aluminum phosphate; $AS01_E$=Adjuvant System 01; CRM=cross-reactive material; PS=pneumococcal serotype; QS-21=*Quillaja saponaria* Molina, fraction 21; MPL=monophosphoryl lipid A.

*Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation.

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

***Labeling is compliant with the requirements of applicable regulatory agencies.

### 6.1.1 Medical Devices

There are no GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study. Other medical devices (not manufactured by or for GSK) provided for use in this study are: thermometer, syringe, needle, and pre-filled syringe for PCV20. All medical devices are CE marked and will be used for their intended use. Instructions for medical device use are provided in the package insert.

All device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Sections 8.3.6 and 10.3) and appropriately managed by GSK.

## 6.2 Preparation, Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized study site staff may supply or administer study intervention.

All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study site staff. The storage temperature should be continuously monitored and recorded with a calibrated (if not validated) temperature monitoring device(s).

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

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

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

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Participation Identification

Participant identification numbers (IDs) will be assigned sequentially to the participants who have consented to participate in the study, according to the range of participant IDs allocated

to each study center. The participant IDs will be documented in the electronic Case Report Form (eCRF).

The eligibility of the participant will be determined based on the inclusion and exclusion criteria listed in Section 5.0. The participant ID will be the participant's unique identification number for all eCRFs and associated study documentation that will be used for duration of the study. If the participant is terminated from the study, their participant ID cannot be re-assigned.

### 6.3.2 Randomization to Study Intervention

All eligible participants will be centrally randomized to the study group at a 1:1 ratio using Interactive Web Response System (IWRS) randomization (refer to Glossary of Terms for a definition of IWRS).

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

### 6.3.3 Intervention Allocation to the Participant

Approximately 1090 eligible participants will be randomly (1:1) assigned to 2 study groups using a centralized randomization system on internet at Visit 1 (Day 1). The randomization algorithm will use a minimization procedure accounting for age (60 to 69, 70 to 79 or ≥80 years) and center. Minimization factors will have equal weight in the minimization algorithm.

After obtaining the signed and dated Informed Consent Form (ICF) from the participant and if the participant eligible, the delegated clinical trial staff will access IWRS. Upon entering the participant ID and age, the randomization system will determine the treatment group and provide the treatment number to be used for the trial intervention. The treatment number(s) to be used for subsequent dose administration(s) will be provided by the same IWRS.

Instructions related to instances when IWRS is not available will be provide to the site.

Refer to the IWRS user manual for additional information related to the treatment number allocation.

### 6.3.4 Allocation of Participants to Assay Subsets

Immunogenicity assessments are planned as outlined in Section 8.1.

Refer to Section 9.2 for descriptions of analysis populations.

### 6.3.5 Blinding and Unblinding

This is an open-label study. The participant and principal investigator will not be blind to the intervention administered.

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

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The mode of administration (i.e., intramuscularly), laterality, as well as the date and time of each dose administered in the clinic will be recorded in the source documents. See Section 6.1 for details in intervention administration.

## 6.5 Dose Modification

Not applicable.

## 6.6 Treatment of Overdose

Any dose of any study vaccine greater than the one required per protocol is considered an overdose. All cases of vaccine overdose should be reported as protocol deviations. Any signs or symptoms resulting from an overdose should be reported as AEs, or SAEs if SAE criteria are met; overdose per se should not be reported as an AE/SAE. GSK does not recommend specific treatment for an overdose; however, any resulting adverse reaction should be treated symptomatically.

## 6.7 Concomitant Therapy

At each study visit/contact, the investigator or his/her delegate should question the participant and/or the participant's caregiver about all medications/products taken, and vaccinations received by the participant.

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

- All concomitant medications including vaccines, except vitamins and dietary supplements, administered after the first dose of study intervention (Day 1 to EoS).
- All concomitant medications leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines (Refer to Section 5.2.2 and Section 9.2.1).

- All concomitant medication which may explain/cause/be used to treat an SAE including vaccines/products, as defined in Sections 8.3.1 and 10.3.6. These must also be recorded in the Expedited Adverse Event report.
- Any prophylactic medication (eg, analgesics, antipyretics) administered on the day of study vaccination in the absence of any symptom and in anticipation of a reaction to the vaccination.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

# 7.0 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific study sites or of the study as a whole are detailed in Section 10.1.10.

## 7.1 Discontinuation of Study Intervention

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

The primary reason for premature discontinuation of the study intervention will be documented on the eCRF as follows:

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

If a participant who does not meet enrollment criteria is inadvertently enrolled, that participant must be discontinued from study intervention and IQVIA must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the participant to continue. In these rare cases, the investigator must obtain documented approval from GSK, or designee, to allow the participant to continue in the study.

Participants who discontinue study intervention will not be replaced.

### 7.1.1 Contraindications to Subsequent Study Intervention Administration

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

Participants who meet any of the criteria listed below or criteria listed in sections 5.2.1 and 5.2.2 should not receive additional doses of study intervention. Such participants should be encouraged to continue other study procedures, at the investigator's discretion (10.3). All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to the first study intervention (PCV20 vaccine) and that, in the opinion of the investigator, may pose

additional risk to the participant if he/she receives the second study intervention (RSV investigational vaccine).
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participant if he/she continues to participate in the study.
- Anaphylaxis following the administration of study intervention(s) from Visit 1 onwards.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.

## 7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance, or administrative reasons. This is expected to be uncommon.

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

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

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

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

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

- Adverse events requiring expedited reporting to IQVIA (see Appendix 3 for details regarding such events)
- Unsolicited non-serious AEs
- Solicited event
- Withdrawal by participant, not due to an AE*
- Migrated/Moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify)

*If a participant is withdrawn from the study because he/she/the participant's caregiver(s) has 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 AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Appendix 3 for details regarding follow-up AEs).

## 7.3 Lost to Follow-up

A participant will be considered 'lost to follow-up' if he/she fails to return for scheduled visits and cannot be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Study site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.
- If the participant indicates he/she does not want to continue with the study, he/she will be contacted for a final assessment for safety reasons; he/she will be withdrawn from the study with reason of "withdrawal of consent.

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

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

Adherence to the study design requirements, including those specified in Section 1.3, is essential and required for study conduct.

All screening evaluations must be completed, and the results reviewed before confirming that potential participants meet all eligibility criteria. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure' (Section 5.5).

If local regulations allow and quality of study procedures is maintained, participants can be offered remote visits (e.g., telemedicine, home visits) for the collection of biological samples and/or safety data/safety assessment(s). These remote visits must be performed by qualified study staff/healthcare professionals (HCPs).

Following procedures can be performed remotely/virtually (refer to the Glossary of Terms for the definitions of telemedicine, remote and virtual visits):

- Safety follow-up may be performed by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application (or eDiary) as a way of communicating with the participant and monitoring the participant's progress. In addition, qualified study staff/HCPs may also identify AEs and report them to the investigator for evaluation.
- Biological samples may be collected remotely by qualified study staff/HCPs. Biological samples should be collected only if they can be processed in a timely manner and appropriately stored until the intended use. Remote collection of cell-mediated immunity (CMI) samples is not allowed except for in special circumstances and with the approval of the GSK Central study team.
- In exceptional situations (e.g., pandemic), the following approach may be considered:
    - If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol, additional 30 days may be added to the Visit 2 interval (only for RSV investigational vaccine administration in the Control group).

Impact on the per protocol set (PPS) for immunogenicity will be determined on a case-by-case basis.

For information on the role of a caregiver in study assessments and procedures, please refer to Section 5.3.

Procedures conducted as part of routine clinical management (e.g., hematologic profiles), and obtained before the participant/participant's caregiver signed the ICF, may be used for screening and/or for establishing a clinical baseline (provided the procedure met protocol specified criteria and was performed within the time frame defined in the SoA [Section 1.3]).

## 8.1 Immunogenicity Assessments

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 in countries where this is allowed will be asked to give consent to allow GSK or a contracted partner, to use the samples for further research. The further research will be subject to prior IEC/IRB approval, if required by local legislation.

More specifically, part of the blood sample collected from the participants in this study may be used to perform qualification, validation and/or assay maintenance of future streptococcus pneumonia humoral assays.

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 individual participant/participant's caregiver.

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 or designee.

### 8.1.1 Biological Samples

An overall approximate volume of 15 mL per visit will be collected during the entire study period. Refer to Table 6 and Section 1.3 for details of volumes collected for different assessments.

**Table 6 Biological Samples**

| Sample type | Quantity | Unit | Timepoint | Group |
|---|---|---|---|---|
| Blood for humoral response | ~15 per visit | mL | Visit 1 (Day 1)<br>Visit 2 (Day 31) | All participants in the Co-ad group |
| Blood for humoral response | ~15 per visit | mL | Visit 1 (Day 1)<br>Visit 2 (Day 31)<br>Visit 3 (Day 61) | All participants in the Control group |

The approximate volume of blood that will be collected per participant during the entire study period is as follows:

- Co-ad group: 2 × ~15 mL = ~30 mL
- Control group: 3 × ~15 mL = ~45 mL

### 8.1.2 Laboratory Assays

All laboratory testing will be performed at a GSK laboratory or in a laboratory designated by GSK.

**Table 7 Laboratory Assays**

| Assay Type | System | Component | Method | Laboratory |
|---|---|---|---|---|
| Humoral immunity (antibody determination) | Serum | RSV-A Ab | Neutralization | GSK* |
| | | RSV-B Ab | Neutralization | |
| | | Streptococcus pneumoniae - serotype 1 Ab<br>Streptococcus pneumoniae - serotype 3 Ab<br>Streptococcus pneumoniae - serotype 4 Ab<br>Streptococcus pneumoniae - serotype 5 Ab<br>Streptococcus pneumoniae - serotype 6A Ab<br>Streptococcus pneumoniae - serotype 6B Ab<br>Streptococcus pneumoniae - serotype 7F Ab<br>Streptococcus pneumoniae - serotype 8 Ab<br>Streptococcus pneumoniae - serotype 9V Ab<br>Streptococcus pneumoniae - serotype 10A Ab<br>Streptococcus pneumoniae - serotype 11A Ab<br>Streptococcus pneumoniae - serotype 12F Ab | Multiplexed Opsonophagocytosis Assay (MOPA) | |

| Assay Type | System | Component | Method | Laboratory |
|---|---|---|---|---|
| | | Streptococcus pneumoniae - serotype 14 Ab<br>Streptococcus pneumoniae - serotype 15B Ab<br>Streptococcus pneumoniae - serotype 18C Ab<br>Streptococcus pneumoniae - serotype 19A Ab<br>Streptococcus pneumoniae - serotype 19F Ab<br>Streptococcus pneumoniae - serotype 22F Ab<br>Streptococcus pneumoniae - serotype 23F Ab<br>Streptococcus pneumoniae - serotype 33F Ab | | |

Abbreviations: Ab=antibodies; MOPS=multiplexed opsonophagocytosis assay; RSV=respiratory syncytial virus.
*GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. CLS may delegate testing to a contracted Contract Research Organization

Refer to Appendix 2 for a brief description of the assays performed in the study.

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

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

### 8.1.3 Immunological Read-Outs

**Table 8 Immunological Read-outs**

| Blood sampling timepoint | | Subset tested | N of participants | Component |
|---|---|---|---|---|
| Type of contact and timepoint | Sampling timepoint | | | |
| **Co-ad group** | | | | |
| Visit 1 (Day 1) | Pre-dose 1 | All participants | 545 | RSV-A neutralizing antibody |
| | | All participants | 545 | RSV-B neutralizing antibody |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 1 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 3 Opsonophagocytic Antiboides |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 4 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 5 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 6A Opsonophagocytic Antibodies |

| Blood sampling timepoint | | Subset tested | N of participants | Component |
|---|---|---|---|---|
| **Type of contact and timepoint** | **Sampling timepoint** | | | |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 6B Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 7F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 8 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 9V Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 10A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 11A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 12F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 14 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 15B Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 18C Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 19A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 19F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 22F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 23F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 33F Opsonophagocytic Antibodies |
| Visit 2 (Day 31) | Post-dose 1 | All participants | 545 | RSV-A neutralizing antibody |
| | | All participants | 545 | RSV-B neutralizing antibody |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 1 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 3 Opsonophagocytic Antiboides |

| Blood sampling timepoint | | Subset tested | N of participants | Component |
|---|---|---|---|---|
| Type of contact and timepoint | Sampling timepoint | | | |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 4 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 5 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 6A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 6B Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 7F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 8 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 9V Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 10A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 11A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 12F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 14 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 15B Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 18C Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 19A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 19F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 22F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 23F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 33F Opsonophagocytic Antibodies |

| Blood sampling timepoint | | Subset tested | N of participants | Component |
|---|---|---|---|---|
| **Type of contact and timepoint** | **Sampling timepoint** | | | |
| **Control group** | | | | |
| Visit 1 (Day 1) | Pre-PCV dose | All participants | 545 | Streptococcus pneumoniae - serotype 1 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 3 Opsonophagocytic Antiboides |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 4 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 5 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 6A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 6B Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 7F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 8 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 9V Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 10A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 11A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 12F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 14 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 15B Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 18C Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 19A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 19F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 22F Opsonophagocytic Antibodies |

| Blood sampling timepoint | | Subset tested | N of participants | Component |
|---|---|---|---|---|
| **Type of contact and timepoint** | **Sampling timepoint** | | | |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 23F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 33F Opsonophagocytic Antibodies |
| Visit 2 (Day 31) | Post-PCV dose | All participants | 545 | Streptococcus pneumoniae - serotype 1 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 3 Opsonophagocytic Antiboides |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 4 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 5 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 6A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 6B Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 7F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 8 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 9V Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 10A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 11A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 12F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 14 Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 15B Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 18C Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 19A Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 19F Opsonophagocytic Antibodies |

| Blood sampling timepoint | | Subset tested | N of participants | Component |
|---|---|---|---|---|
| **Type of contact and timepoint** | **Sampling timepoint** | | | |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 22F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 23F Opsonophagocytic Antibodies |
| | | All participants | 545 | Streptococcus pneumoniae - serotype 33F Opsonophagocytic Antibodies |
| | Pre-RSV dose | All participants | 545 | RSV-A neutralizing antibody |
| | | All participants | 545 | RSV-B neutralizing antibody |
| Visit 3 (Day 61) | Post-RSV dose | All participants | 545 | RSV-A neutralizing antibody |
| | | All participants | 545 | RSV-B neutralizing antibody |

Abbreviations: N=number; RSV=respiratory syncytial virus; PCV=pneumococcal conjugate vaccine

### 8.1.4 Immunological Correlates of Protection

No generally accepted immunological correlate of protection has been demonstrated so far for the antigen(s) used in the RSVPreF3 OA investigational vaccine.

## 8.2 Safety Assessments

The investigator and his/her designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and designees are responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant's withdrawal from the study intervention or study.

### 8.2.1 Pre-Vaccination Procedures

#### *8.2.1.1 Collection of Demographic Data*

Record demographic data according to local regulations such as year of birth, sex, race, and ethnicity will be collected on the eCRF. Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants.

*Differences in the safety and efficacy of certain medical products, including vaccines, have been observed in racially and ethnically distinct subgroups.[6,7,8] These differences may be attributable to intrinsic factors (e.g., genetics, metabolism, elimination), extrinsic factors (e.g., diet, environmental exposure, sociocultural issues), or interactions between these factors. Therefore, both geographic ancestry (race) and ethnicity will be collected for all study participants.

#### *8.2.1.2 Medical History*

Obtain the participant's medical history by interviewing the participant and/or review of the participant's medical records. Record any relevant pre-existing conditions, signs and/or symptoms present prior to the study intervention in the eCRF.

#### *8.2.1.3 Vaccination History*

Obtain the participant's vaccination history by interviewing the participant and/or review of the participant's vaccination records.

History of following vaccine administration should be recorded in eCRF.

- Any vaccine administered up to 1 year before study vaccine administration (if possible, with the date of vaccination)
- PPSV administration up to 5 years before first study vaccine administration
- PCV administration any time before study vaccine administration
- Recombinant zoster vaccine (Shingrix) administration any time before study vaccine administration

#### *8.2.1.4 Targeted Physical Examinations*

History directed physical examination will be performed for each participant on Day 1. If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to the Section 5.6 for the list of criteria for temporary delay of study intervention administration.

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

Physical examination at each study visit after the study intervention administration visit, will be performed only if the participant/participant's caregiver indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.

#### *8.2.1.5 Body Temperature*

The body temperature of each participant needs to be measured prior to any study intervention administration and recorded in the eCRF. The route for measuring temperature can be oral or axillary. If the participant has fever (fever is defined as temperature ≥38.0 °C (100.4 °F) regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit.

### 8.2.2 Safety Contact at 6 Months Post-Last Vaccination

Six months after the last dose of study vaccine (i.e., Month 6 for participants in the co-ad group and Month 7 for participants of the control group), each participant should be contacted to check if he/she has experienced any SAEs or any pIMDs since last study intervention administration, and to collect information on concomitant medications/vaccinations.

Multiple formats can be proposed by the site staff to organize these contacts. This contact may be done via email, text message, fax, or phone call for example. The most appropriate format should be agreed between site staff and the study participant.

Text messages, email, and fax may be used as a screening to check if the participant has anything to report. If the participant answers "Yes" for at least one of the items of interest, a phone call must be made to get the details on the event(s).

Data collected via phone calls and text messages will have to be recorded in source documents. E-mails and faxes can be archived in source documents. Receipt of the message must be confirmed by the participant or caregiver, as applicable.

### 8.2.3 Clinical Safety Laboratory Tests

No clinical safety laboratory tests are scheduled for this study.

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

Solicited and unsolicited AEs, SAEs and other safety reporting (potential immune-mediated diseases [pIMDs]) are to be reported as indicated in this protocol; Refer to Table 1 (co-ad group) and Table 2 (control group). The administration site solicited AEs that will be collected are erythema, pain, and swelling. The systemic solicited AEs that will be collected are arthralgia, fatigue, fever, headache, and myalgia.

Safety monitoring is specified in Figure 1 and in the endpoints (Section 3.0).

The definitions of AEs and SAEs can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study/study intervention (see Section 7.0).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

### 8.3.1 Time Period and Frequency for Collecting AE, SAE, and pIMD Information

All AEs (regardless of the assessment of relatedness to the study vaccines), including all SAEs and all pIMDs will be collected from the first study intervention administration. All SAEs and all pIMDs will be collected until 6 months after the last study intervention administration at the timepoints specified in the SoA (Section 1.3).

AEs (including SAEs and pIMDs) leading to withdrawal from the study will be collected from the time of the first study intervention administration until the participant is discharged from the study.

In addition, SAEs assessed as related to study participation (e.g., protocol-mandated invasive procedures) or assessed as related to any other GSK product (non-IMP) will be recorded from the time a participant consents to participate in the study until the participant is discharged from the study.

All AEs will be collected in the timeframe showed in Table 9.

The investigator or designee will record and immediately report all SAEs to IQVIA via the Expedited AE Reporting Form. Reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Appendix 3. The investigator will submit any updated SAE data to IQVIA within 24 hours of it being available.

**Table 9 Timeframes for Collection and Reporting of Safety Information for the Co-ad Group**

| Event | Visit 1 | Visit 1 | | | Visit 2 | Contact 1 |
|---|---|---|---|---|---|---|
| | Day 1 | Day 1 | Day 7 | Day 30 | Day 31 | Month 6** |
| | Pre-Dose* | RSV + PCV20 vacc | | | | Study Conclusion |
| Administration site and systemic solicited events (eDiary) | | | | | | |
| Unsolicited AEs | | | | | | |
| All SAEs | | | | | | |
| All pIMDs | | | | | | |
| SAEs related to study participation or concurrent GSK medication/vaccine | | | | | | |
| AEs/SAEs leading to withdrawal from the study | | | | | | |
| Intercurrent medical conditions | | | | | | |

Abbreviations: AE=adverse event; Co-ad=co-administration; eDiary=electronic diary; pIMD=potential immune-mediated disease; SAE=serious adverse event; Vacc=vaccination.

shading indicates applicable timeframe for reporting of safety information.

shading indicates reporting timeframe applicable if solicited symptoms persist after 7 days.

*Collection of SAEs related to study participation or GSK medication/vaccines starts as of informed consent (prior to study intervention administration).

**Six months after vaccination co-administration.

**Table 10 Timeframes for collection and Reporting of Safety Information for the Control Group**

| Event | Visit 1 | Visit 1 | | | Visit 2 | | | Visit 3 | Contact 1 |
|---|---|---|---|---|---|---|---|---|---|
| | Day 1 | Day 1 | Day 7 | Day 30 | Day 31 | Day 37 | Day 60 | Day 61 | Month 6** |
| | Pre-Dose* | PCV20 vacc. | | | RSV vacc. | | | | End of Study |
| Administration site and systemic solicited events (eDiary) | | | | | | | | | |
| Unsolicited AEs | | | | | | | | | |
| All SAEs | | | | | | | | | |
| All pIMDs | | | | | | | | | |
| SAEs related to study participation or concurrent GSK medication/vaccine | | | | | | | | | |
| AEs/SAEs leading to withdrawal from the study | | | | | | | | | |
| Intercurrent medical conditions | | | | | | | | | |

Abbreviations: AE=adverse event; eDiary=electronic diary; SAE=serious adverse event; pIMD=potential immune-mediated disease; Vacc.=vaccination.

shading indicates applicable timeframe for reporting of safety information.

shading indicates reporting timeframe applicable if solicited symptoms persist after 7 days.

*Collection of SAEs related to study participation or GSK medication/vaccines starts as of informed consent (prior to study intervention administration).

**Six months after the last study vaccination.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 9 and Table 10. Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event/cause of death to be reasonably

related to the study intervention or study participation, the investigator must promptly notify IQVIA.

### 8.3.2 Method of Detecting AEs, SAEs, and pIMDs

Detecting and recording of AE/SAE/pIMDs are detailed in Appendix 3.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting safety reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of participants is the preferred method of acquiring information related to an AE/SAE/pIMD.

### 8.3.3 Follow-up of AEs, SAEs, and pIMDs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and pIMDs as defined in Section 10.3.3.1 will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.5.

### 8.3.4 Regulatory Reporting Requirements for SAEs and Other Events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/pIMD, it must be reported to IQVIA using the required documentation and within the timeframes mentioned in Table 11. This is essential for meeting GSK legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/pIMDs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Appendix 3.

Local regulatory requirements and sponsor policy for preparation of an investigator safety report of Suspected Unexpected Serious Adverse Reactions (SUSAR) must be followed. These reports will be forwarded to investigators as necessary.

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

Refer to Appendix 3 for further details regarding the reporting of SAEs/pIMDs.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from GSK will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

**Table 11 Timeframes for Submitting SAE and Other Events Reports to IQVIA**

| Type of Event | Initial Reports | | Follow-up of Relevant Information on a Previous Report | |
|---|---|---|---|---|
| | Timeframe | Documents | Timeframe | Documents |
| SAEs | 24 hours*, ‡‡ | Electronic‡ Expedited Adverse Events Report | 24 hours* | Electronic‡ Expedited Adverse Events Report |
| pIMDs | 24 hours**, ‡‡ | Electronic‡ Expedited Adverse Events Report | 24 hours* | Electronic‡ Expedited Adverse Events Report |

pIMD=potential immune-mediated disease; SAE=serious adverse events.
* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD.
‡ Paper Expedited Adverse Events Report may be submitted in the case that the electronic Expedited Adverse Report system is not functioning. The paper form will be dated and signed by the investigator (or designee).
‡‡ The investigator will be required to confirm review of the SAE/pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/pIMD.

### 8.3.5 Treatment of Adverse Events

Any medication, vaccine or products which may explain/cause/be used to treat an SAE/pIMD should be recorded in the Expedited Adverse Event Report of the participant's eCRF.

### 8.3.6 Medical Device Deficiencies

Medical devices are being provided for use in this study as the study intervention. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 3.

NOTE: Device deficiencies that lead to an AE/SAE will be reported as an AE/SAE following the processes outlined in Appendix 3 of the protocol.

#### *8.3.6.1 Time Period for Detecting Medical Device Deficiencies*

Medical device deficiencies will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a device deficiency might have led to an SAE if

appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate, the investigator will promptly notify GSK.

The method of documenting medical device deficiencies is provided in Appendix 3.

#### *8.3.6.2 Follow-up of Medical Device Deficiencies*

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

#### *8.3.6.3 Prompt Reporting of Device Deficiencies to the Sponsor*

Device deficiencies will be reported to the Sponsor or designee within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.

The medical device deficiency report form will be sent to GSK as described in Appendix 3.

GSK will be the contact for the receipt of device deficiency reports.

#### *8.3.6.4 Regulatory Reporting Requirements for Device Deficiencies*

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the Sponsor 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.

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 Participant Card

The investigator (or designee) must provide the participant with a “participant card” containing information about the clinical study. The participant must be instructed to always keep the participant card in his/her/their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator or his/her backup.

## 8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

## 8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

## 8.7 Genetics

Genetics are not evaluated in this study.

## 8.8 Biomarkers

Biomarkers are not evaluated in this study.

## 8.9 Immunogenicity Assessments

Immunogenicity is described in Section 8.1.

## 8.10 Health Outcomes

Not applicable for this study.

## 8.11 Health Economics

Health economics parameters are not evaluated in this study.

# 9.0 STATISTICAL CONSIDERATIONS

## 9.1 Statistical Hypotheses

Statistical hypotheses are associated to the confirmatory primary non-inferiority (NI) objectives, which will be tested to control overall Type 1 error. Global Type I error is controlled at 2.5% (1-sided). The NI margins associated to each objective are provided in Table 12.

**Table 12 Study Objectives and Null Hypothesis**

| Objectives | Null hypothesis |
|---|---|
| **Primary** | |
| • To demonstrate the non-inferiority of PCV20 when co-administered with the RSVPreF3 OA investigational vaccine compared to PCV20 administered alone. | • True Group GMT ratio between the Control group (PCV20 vaccine) divided by Co-ad group (RSVPreF3 OA investigational vaccine when co-administered with the PCV20 vaccine) in OP Ab titer for each PCV serotypes one month after the PCV20 is above 2. |
| • To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine *in terms of RSV-A neutralization antibodies* when co-administered with PCV20 compared to RSVPreF3 OA investigational vaccine administered alone. | • True GMT ratio between Control group (RSVPreF3 OA investigational vaccine) divided by Co-ad group (RSVPreF3 OA investigational vaccine when co-administered with the PCV20 vaccine) in RSV-A neutralizing antibody (Ab) titers one month after the RSVPreF3 OA investigational vaccine dose is above 1.5. |
| • To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine *in terms of RSV-B neutralization antibodies* when co-administered with PCV20 compared to RSVPreF3 OA investigational vaccine administered alone. | • True GMT ratio between Control group (RSVPreF3 OA investigational vaccine) divided by Co-ad group (RSVPreF3 OA investigational vaccine when co-administered with the PCV20 vaccine) in RSV-B neutralizing Ab titers one month after the RSVPreF3 OA investigational vaccine dose is above 1.5. |

Abbreviations: Ab=Antibody; GMT=Geometric mean titer; OP=Opsonophagocytic; PCV20=20-valent pneumococcal vaccine; RSVPreF3 OA= respiratory syncytial virus PreFusion protein 3 older adult investigational vaccine.

Statistical testing of each endpoint will be performed sequentially to control the Global Type I error below 2.5% (1-sided). The testing sequence is detailed in Section 9.3.1.1.

## 9.2 Populations for Analysis

Populations for analyses in this study are defined in Table 13.

**Table 13 Analysis Sets**

| Analysis Set | Description |
|---|---|
| Screened set | All participants who were screened for eligibility. |
| Enrolled set | Participants who were randomized or received study intervention or have undergone an invasive procedure. |
| ES | All participants who received a study intervention. Analysis per group is based on the study intervention administered. |
| PPS | All eligible participants:<br>• Who received all study interventions as per protocol<br>• Had immunogenicity results pre- and post-dose<br>• Complied with blood draw intervals (contribution of participants to PPS at specific timepoint will be defined by timepoint)<br>• Without intercurrent medical conditions that may interfere with immunogenicity<br>• Without prohibited concomitant medication/vaccination |

Abbreviations: ES=Exposed set; PPS=Per Protocol set.

### 9.2.1 Criteria for Elimination

If the participant meets one of the criteria mentioned below or any listed in the Section 7.1.1, (contraindication to subsequent vaccination) or Section 5.2.1 (medical conditions) or Section 5.2.2 (prior and concomitant therapy), he/she may be eliminated from per protocol analysis.

In case of unplanned administration of any medication mentioned in Section 5.2.2 during the study, this will be considered as a protocol deviation and the participant may be eliminated from the Per Protocol set (PPS).

Participants may be eliminated from the PPS for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response (intercurrent medical condition) or are confirmed to have an alteration of their initial immune status. Refer to Glossary of Terms for the definition of intercurrent medical conditions.

## 9.3 Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before first subject first visit (FSFV) and will include a more technical and detailed description of the statistical

analyses including the supportive analyses and demography summaries. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

### 9.3.1 Primary Endpoint(s)/Estimand(s) Analysis

The primary endpoints are described in Section 3.0. The confirmatory analyses of non-inferiority will be based on the PPS.

- Method for non-inferiority of the PCV20 in terms of opsonophagocytic (OP) Ab GMT between groups ratio for each of the pneumococcal vaccine serotypes at one month after the PCV20 dose (i.e., at Day 31 for both groups):
    - The 2-sided 95% CI for Group GMT ratio between the PCV20 administered alone (control group) over PCV20 (co-ad group) co--administered with the RSVPreF3 OA investigational vaccine will be derived from an analysis of covariance (ANCOVA) model* on $\log_{10}$ transformed titer.
- Method for non-inferiority of RSV investigational vaccine in terms of RSV-A neutralizing antibody geometric mean titer (GMT) between groups ratio at one after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 for the co-ad group and at Day 61 for the control group):
    - The 2-sided 95% CI for RSV-A neutralizing antibody GMT ratio between RSVPreF3 OA investigational vaccine administered alone (control group) over RSVPreF3 OA investigational vaccine when co-administered with the PCV20 vaccine (co-ad group) will be derived from an ANCOVA model* on $\log_{10}$ transformed titer.
- Method for non-inferiority of RSV investigational vaccine in terms of RSV-B neutralizing antibody geometric mean titer (GMT) between groups ratio at one after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 for the co-ad group and at Day 61 for the control group):
    - The 2-sided 95% CI for RSV-B neutralizing antibody GMT ratio between RSVPreF3 OA investigational vaccine administered alone (control group) over RSVPreF3 OA investigational vaccine when co-administered with the PCV20 vaccine (co-ad group) will be derived from an ANCOVA model* on $\log_{10}$ transformed titer.

**The model will include the intervention/treatment group and age category (age at vaccination: 60 to 69, 70 to 79 or ≥80 years) as fixed effects, and the pre-dose $log_{10}$-transformed titer as covariate. Missing data will not be replaced. Titers below the assay cut-off will be replaced by half the assay cut-off; titers above the upper limit of quantification (ULOQ) will be replaced by the ULOQ.*

#### *9.3.1.1 Success Criteria for Non-inferiority and Testing sequence:*

**1st Sequence:**

- The upper limit (UL) of the 2-sided 95% CI of the GMT ratio (control group divided by co-ad group) for each individual pneumococcal conjugate serotype as measured by OPA is ≤2.
  AND
- The upper limit of the 2 sided 95% CI of the GMT ratio (control group divided by co-ad group) between the control group versus co-ad group for RSV-A neutralizing antibody titer one month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.

**2nd sequence:**

- The upper limit of the 2 sided 95% CI of the GMT ratio (control group divided by co-ad group) between the control group versus co-ad group for RSV-B neutralizing antibody titer one month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.

Testing will progress in the 2nd sequence only if the 1st sequence is a success, so that no further adjustment of alpha is required.

The NI margin of 2 for PCV20 is based on well documented criteria for pneumococcal vaccines which has been used for demonstrating the NI of PCV20 against PCV13.[9] The NI margin of 1.5 for RSV is based on Center for Biologics Evaluation and Research (CBER) feedback.

### 9.3.2 Secondary Endpoint(s)/Estimand(s) Analysis

Method for evaluation of humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with the PCV20 or administered alone

- Mean geometric increase for within participants ratios of the post-dose titer (at 1-month after the RSVPreF3 OA investigational vaccine dose) over the predose titer (at baseline) for RSV-A neutralizing Ab titers
- Mean geometric increase for within participants ratios of the post-dose titer (at 1-month after the RSVPreF3 OA investigational vaccine dose) over the predose titer (at baseline) for RSV-B neutralizing Ab titers

The other secondary endpoints, as detailed in Section 3.0, will have descriptive analyses of demography, immunogenicity, and safety detailed in the SAP.

## 9.4 Interim Analysis

### 9.4.1 Sequence of Analysis

The analyses will be performed stepwise:

- A first analysis will be performed on all immunogenicity, reactogenicity and safety data available and as clean as possible, when data for at least primary and secondary endpoints up to Visit 2 (Day 31) (co-ad group) or Visit 3 (Day 61) (control group) are available for all participants. This analysis will be considered as final for those endpoints.
- An End of Study analysis will include all data obtained until 6 months post-last dose.

## 9.5 Sample Size Determination

The target enrollment will be approximately 1090 participants (545 in the group receiving the RSVPreF3 OA investigational vaccine co-administered with PCV20 (co-ad group) and 545 in the control group where RSVPreF3 OA investigational vaccine and PCV20 are administered in a staggered manner) to obtain at least 980 evaluable participants (490 in the co-ad group and 490 in the control group) for the evaluation of the primary objectives, assuming that approximately 10% of the enrolled participants will not be evaluable.

**Table 14 Overall power to demonstrate primary objectives: non-inferiority of the immunogenicity of RSVPreF3 OA investigational vaccine when co-administered with pneumococcal vaccine (PCV20) as compared to when administered alone- assuming 490 evaluable participants in each group**

| Endpoint | Standard deviation of log10 concentration | Reference ratio | Non inferiority margin | Type II error | Power |
|---|---|---|---|---|---|
| **PCV Non-inferiority* (1-sided test with alpha=2.5%)** | | | | | |
| **GMTs Opsonophagocytic (OP) antibody (Ab)** | | | | | |
| 3 | 0.572 | 1.05 | 2 | <0.01% | >99.99% |
| 7F | 0.733 | 1.05 | 2 | 0.01% | 99.99% |
| 19A | 0.771 | 1.05 | 2 | 0.01% | 99.99% |
| 5 | 0.782 | 1.05 | 2 | 0.02% | 99.98% |
| 1 | 0.789 | 1.05 | 2 | 0.02% | 99.98% |
| 14 | 0.792 | 1.05 | 2 | 0.02% | 99.98% |
| 8 | 0.797 | 1.05 | 2 | 0.03% | 99.97% |
| 33F | 0.797 | 1.05 | 2 | 0.03% | 99.97% |
| 9V | 0.825 | 1.05 | 2 | 0.05% | 99.95% |
| 10A | 0.839 | 1.05 | 2 | 0.06% | 99.94% |
| 11A | 0.843 | 1.05 | 2 | 0.07% | 99.93% |
| 19F | 0.845 | 1.05 | 2 | 0.07% | 99.93% |
| 6B | 0.882 | 1.05 | 2 | 0.14% | 99.86% |
| 4 | 0.902 | 1.05 | 2 | 0.20% | 99.80% |
| 18C | 0.910 | 1.05 | 2 | 0.22% | 99.78% |
| 6A | 0.927 | 1.05 | 2 | 0.29% | 99.71% |
| 12F | 0.943 | 1.05 | 2 | 0.37% | 99.63% |
| 22F | 0.966 | 1.05 | 2 | 0.51% | 99.49% |
| 15B | 1.088 | 1.05 | 2 | 1.96% | 98.04% |
| 23F | 1.096 | 1.05 | 2 | 2.10% | 97.90% |
| **Global Type II error to show non-inferiority** | | | | **~6.2%** | |
| **Global power for PCV** | | | | | **~93.8%** |
| **RSV-A Non-inferiority* (1-sided test with alpha = 2.5%)** | | | | | |
| **GMTs RSV-A neutralization antibody** | **0.45** | **1.05** | **1.5** | **0.04%** | **99.96%** |

| Endpoint | Standard deviation of log10 concentration | Reference ratio | Non inferiority margin | Type II error | Power |
|---|---|---|---|---|---|
| **RSV-B Non-inferiority* (1-sided test with alpha = 2.5%)** | | | | | |
| **GMTs RSV-B neutralization antibody** | **0.45** | **1.05** | **1.5** | **0.04%** | **99.96%** |
| **Global Power for the study** | | | | **~6.28** | **~93.7** |

Abbreviations: Ab=antibody; GMT=geometric mean titer; OA=older adult; OP=opsonophagocytic; PCV=pneumococcal vaccine; RSV=respiratory syncytial virus.

*Pass 2019 alpha=2.5%, Two-Sample T-Tests for Non-Inferiority Assuming Equal Variance and Equal mean, Power=100-the Type II error (Beta). The Global Type II error (Beta) has been adjusted using Bonferroni's method (Global Type II error=sum of the individual Type II errors).

For RSV: non-inferiority limit=0.176 (=log10[1.5]).

For each PCV vaccine strain: non-inferiority limit=0.301 (=log10[2.0]).

Reference Ratio=0.0212 (=log10[1.05])

Considering a ***slight interference of 1.05*** in true GMTs in both groups with a common population standard error of 0.45 for the RSV-A and RSV-B neutralizing Ab and the respective SD's for each of the PCV serotype in $\log_{10}$ transformed concentration, the study has at least 93.7% power to meet the primary objectives.

# 10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

### 10.1.1 Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs, Device Deficiency or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

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

### 10.1.2 Adequate Resources

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

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

### 10.1.3 Financial Disclosure

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

### 10.1.4 Recruitment Arrangements and Informed Consent Process

**Recruitment Arrangements**

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

**Informed Consent Process**

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.

- Potential participants must be informed that their participation is voluntary. They will be required to physically sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that physical 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 must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical copy of the ICF(s) must be provided to the participant and/or their caregiver(s).
- The participant must provide consent by signing an ICF, which summarizes the study, includes a consent statement and provides documentation that the participant agrees to continue participating in the study.
- Participants who are rescreened are required to sign a new ICF.

### 10.1.5 Data Protection

Participants will be assigned a unique identifier (Section 6.3.1) by the investigator. Any participant records or datasets transferred to GSK will contain only the identifier. Name and any other information which would identify the participant will not be transferred.

GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.

- The participant/participant's caregiver(s) must be informed that their personal study-related data will be used by GSK in accordance with local data protection law. The level of disclosure must also be explained to the caregiver(s), that the participant's data will be used as described in the informed consent.
- The participant/participant's caregiver(s) must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by GSK, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

The participants must be notified about their rights regarding the use of their personal data in accordance with the data privacy section of the ICF.

### 10.1.6 Committees Structure

Safety oversight will be provided by a SRT composed of GSK RSV OA project team members. An SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contributes to the continual assessment of incoming new efficacy and safety information.

GSK will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country. This includes IRBs/IECs for review and approval of the protocol and subsequent amendments, ICF and any other documentation.

### 10.1.7 Dissemination of Clinical Study Data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with 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 trial 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, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary results with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.

GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.

GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding.

### 10.1.8 Data Quality Assurance

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 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.

GSK or designee is responsible for the data management of this study including quality checking of the source data (see Glossary of Terms for the exact definition of source data).

GSK assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Quality tolerance limits (QTLs) will be pre-defined in the state location(s) to identify systematic issues that can impact participant safety and/or the reliability of study results. These pre-defined parameters will be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarized in the Clinical Study Report (CSR).

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

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 regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of GSK. No records may be transferred to another location or party without written notification to GSK.

### 10.1.9 Source Documents

The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's participants. Source data should be attributable, legible, contemporaneous, original, accurate, and

complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in Glossary of Terms.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

### 10.1.10 Study and Site Start and Closure

**First Act of Recruitment**

The start of study and the first act of recruitment are defined as first subject first visit (first ICF signature date) at a country-level.

**Study/Site Termination**

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion, provided there is sufficient notice given to account for all participants safe exit from study.

Regular closure of study sites will occur upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site 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 site by GSK or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For study site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) 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 shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any Contract Research Organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

### 10.1.11 Publication Policy

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the sponsor's internal policy. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## 10.2 Appendix 2: Clinical Laboratory Tests

**RSV-A and RSV-B neutralization assays**

The serum neutralization assay is a functional assay that measures the ability of serum antibodies to neutralize RSV entry and replication in a host cell line.

Virus neutralization is performed by incubating a fixed amount of RSV-A strain (Long, ATCC No. VR-26) or RSV-B strain (18537, ATCC No. VR-1580) with serial dilutions of the test serum. The serum-virus mixture is then transferred onto a Vero cells culture (African Green Monkey, kidney, Cercopitheus aethiops, ATCC CCL 81) and incubated for 2 days to allow infection of the Vero cells by non-neutralized virus and the formation of plaques in the cell monolayer. Following a fixation step, RSV-infected cells are detected using a primary antibody directed against RSV (Polyclonal anti-RSV-A/B IgG) and a secondary antibody conjugated to horse-radish peroxidase (HRP), allowing the visualization of plaques after coloration with TrueBlue peroxidase substrate.

Viral plaques are counted using an automated microscope coupled to an image analyzer (Scanlab system with a Reading software or equivalent). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at each serum dilution and the number of plaques in the virus control wells (no serum added). The serum neutralizing antibody titer is expressed in Estimated Dilution 60 (ED60) and corresponds to the inverse of the interpolated serum dilution that yields a 60% reduction in the number of plaques compared to the virus control wells, as described by others.[10,11] For the testing of Phase III studies, secondary standards calibrated against the international reference[12,13] will be included in every run to allow conversion into international units.

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

### 10.3.1 Definition of AE

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, which does not necessarily have a causal relationship with study intervention<br>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention/treatment, whether or not considered related to the study intervention/treatment. |
| **Medical Device AE and ADE** |
| • 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 the investigational 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 an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.<br>• An adverse device defect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device. |
| **Device Deficiency Definition** |
| 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. |

| **Definition of Unsolicited AEs and Solicited Events** |
|---|
| • An **unsolicited AE** is an AE that was either not included in the list of solicited events or could be included in the list of solicited events but with an onset outside the specified period of follow-up for solicited events. Unsolicited AEs must have been communicated by participant/participant's caregiver(s) who has signed the informed consent. Unsolicited AEs include both serious and nonserious AEs.<br>• Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant/participant's caregiver(s) will be instructed to contact the study site as soon as possible to report medically attended event(s), as well as any events that, though not |

medically attended, are of participant/participant's caregiver(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified study site personnel and documented in the participant's records.

- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/participant's caregiver(s) will be collected during an interview with the participant/participant's caregiver(s) and by review of available medical records at the next visit.
- **Solicited events** are predefined administration site events and systemic events for which the participant/participant's caregiver(s) is especially questioned, and which are noted by the participant/participant's caregiver(s) in their eDiary. See Table 15 and Table 16 for list of solicited site events and solicited systemic events.
  - Solicited administration site events:

**Table 15 Solicited Administration Site Events**

| |
|---|
| Pain |
| Erythema/redness |
| Swelling |

  - Solicited systemic events:

**Table 16 Solicited Systemic Events**

| |
|---|
| Fever |
| Headache |
| Fatigue |
| Myalgia |
| Arthralgia |

- Note: participants will be instructed to measure and record their body temperature in the evening. The route for temperature measurement can be oral or axillary. If additional temperature measurements are taken at other times of the day, participants will be instructed to record their highest body temperature in the eDiary.

**Events Meeting the AE Definition**

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms that require medical attention (e.g., hospital stays, physician visits and emergency room visits).
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Significant failure of an expected pharmacologic or biological action.
- Events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).
- Events to be recorded as solicited events are described in Table 15 and Table 16. All other AEs will be recorded as unsolicited AEs.

**Events NOT Meeting the AE Definition**

- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, admission for routine examination).
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the preexisting condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. Pre-existing diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

### 10.3.2 Definition of SAE and Serious Adverse Device Effect (SADE)

| **An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:** |
|---|
| **a. Results in death**<br>• For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form. |
| **b. Is life-threatening**<br>• The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br>• In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.<br>• Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. |
| **d. Results in persistent or significant disability/incapacity**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| **e. Is a congenital anomaly/birth defect**<br>• Is a congenital anomaly/birth defect in the offspring of a study participant. |
| **f. Other situations:**<br>• Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.<br>  ○ Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse. |
| **SADE Definition** |
| • A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. |

- 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.

### 10.3.3 Adverse Events of Special Interest

Potential immune-mediated diseases are the only adverse events of special interest (AESIs) collected during this study.

#### *10.3.3.1 Potential Immune-Mediated Diseases*

Potential immune-mediated disease is a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 17. Please refer to the Appendix 3 for reporting details.

The investigator must exercise his/her medical/scientific judgment to determine whether other diseases have an autoimmune origin (i.e., pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD. In addition, the investigator should categorize each pIMD either as a new onset condition (if it started following vaccination) or as an exacerbation of a preexisting chronic condition (if it exacerbated following vaccination) in the eCRF. In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators at study start.

**Table 17 List of Potential Immune-Mediated Diseases (pIMDs)**

| Medical Concept | Additional Notes |
|---|---|
| Blood disorders and coagulopathies | |
| **Antiphospholipid syndrome** | |
| **Autoimmune aplastic anemia** | |
| **Autoimmune hemolytic anemia** | • Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia |
| **Autoimmune lymphoproliferative syndrome (ALPS)** | |
| **Autoimmune neutropenia** | |
| **Autoimmune pancytopenia** | |
| **Autoimmune thrombocytopenia** | • Frequently used related terms include: "autoimmune thrombocytopenic purpura", "idiopathic thrombocytopenic purpura (ITP)", "idiopathic immune thrombocytopenia", "primary immune thrombocytopenia". |
| **Evans syndrome** | |
| **Pernicious anemia** | |
| **Thrombosis with thrombocytopenia syndrome (TTS)** | |
| • **Thrombotic thrombocytopenic purpura** | • Also known as "Moschcowitz-syndrome" or "microangiopathic hemolytic anemia" |

| Medical Concept | Additional Notes |
|---|---|
| **Cardio-pulmonary inflammatory disorders** | |
| **Idiopathic Myocarditis/Pericarditis** | Including but not limited to:<br>• Autoimmune / Immune-mediated myocarditis<br>• Autoimmune / Immune-mediated pericarditis<br>• Giant cell myocarditis |
| **Idiopathic pulmonary fibrosis** | Including but not limited to:<br>• Idiopathic interstitial pneumonia (frequently used related terms include "Interstitial lung disease", "Pulmonary fibrosis", "Immune-mediated pneumonitis")<br>• Pleuroparenchymal fibroelastosis (PPFE) |
| **Pulmonary alveolar proteinosis (PAP)** | • Frequently used related terms include: "pulmonary alveolar lipoproteinosis", "phospholipidosis" |
| **Endocrine disorders** | |
| **Addison's disease** | |
| **Autoimmune / Immune-mediated thyroiditis** | Including but not limited to:<br>• Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis)<br>• Atrophic thyroiditis<br>• Silent thyroiditis<br>• Thyrotoxicosis |
| **Autoimmune diseases of the testis and ovary** | • Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis |
| **Autoimmune hyperlipidemia** | |
| **Autoimmune hypophysitis** | |
| **Diabetes mellitus type I** | |

| Medical Concept | Additional Notes |
|---|---|
| **Grave's or Basedow's disease** | • Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy |
| **Insulin autoimmune syndrome** | |
| **Polyglandular autoimmune syndrome** | • Includes Polyglandular autoimmune syndrome type I, II and III |
| **Eye disorders** | |
| **Ocular Autoimmune / Immune-mediated disorders** | Including but not limited to:<br>• Acute macular neuroretinopathy (also known as acute macular outer retinopathy)<br>• Autoimmune / Immune-mediated retinopathy<br>• Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia<br>• Cogan's syndrome: an oculo-audiovestibular disease<br>• Ocular pemphigoid<br>• Ulcerative keratitis<br>• Vogt-Koyanagi-Harada disease |
| **Gastrointestinal disorders** | |
| **Autoimmune / Immune-mediated pancreatitis** | |
| **Celiac disease** | |
| **Inflammatory Bowel disease** | Including but not limited to:<br>• Crohn's disease<br>• Microscopic colitis<br>• Terminal ileitis<br>• Ulcerative colitis<br>• Ulcerative proctitis |

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

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

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

| Medical Concept | Additional Notes |
|---|---|
| **Renal disorders** | |
| **Autoimmune / immune-mediated glomerulonephritis** | Including but not limited to:<br>• Immunoglobulin A (IgA) nephropathy<br>• Immunoglobulin M (IgM) nephropathy<br>• C1q nephropathy<br>• Fibrillary glomerulonephritis<br>• Glomerulonephritis rapidly progressive<br>• Membranoproliferative glomerulonephritis<br>• Membranous glomerulonephritis<br>• Mesangioproliferative glomerulonephritis<br>• Tubulointerstitial nephritis and uveitis syndrome |
| **Skin and subcutaneous tissue disorders** | |
| **Alopecia areata** | |
| **Autoimmune / immune-mediated blistering dermatoses** | Including but not limited to:<br>• Bullous Dermatitis<br>• Bullous Pemphigoid<br>• Dermatitis herpetiformis<br>• Epidermolysis bullosa acquisita (EBA)<br>• Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease<br>• Pemphigus |
| **Erythema multiforme** | |
| **Erythema nodosum** | |

| Medical Concept | Additional Notes |
|---|---|
| **Reactive granulomatous dermatitis** | Including but not limited to<br>• Interstitial granulomatous dermatitis<br>• Palisaded neutrophilic granulomatous dermatitis |
| **Lichen planus** | Includes liquen planopilaris |
| **Localized Scleroderma (Morphoea)** | Includes Eosinophilic fasciitis (also called Shulman syndrome) |
| **Psoriasis** | |
| **Pyoderma gangrenosum** | |
| **Stevens-Johnson syndrome (SJS)** | Including but not limited to:<br>• Toxic Epidermal Necrolysis (TEN)<br>• SJS-TEN overlap |
| **Sweet's syndrome** | Includes Acute febrile neutrophilic dermatosis |
| **Vitiligo** | |
| **Vasculitis** | |
| **Large vessels vasculitis** | Including but not limited to:<br>• Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION)<br>• Giant cell arteritis (also called temporal arteritis)<br>• Takayasu's arteritis |

| Medical Concept | Additional Notes |
|---|---|
| **Medium sized and/or small vessels vasculitis** | Including but not limited to:<br>• Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified)<br>• Behcet's syndrome<br>• Buerger's disease (thromboangiitis obliterans)<br>• Churg–Strauss syndrome (allergic granulomatous angiitis)<br>• Erythema induratum (also known as nodular vasculitis)<br>• Henoch-Schonlein purpura (also known as IgA vasculitis)<br>• Microscopic polyangiitis<br>• Necrotizing vasculitis<br>• Polyarteritis nodosa<br>• Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI)<br>• Wegener's granulomatosis |
| **Other (including multisystemic)** | |
| **Anti-synthetase syndrome** | |
| **Capillary leak syndrome** | Frequently used related terms include: "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome" |
| **Goodpasture syndrome** | Frequently used related terms include: "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)" |
| **Immune-mediated enhancement of disease** | Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE) |
| **Immunoglobulin G4 related disease** | |
| **Langerhans' cell histiocytosis** | |

| Medical Concept | Additional Notes |
|---|---|
| **Multisystem inflammatory syndromes** | Including but not limited to:<br>• Kawasaki's disease<br>• Multisystem inflammatory syndrome in adults (MIS-A)<br>• Multisystem inflammatory syndrome in children (MIS-C) |
| **Overlap syndrome** | |
| **Raynaud's phenomenon** | |
| **Sarcoidosis** | Includes Loefgren syndrome |
| **Susac's syndrome** | |

### 10.3.4 Clinical Laboratory Parameters and Other Abnormal Assessments Qualifying as AEs or SAEs

In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Sections 10.3.1 and 10.3.2).

The investigator must exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

### 10.3.5 Recording and Follow-Up of AEs, SAEs, pIMDs, and/or Device Deficiencies

**AE, SAE, and Device Recording**

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the eCRF, in accordance with the investigator's normal clinical practice and on the appropriate form. Each event must be recorded separately. Additionally, any safety event which meets seriousness criteria must be reported on the safety event report form and submit to IQVIA.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to IQVIA, GSK or designee in lieu of completion of the applicable/required report form.
- There may be instances when copies of medical records for certain cases are requested by IQVIA, GSK or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to IQVIA, GSK or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- An Electronic Diary (eDiary) will be used in this study to capture solicited administration site or systemic events. The participant should be trained on how and when to complete the eDiary.
- Anyone who measures administration site or systemic events and who will record the event in the eDiary should be trained on using the eDiary. This training must be documented in the participant's source record.
- If any individual other than the participant/participant's caregiver(s) is making entries in the eDiary, their identity must be documented in the participant's source record.
- Collect and verify completed eDiary during discussions with the participant/participant's caregiver(s) on Visit 2 or Visit 3 (control group).
- Any unreturned eDiary will be sought from the participant/caregiver(s) through telephone call(s) or any other convenient procedure.

- Data on solicited events reported in the eDiary will be electronically transferred to the eDiary vendor, where it can be monitored by appropriately qualified site staff and sponsor staff through a web-based portal. Appropriately qualified site staff should monitor eDiary data online at frequent intervals for subject compliance and reported events that were of concern to the subject.
- Refer to the eDiary Manual for more information regarding the use of eDiary.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.
- If the site during the course of the study becomes aware of any serious, nonserious incident (including device deficiencies and malfunctions) related to any GSK non-IMP product they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system.

#### *10.3.5.1 Time Period for Collecting and Recording AEs, SAEs, and pIMDs*

**Time Period for Collecting and Recording AEs, SAEs, and pIMDs**

- All solicited events that occur during 7 days following administration of the dose of study intervention (Day 1 to Day 7) must be recorded into the eDiary, irrespective of intensity. All other AEs occurring within this time frame should be recorded onto/into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.
- All unsolicited AEs that occur during 30 days following administration of each dose/the dose of study intervention must be recorded onto/into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.
- All SAEs, and pIMDs that occur up to 6 months post last-dose of study intervention must be recorded onto/into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.

### *10.3.5.2 Assessment of Intensity*

**Assessment of Intensity**

**Table 18 Intensity Scales for Solicited Events**

| Event | Intensity grade | Parameter |
|---|---|---|
| Pain at administration site | 0 | None |
| | 1 | Mild: Any pain neither interfering with nor preventing normal everyday activities. |
| | 2 | Moderate: Painful when limb is moved and interferes with everyday activities. |
| | 3 | Severe: Significant pain at rest. Prevents normal everyday activities. |
| Erythema at administration site | | Greatest surface diameter in mm |
| Swelling at administration site | | Greatest surface diameter in mm |
| Temperature* | | Temperature in °C or °F. |
| Headache | 0 | None |
| | 1 | Mild: Headache that is easily tolerated |
| | 2 | Moderate: Headache that interferes with normal activity |
| | 3 | Severe: Headache that prevents normal activity |
| Fatigue | 0 | None |
| | 1 | Mild: Fatigue that is easily tolerated |
| | 2 | Moderate: Fatigue that interferes with normal activity |
| | 3 | Severe: Fatigue that prevents normal activity |
| Myalgia | 0 | None |
| | 1 | Mild: Myalgia that is easily tolerated |
| | 2 | Moderate: Myalgia that interferes with normal activity |
| | 3 | Severe: Myalgia that prevents normal activity |
| Arthralgia | 0 | None |
| | 1 | Mild: Arthralgia that is easily tolerated |
| | 2 | Moderate: Arthralgia that interferes with normal activity |
| | 3 | Severe: Arthralgia that prevents normal activity |

*Refer to the SoA (Section 1.3) for the definition of fever and the location for temperature measurement.

The maximum intensity of local injection site erythema/swelling and fever will be scored by investigator as follows:

| | Erythema/swelling | Fever |
|---|---|---|
| 0: | ≤20 mm | <38.0 °C<br><100.4 °F |
| 1: | > 20 - ≤50 mm | ≥38.0 °C (100.4 °F) - ≤38.5 °C (101.3 °F) |
| 2: | > 50 - ≤100 mm | >38.5 °C (101.3 °F) - ≤39.0 °C (102.2 °F) |
| 3: | >100 mm | >39.0 °C (102.2 °F) |

The intensity of an AE is an estimate of the relative severity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- 1 (Mild): A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- 2 (Moderate): A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- 3 (Severe): A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An AE that is assessed as Grade 3 (severe) should not be confused with an SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets 1 of the pre-defined outcomes as described in the Section 10.3.2.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- For causality assessments, events assessed as having a reasonable possibility of being related to study intervention will be considered "related." Events assessed as having no reasonable possibility of being related to study intervention will be considered "unrelated."
- The investigator will also consult the Investigator's Brochure and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Medically Attended Visits**

For each solicited event and unsolicited AE the participant experiences, the participant/caregiver(s) will be asked if he/she/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, and/or, if applicable in the eDiary.

**Assessment of Outcomes**

The investigator will assess the outcome of all serious and non-serious unsolicited AEs (including pIMDs) recorded during the study as:

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

**Follow-up of AEs, SAEs, pIMDs, and Device Deficiencies**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by IQVIA, GSK or designee to elucidate the nature and/or causality of the AE, SAE, pIMD, or device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- AEs (serious or non-serious) or pIMDs 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 end of the study or the participant is lost to follow-up.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide IQVIA with a copy of any postmortem findings including histopathology if such records are available to PI.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE/device deficiency data to IQVIA within 24 hours of the investigator's awareness of the information.

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

The investigator will provide any new or updated relevant information to on a previously reported SAE to IQVIA using a paper/electronic Expedited Adverse Events Report and/or pregnancy 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 SAE/pIMD as fully as possible.

**Updating of SAE and pIMD Information After Removal of Write Access to the Participant's eCRFs**

When additional SAE or pIMD information is received after write access to the participant's eCRF is removed, 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.

### 10.3.6 Reporting of SAEs, pIMDs, Medical Device SAEs

**SAE, pIMD, and Medical Device SAE Reporting to the Sponsor or Designee via an Electronic Data Collection System**

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection system. The study site will enter the event into the electronic data collection system within 24 hours of the investigator's awareness of the event.
- If the electronic system is unavailable, then the study site will use the paper SAE report form (see next section) to report the event and will enter the event into the electronic data collection system as soon as the system becomes available.
- After the study is completed at a given study site, the electronic data collection system will be taken offline to prevent the entry of new data or changes to existing data.
- If a study site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection system has been taken offline, then the study site can report this information on a paper SAE report form (see next section) to GSK.
- If the site during the course of the study or post-study becomes aware of any serious, nonserious AEs, related to any GSK non-investigational medicinal product (IMP) they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous individual case safety reports.
- Contacts for SAE reporting can be found in SRM or other study materials.

| **Events Requiring Expedited Reporting to IQVIA** |
|---|
| • Once an investigator becomes aware that an SAE has occurred in enrolled participant, the investigator (or designee) must complete the electronic Expedited Adverse Events Report WITHIN 24 HOURS, even if the investigator does not have complete information on the SAE. It must be completed as thoroughly as possible, with all available details of the event.<br>• The SAE report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE. The investigator will always provide an assessment of causality at the time of the initial report.<br>• Refer to the Table 11 for the details on timeframes for reporting of SAEs/pIMDs.<br>• The investigator will be required to confirm the review of SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.<br>• Refer to Section below for information on back-up systems in case the electronic reporting system does not work. |

| **SAE Reporting to IQVIA via Paper SAE Report Form** |
|---|
| • Fax transmission of the SAE paper Expedited AE Report is the preferred method to transmit this information to the Medical Monitor.<br>• 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.<br>• 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.<br>• Contacts of the Medical Monitor for SAE reporting can be found in the SRM. |

## 10.4 Appendix 4: Abbreviations and Glossary of Terms

**Table 19 Abbreviations List**

| Abbreviation | Definition |
|---|---|
| Ab | Antibody |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ANCOVA | Analysis of Covariance |
| C | Celsius |
| CBER | Center for Biologics Evaluation and Research |
| CD4 | Cluster of Differentiation 4 |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CMI | Cell-mediated immunity |
| Co-ad | Co-administration group |
| COVID-19 | Coronavirus disease 2019 |
| CSR | Clinical Study Report |
| CTR | Clinical Trial Regulation |
| eCRF | Electronic case report form |
| DTaP | Diphtheria-tetanus-pertussis |
| EEC | European Economic Community |
| EoS | End of Study |
| EU | European Union |
| F | Fahrenheit |
| FSFV | First subject first visit |
| GCP | Good Clinical Practice |
| GMT | Geometric mean titer |
| GSK | GlaxoSmithKline |
| HCP | Health care professional |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |

| Abbreviation | Definition |
|---|---|
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ID | Identification |
| IEC | Independent Ethics Committee |
| IMP | Investigational medicinal product |
| IRB | Institutional Review Board |
| IWRS | Interactive Web Response System |
| LSLV | Last subject last visit |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MGI | Mean geometric increase |
| MMSE | Mini-Mental State Examination |
| MoCA | Montreal Cognitive Assessment |
| MOPA | Multiplexed Opsonophagocytosis |
| OA | Older adult |
| OP | Opsonophagocytic |
| PCV | Pneumococcal Conjugate Vaccine |
| pIMD | Potential Immune-Medicated Disease |
| PPS | Per Protocol Set |
| PPSV | Pneumococcal polysaccharide vaccine |
| RSV | Respiratory syncytial virus |
| SADE | Serious adverse device effect |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SAR | Serious adverse reaction |
| SoA | Schedule of activities |
| SRM | Study Reference Manual |
| SRT | Safety Review Team |
| ST | Serotype |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| UADE | Unanticipated adverse device effect |
| UL | Upper limit |
| YOA | Years of age |

**Table 20 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 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 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 trial 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 trial, 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 AEs<br>In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned. |
| **Caregiver:** | A ‘caregiver’ is a person who has a continuous caring role for a participant or may be a person having substantial periods of contact with a participant and/or is engaged in his/her daily health care (e.g., a relative of the participant including family members or friends).<br>In the context of this study, a caregiver can be appointed by the participant to oversee and support the participant’s compliance with protocol-specific procedures (such as transcribing responses to diaries, receiving phone calls, planning study visits, etc.). However, at no time, the caregiver should evaluate the participant’s health status while answering diaries or make decisions on behalf of the participant. |
| **Eligible:** | Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria. |

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| **Enrolled participant:** | 'Enrolled' means a participant'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, unless otherwise specified by the protocol.<br>Refer to the Section 9.2 of the protocol for the definition of 'enrolled set' applicable to the study. |
| **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. |
| **Intercurrent medical condition:** | A condition that has the capability of altering the immune response to the study vaccine or is confirmed to have an alteration of the participant's initial immune status. |
| **Intervention number:** | A number identifying an intervention to a participant, according to intervention allocation. |
| **Intervention:** | Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. |
| **Investigational vaccine:** | A pharmaceutical form of an active ingredient being tested in a clinical trial, 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.<br>Synonym: Investigational Medicinal Product. |
| **Investigator:** | A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.<br>The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions. |
| **Participant:** | Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in |

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|---|---|
| | the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control).<br>Synonym: subject. |
| **Randomization:** | Process of random attribution of intervention to participants to reduce selection bias. |
| **Remote visit** | This term refers to the visit conducted in the place other than the study site. |
| **Serious Adverse Reaction** | All noxious and unintended responses to an IMP related to any dose administered that result in death, are life-threatening, require patient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, or are a congenital anomaly or birth defect. |
| **Source data:** | All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). |
| **Source documents:** | Original legible documents, data, and records (eg, 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, laboratories and at medico-technical departments involved in the clinical trial). |
| **Study intervention:** | Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study. |
| **Suspected Unexpected Serious Adverse Reaction** | A Suspected Unexpected Serious Adverse Reaction is a Serious Adverse Reaction whose nature, severity or outcome is not consistent with the reference safety information. |
| **Telemedicine** | The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate |

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|---|---|
| | remote health care delivery, participant and professional health-related education, public health and health administration. |
| **Unsolicited adverse event:** | Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event. |
| **Virtual visit** | This term refers to study visits conducted using multimedia or technological platforms. |

## 10.5 Appendix 5: Protocol Amendment History

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

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

Overall Rationale for Protocol Update:

The Original Protocol is updated to version 2.0 to clarify the timeframe to collect adverse events, serious adverse events, and pIMDs in Appendix 3 of this document. Additionally, the Protocol Investigator Agreement has been added to this document. During this protocol update minor clarifications were added.

(Added text is ***bold italic***, deleted text is ~~strikethrough~~)

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Protocol Investigator Agreement | Added to the page after the Sponsor Signatory page. | Included to avoid separate collection of signed Protocol Investigator Agreement. |
| Sponsor signatory page | Updated signatory:<br>~~Mathieu Peeters, MD~~<br>***Maria Van Der Wielen, MD*** | Original signatory on leave. |
| 1.1 Synopsis | Edited text:<br>~~Data Monitoring Committee/Other Committee: None~~<br>***Safety monitoring: the study will be conducted with oversight by the project Safety Review Team.*** | Clarification |
| 1.3 Schema | Edited text:<br>AEs/SAEs leading to withdrawal from the study ***start*** up to study end | Clarification |
| 2.3.1 Risk Assessment | Added text to RSV investigational vaccine Mitigation Strategy:<br>***Participants with a history of hypersensitivity or severe allergic reaction to any component of the vaccine are excluded from study enrollment.*** | Additional mitigation strategy for known hypersensitivity or severe allergic reaction. |
| 5.2.2 Prior and Concomitant Therapy | Deleted bullet:<br>• ~~Administration of long-acting immune-modifying drugs or planned administration at any~~ | To minimize the interference due to external factors among study participants. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | ~~time during the study period (e.g., infliximab).~~<br>Added bullet:<br>• ***Administration of long-acting immune-modifying drugs during the period starting 180 days before the administration of first dose of study interventions or planned administration at any time during the study period (e.g., infliximab).*** | |
| 5.6 Criteria for Temporarily Delaying | Added bullet:<br>• ***Use of antipyretics and/or analgesics and/or antibiotics within 3 days prior to study intervention administration.*** | Use of antipyretics and/or analgesics and/or antibiotics within 3 days may indicate an acute condition. |
| 6.1 Study Interventions Administered | Edited text:<br>Vial; suspension ***for suspension*** for injection | Clarification |
| 6.6 Treatment of Overdose | Added section | To better guide investigators about what to do in case of an overdose. |
| 7.1 Discontinuation of Study Intervention | Edited text:<br>Adverse event requiring expedited reporting to ***IQVIA*** ~~GSK~~ | Clarification |
| 10.3.5.1 Time Period for Collecting and Recording AEs, SAEs, and pIMDs | Edited text:<br>•All ***unsolicited*** AEs that occur during 30 days following administration of each dose/the dose of study intervention must be recorded onto/into the appropriate section of the eCRF (…)<br><br>Added text:<br>•***All SAEs, and pIMDs that occur up to 6 months post last-dose of study intervention must be recorded onto/into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.*** | Clarification on timing of AE, SAE, and pIMD collection for this study. |
| Summary of Changes | Summary of Changes table was added to document updates to Original Protocol. | Version control |

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**Signature of Investigator**

PROTOCOL TITLE: A Phase III, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with 20 valent pneumococcal conjugate vaccine (PCV20) in adults aged 60 years and older.

PROTOCOL NO: 219276

VERSION: Amendment v1.0

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

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

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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