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 Herpes Zoster recombinant subunit (HZ/su) vaccine in adults aged 50 years and older.

Protocol Number: 219331

Compound: RSVPreF3 OA

Study Phase: III

Sponsor: GlaxoSmithKline Biologicals S.A.

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

Date of Original Protocol: 17 April 2023

Approval Date: 17 April 2023

Sponsor Signatory

PPD

Mathieu Peeters, MD
Clinical Project Lead
RSV Older Adults

Date

Medical monitor name and contact can be found in local study contact information document

PROTOCOL SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY			
Document	**Date**	**Substantial**	**Region**
Original Protocol v2.0	17-April-2023	No	Global
Original Protocol	21-March-2023	-	-

Original Protocol v2.0 (17-April-2023)

This protocol update 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 add the Day 8 remote contact visit to the tables describing the timeframe for collecting and reporting safety information and to correct the participant age range in one instance of this document.

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

Section # and Name	**Description of Change**	**Brief Rationale**
1.3 Schedule of Activities	Edited footnote of Table 1 Schedule of Activities for the Co-administration Group [11]***At Visits 1 and 3 (Co-ad group), pregnancy information must be recorded prior to study intervention administration.*** *Pregnancies will be followed as described in Section 10.4.3.* and Table 2 Schedule of Activities for the Control Group [12]***At Visits 1, 2, and 3 (Control group), pregnancy information must be recorded prior to study intervention administration.*** *Pregnancies will be followed as described in Section 10.4.3.*	Clarification
8.3.1 Time Period and Frequency for Collecting AE, SAE, and Other Safety Information	Added ***Day 8*** visit column to Table 13 Timeframes for Collecting and Reporting of Safety Information for the Co-ad Group, and Table 14 Timeframes for Collecting and Reporting of Safety Information for the Control Group	Clarification

Section # and Name	Description of Change	Brief Rationale
	Edited Recording of pregnancies row in Tables 13 and 14 to show visits in which pregnancy information is recorded.	
9.3.1 Primary Endpoints/Estimands Analysis	Deleted text: **The model will include the treatment group and the age category (age at vaccination: 50 to 59, 60 to 69, or ≥70 ~~to 79~~) as fixed effects, and the pre-vaccination log_{10}-transformed titer as covariate.*	Correction
Summary of Changes	Summary of Changes table was added to document updates to Original Protocol.	Version control

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: _____

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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 Herpes Zoster recombinant subunit (HZ/su) vaccine in adults aged 50 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) adjuvanted with liposome-based $AS01_E$ system, against RSV-associated (subtypes A and B) disease. In a large phase III vaccine clinical trial in adults aged 60 years and above, the vaccine candidate demonstrated overall vaccine efficacy of 82.6% (96.95% Confidence Interval [CI], 57.9–94.1) against RSV lower respiratory tract disease (RSV-LRTD). The vaccine was well tolerated with a favorable safety profile. The study is still ongoing to assess other endpoints. GSK is aiming to expand the label indication to include a population of 50 to 59 years of age. A study to evaluate immune response and safety of RSVPreF3 OA investigational vaccine in adults 50 to 59 YOA, versus adults ≥60 YOA is ongoing.

GSK's herpes zoster (HZ) vaccine is a non-live, recombinant subunit (su) vaccine (Shingrix, hereby referred to as HZ/su vaccine) and consists of the varicella zoster virus (VZV) glycoprotein E (gE) as an active ingredient, together with the liposome-based adjuvant system $AS01_B$. Earlier studies have established that HZ/su vaccine is highly efficacious and induces strong cellular and humoral immune responses with a clinically acceptable safety profile in adults ≥50 YOA.

The HZ/su vaccine is indicated for use in adults ≥50 YOA in USA, Canada, and UK (proposed study countries). Since both the vaccines will be indicated for use in individuals of overlapping age groups, evaluation of the co-administration of the RSVPreF3 OA and HZ/su vaccines is of interest.

The present study will assess the immunogenicity, safety and reactogenicity of the RSVPreF3 OA investigational vaccine when co-administered with HZ/su vaccine in adults ≥50 YOA, as compared to when the RSVPreF3 OA investigational vaccine and the HZ/su vaccine are administered separately.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary*	
To demonstrate non-inferiority of the humoral immune response to two doses of HZ/su vaccine when the first dose of HZ/su vaccine is co-administered with RSVPreF3 OA investigational vaccine, compared to two doses of HZ/su vaccine administered alone.	• Anti-gE antibody concentrations expressed as group GMC ratio between the Control group and the Co-ad group, 1-month after the second dose of HZ/su vaccine.

Objectives	Endpoints
To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with the first dose of HZ/su vaccine, compared to RSVPreF3 OA investigational vaccine administered alone.	• RSV-A neutralizing titers expressed as group GMT ratio between the Control group and the Co-ad group, 1-month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralizing titers expressed as group GMT ratio between the Control group and the Co-ad group, 1-month after the RSVPreF3 OA investigational vaccine dose.
Secondary	
To evaluate the anti-gE humoral immune response to two doses of HZ/su vaccine, when the first dose of HZ/su vaccine is co-administered with RSVPreF3 OA investigational vaccine or administered alone.	• Anti-gE antibody concentrations expressed as seropositivity rate with exact 95% CI at pre vaccination and at 1-month post-second dose of HZ/su vaccine. • Anti-gE antibody concentrations expressed as GMC with 95% CI at pre-vaccination and at 1-month post-second dose of HZ/su vaccine. • Anti-gE antibody concentrations expressed as MGI with 95% CI from pre-vaccination to 1-month post-second dose of HZ/su vaccine. • Vaccine response rate with exact 95% CIs at 1-month post-second dose of HZ/su vaccine.
To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with the first dose of HZ/su vaccine or administered alone.	• RSV-A neutralizing titers expressed as GMT at pre-vaccination and at 1-month after the RSVPreF3 OA investigational vaccine dose. • RSV-A neutralizing titers expressed as MGI at 1-month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralizing titers expressed as GMT at pre-vaccination and at 1-month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralizing titers expressed as MGI 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 the HZ/su vaccine, co-administered or administered alone.	• Percentage of participants reporting each solicited administration site and systemic event with onset within 7 days after vaccine administration (i.e., the day of vaccination and 6 subsequent days). • Percentage of participants reporting unsolicited AEs with onset within 30 days after vaccine administration (i.e., the day of vaccination and 29 subsequent days). • Percentage of participants reporting all SAEs after vaccine administration (Day 1) up to study end (6 months after last vaccination). • Percentage of participants reporting all pIMDs after vaccine administration (Day 1) up to study end (6 months after last vaccination).

Abbreviations: AE=adverse event; CI=confidence interval; gE=glycoprotein E; GMC=geometric mean concentration; GMT=geometric mean titer; HZ/su=herpes zoster recombinant subunit; MGI=mean geometric increase; OA=older adult; pIMD=potential immune-mediated disease; RSV=respiratory syncytial virus; SAE=serious adverse event.

* Zoster and RSV-A related endpoints will be assessed as co-primary. RSV-B related endpoints will be assessed as sequential to the success of Zoster and RSV-A.

Overall Design:

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

Study groups and Randomization: Approximately 530 eligible participants will be randomly (1:1) assigned to 2 study groups (approximately 265 participants each) using a centralized randomization system on internet at Visit 1 (Day 1). The randomization algorithm will use a minimization procedure accounting for age (50 to 59, 60 to 69, or ≥70 years) and center. Minimization factors will have equal weight in the minimization algorithm.

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

Approximately 30% of participants 50 to 59 YOA, approximately 30% of participants 60 to 69 YOA, approximately 25% of participants ≥70 YOA. The remaining 15% can be distributed freely across the three age categories. The enrollment of participants as per the age categories, and percentage of participants in each age category, if any, will be guided by the feasibility assessment.

Approximately 40% of participants from each sex; the remaining 20% can be distributed freely between the two sexes.

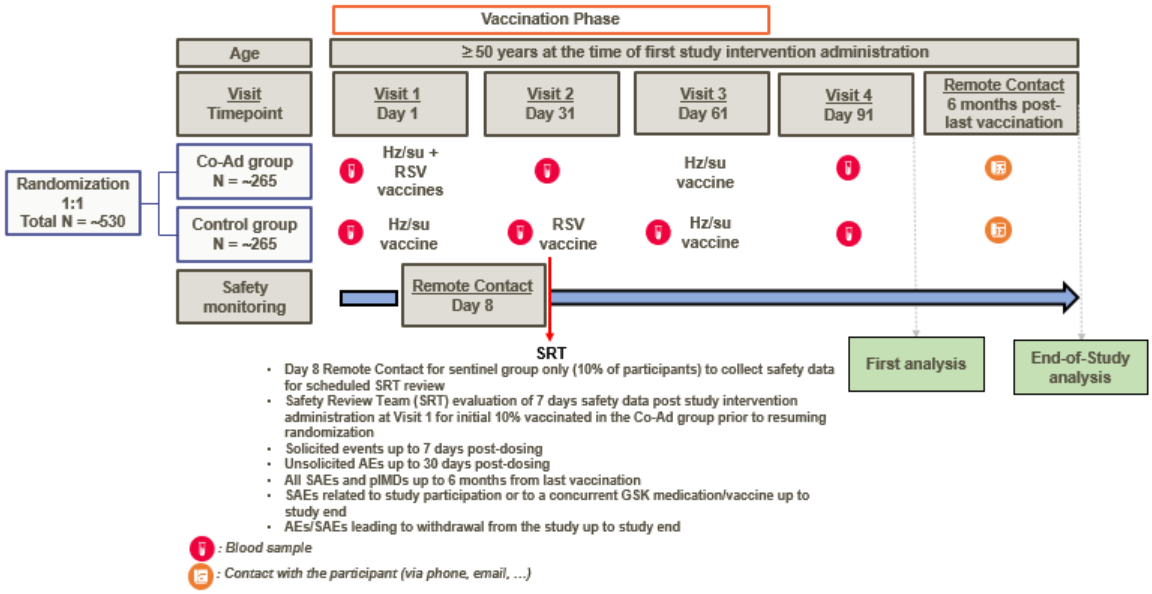
Duration of study: The total duration of the study, per participant, will be approximately 8 months.

- **Co-administration (Co-ad) group**: Study interventions will be administered on Visit 1 (Day 1) in which participants will receive both HZ/su vaccine and RSV PreF3 OA investigational vaccine; and on Visit 3 (Day 61) in which the second dose of HZ/su vaccine will be administered. A total of four site visits (Visit 1 [Day 1], Visit 2 [Day 31], Visit 3 [Day 61] and Visit 4 [Day 91]) and a remote contact 6 months post-last vaccination are needed.
- **Control group**: Study interventions will be administered on Visit 1 (Day 1) in which participants will receive HZ/su vaccine; Visit 2 (Day 31) in which participants will receive RSV PreF3 OA investigational vaccine; and Visit 3 (Day 61) in which participants will receive the second dose of HZ/su vaccine. A total of four site visits (Visit 1 [Day 1], Visit 2 [Day 31], Visit 3 [Day 61] and Visit 4 [Day 91]) and a remote contact 6 months post-last vaccination are needed.

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

1.2 Schema

Figure 1 Study Schema



Abbreviations: AE=Adverse Event; Co-ad group=Co-administration group; D=Day; Hz/su=herpes zoster recombinant subunit; GSK=GlaxoSmithKline; N=Number of participants; pIMD=potential Immune-Mediated Disease; RSV=RSVPreF3 OA investigational vaccine; SAE=Serious Adverse Event; SRT=Safety Review Team.

1.3 Schedule of Activities

Table 1 Schedule of Activities for the Co-administration Group

Type of contact	Visit 1	Remote Contact[1]	Visit 2[2]	Visit 3	Visit 4[2]	Remote Contact[3]
Timepoints	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 91**	**6-months post-last vaccination**
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	○					
Urine pregnancy test (WOCBP only) before study intervention administration[4]	●			●		
Laboratory assessment						
Blood sampling from all participants for antibody determination (~10 mL)	●[5]		●[6]		●[7]	
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	●					

Type of contact	Visit 1	Remote Contact[1]	Visit 2[2]	Visit 3	Visit 4[2]	Remote Contact[3]
Timepoints	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 91**	**6-months post-last vaccination**
Intervention numbers allocation	○			○		
Record body temperature before study interventions administration[8]	●			●		
Study interventions administration (RSVPreF3 OA investigational vaccine + HZ/su vaccine first dose) (including at least 30-minute post-vaccination observation)	●					
Study interventions administration (HZ/su vaccine second dose) (including at least 30-minute post-vaccination 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-vaccination)	Δ			Δ		
Recording of ongoing solicited events in eDiary, if applicable (Days 8 - 30 post-vaccination)	Δ		Δ	Δ	Δ	
Review eDiary[9]			○		○	
Collect eDiary or assist participant to delete application					○	
Recording of unsolicited AEs (Days 1 - 30 post-vaccination)	●	●	●	●	●	
Recording of concomitant medications	●	●	●	●	●	●
Recording of concomitant vaccinations	●	●	●	●	●	●
Recording of intercurrent medical conditions	●	●	●	●	●	●
Recording of SAEs and pIMDs (up to 6 months post-last vaccination)	●	●	●	●	●	●

Type of contact	Visit 1	Remote Contact[1]	Visit 2[2]	Visit 3	Visit 4[2]	Remote Contact[3]
Timepoints	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 91**	**6-months post-last vaccination**
Recording of AEs/SAEs leading to withdrawal from the study until study end	●	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine until study end[10]	●	●	●	●	●	●
Recording of pregnancies[11] (up to EoS)	●	●	●	●	●	●
Contact for safety follow-up						●
Study conclusion						●

Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; eDiary=electronic diary; EoS=end of study; gE=glycoprotein E; GSK=GlaxoSmithKline; HZ=herpes zoster; pIMD=potential immune-mediated disease; SAE=serious adverse event; su=subunit.

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

[1]Day 8 Remote Contact for the sentinel group only for both groups.

[2]Visit 2 and Visit 4 should preferably be done on site but if deemed necessary (during special circumstances such as the Coronavirus Disease 2019 [COVID-19] pandemic), this site 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 other means (e.g., phone call, email, text message, or fax) conducted by the site staff.

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

[4]Urine pregnancy test (WOCBP only) must be performed prior to study intervention administration.

[5]Sample collected at Day 1 will be used as baseline for RSV neutralizing titers and HZ/su anti-gE antibody concentrations.

[6]Sample collected at Day 31 will be used for the post-vaccination RSV antibodies-related testing.

[7]Sample collected at Day 91 will be used for the post-vaccination HZ/su antibodies-related testing.

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

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

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

[11]At Visits 1 and 3 (Co-ad group), pregnancy information must be recorded prior to study intervention administration. Pregnancies will be followed as described in Section 10.4.3.

Table 2 Schedule of Activities for the Control Group

Type of contact	Visit 1	Remote Contact[1]	Visit 2	Visit 3	Visit 4[2]	Remote Contact[3]
Timepoints	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 91**	**6-months post-last vaccination**
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	○					
Urine pregnancy test (WOCBP only) before study intervention administration[4]	●		●	●		
Laboratory assessment						
Blood sampling from all participants for antibody determination (~10 mL)	●[5]		●[6]	●[7]	●[8]	
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 number allocation (HZ/su vaccine)	○			○		

Type of contact	Visit 1	Remote Contact[1]	Visit 2	Visit 3	Visit 4[2]	Remote Contact[3]
Timepoints	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 91**	**6-months post-last vaccination**
Intervention number allocation (RSVPreF3 OA investigational vaccine)			○			
Record body temperature before study intervention administration[9]	●		●	●		
Study intervention administration (HZ/su vaccine first dose) (including at least 30-minute post-dosing observation)	●					
Study intervention administration (RSVPreF3 OA investigational vaccine) (including at least 30-minute post-dosing observation)			●			
Study intervention administration (Hz/su vaccine second dose) (including at least 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-vaccination)	Δ		Δ	Δ		
Recording of ongoing solicited events in eDiary if applicable (Days 8 - 30 post-vaccination)	Δ		Δ	Δ	Δ	
Review eDiary[10]			○	○	○	
Collect eDiary or assist participant to delete application					○	
Recording of unsolicited AEs (Days 1 - 30 post-vaccination)	●	●	●	●	●	
Recording of concomitant medications/vaccinations	●	●	●	●	●	●
Recording of intercurrent medical conditions	●	●	●	●	●	●

Type of contact	Visit 1	Remote Contact[1]	Visit 2	Visit 3	Visit 4[2]	Remote Contact[3]
Timepoints	**Day 1**	**Day 8**	**Day 31**	**Day 61**	**Day 91**	**6-months post-last vaccination**
Recording of SAEs and pIMDs (up to 6 months post-last vaccination)	●	●	●	●	●	●
Recording of AEs/SAEs leading to withdrawal from the study until study end	●	●	●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine until study end[11]	●	●	●	●	●	●
Recording of pregnancies[12] (up to EoS)	●	●	●	●	●	●
Contact for safety follow-up						●
Study conclusion						●

Abbreviations: AE=adverse event; COVID-19=coronavirus disease 2019; eDiary=electronic diary; EoS=end of study; gE=glycoprotein E; GSK=GlaxoSmithKline; HZ=herpes zoster; pIMD=potential immune-mediated disease; SAE=serious adverse event; su=subunit.

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.

[1]Day 8 Remote Contact for the sentinel group only for both groups.

[2]Visit 4 should preferably be done on site but if deemed necessary (during special circumstances such as the Coronavirus Disease 2019 [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.

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

[4]Urine pregnancy test (WOCBP only) must be performed prior to study intervention administration.

[5]Sample collected at Day 1 will be used as baseline for HZ/su anti-gE antibody concentrations.

[6]Sample collected at Day 31 will be used as the baseline for RSV neutralizing antibody titers in the Control group.

[7]Sample collected at Day 61 will be used for post-vaccination RSV antibody-related testing.

[8]Sample collected at Day 91 will be used for the post-vaccination HZ/su antibody-related testing.

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

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

[11]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 study end.

[12]At Visits 1, 2, and 3 (Control group), pregnancy information must be recorded prior to study intervention administration. Pregnancies will be followed as described in Section 10.4.3.

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

Interval	Planned visit interval	Allowed interval range*
Visit 1 (Day 1)→Remote Contact (Day 8)**	8 days	-
Visit 1 (Day 1)→Visit 2 (Day 31)	30 days	30-42 days
Visit 1 (Day 1)→Visit 3 (Day 61)	60 days	60-84 days
Visit 3 (Day 61)→Visit 4 (Day 91)	30 days	30-42 days
Visit 3 (Day 61)→Phone contact	180 days	180-210 days

*Participants may not be eligible for the HZ/su and RSV Per Protocol Set (PPS) if the visits happen beyond this interval. Intervals between visits and phone contact do not affect HZ/su and RSV PPS eligibility.

**Day 8 Remote Contact is applicable to the sentinel group only.

Table 4 Interval Between Study Visits (Control Group)

Interval	Planned visit interval	Allowed interval range*
Visit 1 (Day 1)→Remote Contact (Day 8)**	8 days	-
Visit 1 (Day 1)→Visit 2 (Day 31)	30 days	30-42 days
Visit 2 (Day 31)→Visit 3 (Day 61)	30 days	30-42 days
Visit 3 (Day 61)→Visit 4 (Day 91)	30 days	30-42 days
Visit 3 (Day 61)→Phone contact	180 days	180-210 days

*Participants may not be eligible for the HZ/su and RSV Per Protocol Set (PPS) if the visits happen beyond this interval. Intervals between visits and phone contact do not affect HZ/su and RSV PPS eligibility.

**Day 8 Remote Contact is applicable to the sentinel group only.

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) adjuvanted with liposome-based $AS01_E$ system, against RSV-associated (subtypes A and B) disease. In a large phase III vaccine clinical trial in adults aged 60 years and above, the vaccine candidate demonstrated overall vaccine efficacy of 82.6% (96.95% Confidence Interval [CI], 57.9 – 94.1) against RSV lower respiratory tract disease (RSV-LRTD).[1] The vaccine was well tolerated with a favorable safety profile. The study is still ongoing to assess other endpoints.

The present study will assess the immunogenicity, safety and reactogenicity of the RSVPreF3 OA investigational vaccine when co-administered with Herpes Zoster recombinant subunit (HZ/su) vaccine in adults ≥50 YOA, as compared to when the RSVPreF3 OA investigational vaccine and the HZ/su vaccine are administered alone.

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.[2] 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.[3] Further information on RSV incidence and disease burden can be found in the Investigator's Brochure (IB).

GSK's herpes zoster (HZ) vaccine is a non-live, recombinant subunit (su) vaccine (Shingrix, hereby referred to as HZ/su vaccine) and consists of the varicella zoster virus (VZV) glycoprotein E (gE) as an active ingredient, together with the liposome-based adjuvant system $AS01_B$. Earlier studies have established that HZ/su vaccine is highly efficacious, and induces strong cellular and humoral immune responses with a clinically acceptable safety profile in adults ≥50 YOA.[4,5,6]

The HZ/su vaccine is indicated for use in healthy adults ≥50 YOA in United States (US), Canada, and United Kingdom (UK).[7,8,9] Since both vaccines will be indicated for use in

individuals of overlapping age groups, evaluation of the co-administration of the RSVPreF3 OA and HZ/su vaccines is of interest.

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).

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

Table 5 Potential/Identified Risk and Mitigation Strategy

Important Potential/Identified Risk	Mitigation Strategy
RSV Investigational Vaccine	
Potential immune-mediated diseases 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).	Participants with a history of hypersensitivity or severe allergic reaction to any component of the vaccine are excluded from study enrollment. All participants will remain under observation at the clinical center for at least 30 minutes after vaccination. Appropriate medical care must be readily available during this period
HZ/su Vaccine	
Guillain-Barré Syndrome	Close monitoring of GBS will be conducted per study protocol and analysis of safety data generated through clinical trials and other sources as part of pIMDs (including GBS). The potential risk of events of possible autoimmune etiology to occur is mentioned in the ICF. In addition, the ICF advises participants to contact the study doctor or study staff immediately, should any symptoms be considered of concern. All pIMDs (including GBS) will be collected up to end of study.
Potential immune-mediated diseases 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	Participants with a history of hypersensitivity or

anaphylaxis).	severe allergic reaction to any component of the vaccine are excluded from study enrollment. All participants will remain under observation at the clinical center for at least 30 minutes after vaccination. Appropriate medical care must be readily available during this period
Study Procedures	
Intramuscular vaccination commonly precipitates a transient and self-limiting administration site 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.	Blood samples will be obtained in seated or supine position by a trained professional and medical assistance will be available. 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 care must be readily available during this period.

Abbreviations: GBS=Guillain-Barré Syndrome; ICF=informed consent form; pIMD=potential immune-mediated disease; RSV=respiratory syncytial virus.

In this study women of childbearing potential of 50-59 years of age can be included.

On 25 February 2022, GSK decided to stop enrollment and vaccination in RSV maternal vaccine studies involving pregnant women. This decision was taken because of an observed imbalance in the proportions of both preterm births (PTB) and neonatal deaths (death of an infant within the first 28 days of life) in the treatment group vs. the placebo group in the RSV-MAT-009 study. Subsequently, the enrollment and vaccination in all studies of the RSV maternal vaccine candidate involving women of childbearing potential have also been stopped.

Following Day 43 post-birth interim analysis (DLP 04 October 2022) of RSV MAT-009 study, GSK agreed that preterm birth is an identified risk for the pregnant women population, for the RSV maternal vaccine candidate. The observed numerical imbalance in neonatal deaths is not an independent safety signal but a consequence of the imbalance in preterm birth. GSK has discontinued the further development on this RSV maternal candidate vaccine.

The safety concern is specific to women who received the RSV maternal vaccine candidate during the late second or third trimester of pregnancy. To date, analyses of the available safety data have not established what caused the imbalances that were observed. Further analysis of the data to better understand the safety concerns is ongoing.

The vaccine candidate for older adults (OA) contains the same RSV antigen as the RSV maternal candidate vaccine but RSV OA vaccine is combined with GSK's established $AS01_E$ adjuvant to boost the immune response in the older adult population.

The Older Adult RSV vaccine trials in participants 60 years of age and older are closely monitored for safety with all available safety data reviewed internally. In addition, the phase III RSV OA=ADJ-006 clinical study is monitored by an IDMC on an ongoing basis. The IDMC met most recently on 1 December 2022 and did not raise any concerns in the older adult population. The RSV OA vaccine has not been studied in pregnant women to date.

In the current study the inclusion of all participants will be restricted to those 50 years of age and above. This age cut-off has been chosen since there is a recommendation for use of Shingrix as of 50 YOA. For women, the incidence of spontaneous pregnancies is 4 in 100,000 in this age group.[10] As a precautionary measure, all women of childbearing potential will be required to use adequate contraception and have a negative pregnancy test prior to vaccination.

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 older, 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). The vaccine was well tolerated with a favorable safety profile.

All participants in this study will also receive herpes zoster recombinant subunit (HZ/su) vaccine as part of this study which is indicated for the prevention of herpes zoster among healthy adults ≥50 YOA.

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 HZ/su 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

Considering the measures taken to minimize risk to participants participating in this study, the potential or recognized risks identified in association with the study vaccines and study

2.3.3 Overall Benefit Risk Conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential or recognized risks identified in association with the study vaccines and study procedures are justified by the potential benefits that may be afforded to the participants receiving these vaccines and by the value of the information to be gained.

3.0 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 6 Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary*	
To demonstrate non-inferiority of the humoral immune response to two doses of HZ/su vaccine when the first dose of HZ/su vaccine is co-administered with RSVPreF3 OA investigational vaccine, compared to two doses of HZ/su vaccine administered alone.	• Anti-gE antibody concentrations expressed as group GMC ratio between the Control group and the Co-ad group, 1-month after the second dose of HZ/su vaccine.
To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with the first dose of HZ/su vaccine, compared to RSVPreF3 OA investigational vaccine administered alone.	• RSV-A neutralizing titers expressed as group GMT ratio between the Control group and the Co-ad group, 1-month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralizing titers expressed as group GMT ratio between the Control group and the Co-ad group, 1-month after the RSVPreF3 OA investigational vaccine dose.
Secondary	
To evaluate the anti-gE humoral immune response to two doses of HZ/su vaccine, when the first dose of HZ/su vaccine is co-administered with RSVPreF3 OA investigational vaccine or administered alone.	• Anti-gE antibody concentrations expressed as seropositivity rate with exact 95% CI at pre vaccination and at 1-month post-second dose of HZ/su vaccine. • Anti-gE antibody concentrations expressed as GMC with 95% CI at pre-vaccination and at 1-month post-second dose of HZ/su vaccine. • Anti-gE antibody concentrations expressed as MGI with 95% CI from pre-vaccination to 1-month post-second dose of HZ/su vaccine. • Vaccine response rate with exact 95% CIs at 1-month post-second dose of HZ/su vaccine.
To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with the first dose of HZ/su vaccine or administered alone.	• RSV-A neutralizing titers expressed as GMT at pre-vaccination and at 1-month after the RSVPreF3 OA investigational vaccine dose. • RSV-A neutralizing titers expressed as MGI at 1-month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralizing titers expressed as GMT at pre-vaccination and at 1-month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralizing titers expressed as MGI at 1-month after the RSVPreF3 OA investigational vaccine dose.
To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational	• Percentage of participants reporting each solicited administration site and systemic

Objectives	Endpoints
vaccine and the HZ/su vaccine, co-administered or administered alone.	event with onset within 7 days after vaccine administration (i.e., the day of vaccination and 6 subsequent days). • Percentage of participants reporting unsolicited AEs with onset within 30 days after vaccine administration (i.e., the day of vaccination and 29 subsequent days). • Percentage of participants reporting all SAEs after vaccine administration (Day 1) up to study end (6 months after last vaccination). • Percentage of participants reporting all pIMDs after vaccine administration (Day 1) up to study end (6 months after last vaccination).

Abbreviations: AE=adverse event; CI=confidence interval; gE=glycoprotein E; GMC=geometric mean concentration; GMT=geometric mean titer; HZ/su=herpes zoster recombinant subunit; MGI=mean geometric increase; OA=older adult; pIMD=potential immune-mediated disease; RSV=respiratory syncytial virus; SAE=serious adverse event.

* Zoster and RSV-A related endpoints will be assessed as co-primary. RSV-B related endpoints will be assessed as sequential to the success of Zoster and RSV-A.

4.0 STUDY DESIGN

4.1 Overall Design

The study design diagram 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 530 eligible participants will be randomly (1:1) assigned to 2 study groups (approximately 265 participants each) using a centralized randomization system on internet at Visit 1 (Day 1). The randomization algorithm will use a minimization procedure accounting for age (50 to 59. 60 to 69, or ≥70 years) and center. Minimization factors will have equal weight in the minimization algorithm.

- Enrollment rules are described in Section 4.1.2.

Duration of study: The total duration of the study, per participant, will be approximately 8 months.

- **Co-administration (Co-ad) group**: Study interventions will be administered on Visit 1 (Day 1) in which participants will receive both HZ/su vaccine and RSVPreF3 OA investigational vaccine; and on Visit 3 (Day 61) in which the second dose of HZ/su vaccine will be administered. A total of four site visits (Visit 1 [Day 1], Visit 2 [Day 31], Visit 3 [Day 61] and Visit 4 [Day 91]) and a remote contact 6 months post-last vaccination are needed.
- **Control group**: Study interventions will be administered on Visit 1 (Day 1) in which participants will receive HZ/su vaccine; Visit 2 (Day 31) in which participants will receive RSVPreF3 OA investigational vaccine; and Visit 3 (Day 61) in which participants will receive the second dose of HZ/su vaccine. A total of four site visits (Visit 1 [Day 1], Visit 2 [Day 31], Visit 3 [Day 61] and Visit 4 [Day 91]) and a remote contact 6 months post-last vaccination are needed.

The description of the vaccine(s)/product is presented in Table 8.

4.1.1 Overview of 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.

Randomization will be put on pause while the Safety Review Team (SRT, Section 10.1.6) reviews the 7-day safety data for the sentinel group (10% of total sample size, 27 participants in the co-administration group and 27 participants in the control group) and will resume if the recommendation of the SRT is to continue with randomization.

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 three age categories reflecting an approximate age distribution and disease burden in the general population with a balance between males and females. It is therefore intended to enroll:

- Approximately 30% participants 50 to 59 YOA, approximately 30% of participants 60 to 69 YOA, and approximately 25% of participants ≥70 YOA. The remaining 15% can be distributed freely across the three age categories. The enrollment of participants as per the age categories, and percentage of participants in each age category, if any, will be guided by the feasibility assessment.
- Approximately 40% of participants from each sex; the remaining 20% can be distributed freely between the two 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. 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.

Shingrix is a vaccine indicated for active immunization for the prevention of shingles and its complications among healthy from 50 years and above.

Both RSVPreF3 OA investigational vaccine and HZ/su vaccine will be available for individuals with overlapping age groups. The current study is designed to provide reactogenicity, safety, and immunogenicity data when RSV PreF3 OA vaccine is co-administered with HZ/su vaccine or when administered with a gap of 4 weeks. These data are expected to help public health authorities provide more evidence-based guidance and health care providers to make decisions on such vaccine co-administrations.

4.3 Justification for Dose of RSVPreF3 OA Investigational Vaccine

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.[6] 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 geometric mean titers (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 AS01E-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.

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 Holding Rules

Vaccine administration in this study will be staggered: first, a sentinel group of participants (10% of total sample size, 27 participants in the co-administration group and 27 participants in control group) will be vaccinated and followed-up for 7 days after Visit 1. Randomization will be paused after participants in the sentinel group have received Visit 1 vaccinations. All cumulative safety data from the 7 days following Visit 1 vaccinations from the sentinel group participants of both study groups will be reviewed at the predefined scheduled SRT (Figure 1 and Section 10.1.6) as per study protocol.

The holding rules will be applicable for the cumulative safety data from the 27 participants of co-administration group. The holding rules are defined in the Table 7. If SRT judges that no safety concerns have been identified based on cumulative safety data assessment, then randomization pause can be lifted and remaining 90% of participants can be randomized and vaccinated.

If the Investigator, site staff, any study team member from IQVIA, or GSK identify that any of the holding rule criteria or other safety concerns are met at any time during the recruitment of the sentinel group, randomization shall be temporarily put on pause and an *ad hoc* SRT review will be performed to review all cumulative safety data. Randomization shall also be temporarily put on pause and an *ad hoc* SRT review be performed if any safety concern is seen at any time during the study. Randomization can only be resumed following SRT recommendation. Any potential safety concern related to conduct of the study will be managed as per internal GSK process. The decision on whether to continue with randomization as planned or otherwise (including but not limited to, modification of the study conduct/study protocol or stopping the study) will be communicated to the study sites. The investigator is not permitted to restart randomization until the receipt of favorable written documentation of safety evaluation.

No formal assessment of holding rules will be observed after the predefined scheduled SRT review.

Table 7 Study Holding Rules

Holding rule	Event	Number or percentage of participants
1a	Death or any life-threatening SAE that cannot be reasonably attributed to a cause other than vaccination as per Investigator or Sponsor assessment	1/27 participants

1b	Any non-life-threatening SAE that cannot be reasonably attributed to a cause other than vaccination as per Investigator or Sponsor assessment	3/27 participants
1c	Any withdrawal from the study (by investigator or subject request) following a Grade 3 AE that cannot be reasonably attributed to a cause other than vaccination as per Investigator or Sponsor assessment	3/27 participants
1d	Any solicited systemic AE leading to hospitalization within the 7-day (Days 1-7) post-vaccination period	2/27 participants
2a	Any Grade 3 solicited systemic AE (lasting 48 hours or more) within the 7-day (Day 1-7) post-vaccination period	6/27 participants
2b	Any Grade 3 unsolicited AE, that can be reasonably attributed to the vaccination as per Investigator or Sponsor assessment, within the 7-day (Day 1-7) post-vaccination period	3/27 participants

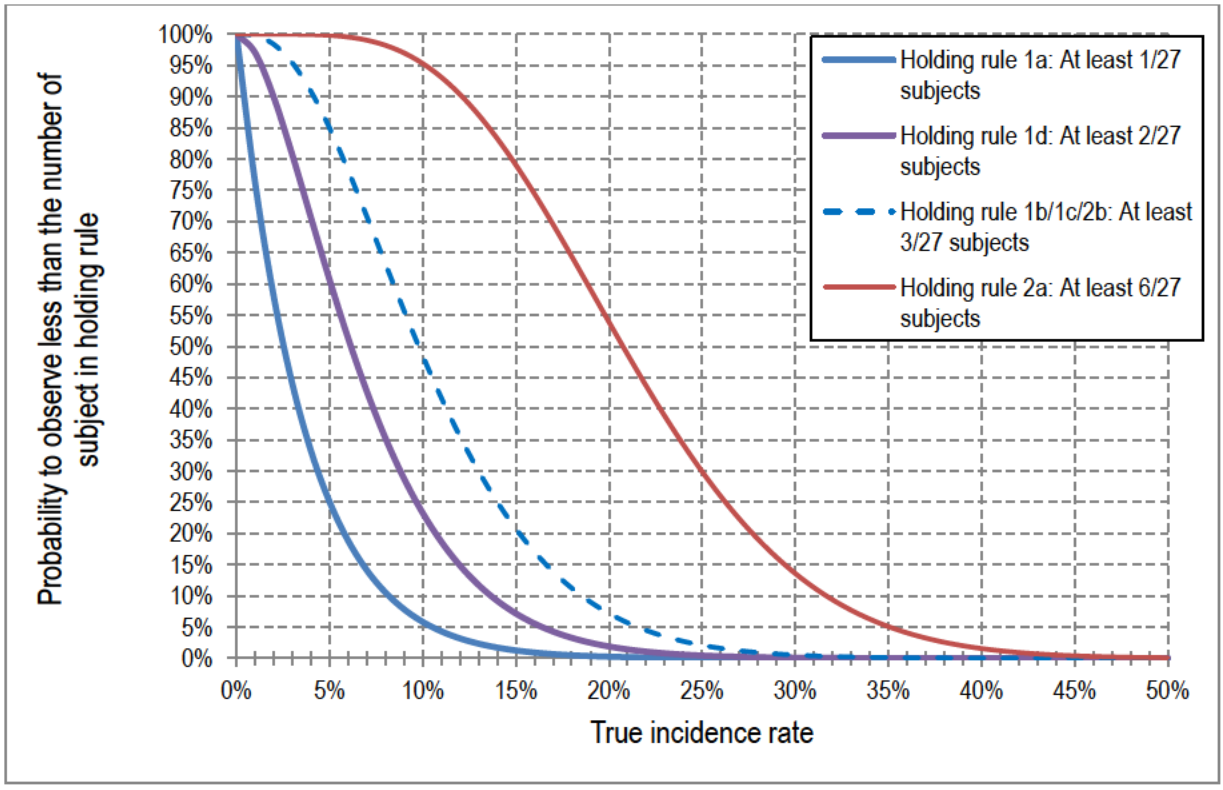
Abbreviations: AE=adverse events; SAE=serious adverse events.

Risk assessment for study holding rules

Figure 1 illustrates that, with 27 participants in the co-administration group in the pre-specified scheduled SRT review:

- Holding rule 1a has more than 76% chance of not being met for vaccination with a true incidence rate of 1% and has more than 94% chance of being met for vaccination with a true incidence rate above 10%.
- Holding rule 1d has more than 61% chance of not being met for vaccination with a true incidence rate of 5% and has more than 93% chance of being met for vaccination with a true incidence rate above 15%.
- Each holding rule 1b, 1c and 2b has more than 48% chance of not being met for vaccination with a true incidence rate below 10% and more than 79% chance of being met for vaccination with a true incidence rate above 15%.
- Holding rule 2a has more than 79% chance of not being met for vaccination with a true incidence rate below 15% and more than 70% chance of being met for vaccination with a true incidence rate above 25%.

Figure 2 Evaluations Based on 27 Participants in the Co-administration Group. Risk Assessment Curve Based on the Proposed Safety Holding Rules



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

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

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

- A male or female participant ≥50 YOA at the time of the first study intervention administration.
- Female participants of non-childbearing potential may be enrolled in the study. Non childbearing potential is defined as hysterectomy, bilateral oophorectomy, bilateral salpingectomy or post-menopause. Refer to Section 10.4.1 for definitions of women not considered as women of childbearing potential, and menopause.
- Female participants of childbearing potential may be enrolled in the study, if the participant:
  - has practiced adequate contraception from 1 month prior to study intervention administration.
  - has a negative pregnancy test on the day of and prior to study intervention administration.
  - has agreed to continue effective contraception until the end of the study.
  - Refer to Section 10.4 for definitions of woman of childbearing potential and adequate contraception.
- Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the electronic diary [eDiary], return for follow-up visits, 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 eDiaries 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 MUST NOT be included in the study if ANY exclusion criterion applies:

5.2.1 Medical conditions

- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions.
- Any confirmed or suspected autoimmune disorders, 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 any component of the study interventions, in particular any history of severe allergic reaction to any vaccine component.
- History of Guillain-Barré syndrome.
- 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 study end).

- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Clinically suspected or polymerase chain reaction (PCR)-confirmed ongoing episode of herpes zoster.

5.2.2 Prior and Concomitant Therapy

- History of previous vaccination with any licensed or investigational recombinant adjuvanted zoster vaccine (HZ/su vaccine; *Shingrix*) before the study start or planned receipt through study participation.
- History of previous vaccination with any licensed or investigational live herpes zoster vaccine (*Zostavax*) in the last 2 years from enrollment[11], or planned receipt through study participation.
- Previous vaccination with 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, 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.
    - In the case of COVID-19 and inactivated/subunit/split influenza vaccines, this time window can be decreased to 14 days before and after each study intervention administration provided COVID-19 vaccine use is in line with local governmental recommendations.

  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 is notified accordingly.
- Planned or actual administration of adjuvanted quadrivalent influenza vaccine 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.
- 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, topical or intra-articular 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 (IMP) (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 Lifestyle Considerations

Meals and Dietary Restrictions

No meal or dietary restrictions are required for study participation. No lifestyle restrictions are applicable for this study.

5.4 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 done 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.

5.5 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 serious adverse events (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 electronic case report form (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, subunit or split influenza vaccines or COVID-19 vaccines (fully licensed or with Emergency Use Authorization [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 abovementioned influenza/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:

- Urine pregnancy test
- Body temperature
- Re-check contraindications, warnings, and 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 (control group), and Visit 3 (co-administration and control groups) the following procedures must be repeated:

- Urine pregnancy test
- 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.

6.1 Study Intervention(s) Administered

Table 8 Study Intervention(s) Administered

Study Treatment Name:	**RSVPreF3 OA Investigational Vaccine**		***Shingrix***	
Vaccines/ product formulation	RSVPreF3 (120 µg)	$AS01_E$: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injections	VZV gE (50 µg)	$AS01_B$: QS-21* (50 µg), MPL (50 µg), liposomes; Water for injections
Presentation	Vial; powder for suspension for injection	Vial; suspension for suspension for injection	Vial; powder for suspension for injection	Vial; suspension for suspension for injection
Route of Administration	Intramuscular use		Intramuscular use	
Product category	Biologic		Biologic	
Type	Study		Study	
Administration site				
Location	Deltoid		Deltoid	
Laterality	Co-ad group: Dominant Control group: Non-dominant		Co-ad group: Non-dominant Control group: Non-dominant	
Number of doses to be administered	1		2	
Dose Volume**	0.5 mL		0.5 mL	
Packaging, labeling***	Refer to Pharmacy Manual for details		Refer to Pharmacy Manual for details	
Manufacturer	GSK		GSK	

Abbreviations: AS01E/AS01B=adjuvant system 01; MPL=monophosphoryl lipid A; QS-21=Quillaja saponaria Molina, fraction 21; RSV=respiratory syncytial virus.

*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, and needle. 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 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 co-administration group and control 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 530 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 (50 to 59, 60 to 69, ≥70 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 is 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 (PI) 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 to be tested in the laboratory. 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

Dose modifications are not planned or allowed in this study.

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 ongoing at screening, and all concomitant medications including vaccines, administered after the first dose of study intervention (Visit 1 [Day 1] to EoS), except vitamins and dietary supplements.
- 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/pIMD 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 (e.g., 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 planned study procedures (e.g., safety or immunogenicity) described 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:

Table 9 Reasons for Premature Discontinuation of Study Intervention

Reasons	Additional items/Sub-reasons
AE	Unsolicited AE
	Solicited AE
	SAEs / pIMDs
Lost to follow-up	-
Withdrawal by Participant	-
Investigator Decision	Specify
Protocol Deviation	Specify
Site Terminated by Sponsor	–
Study Terminated by Sponsor	–
Death	-
Pregnancy	-
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.

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 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 (Section 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 previously administered study intervention (HZ/su vaccine or RSV investigational vaccine) and that, in the opinion of the investigator, may pose additional risk to the participant if he/she receives the subsequent study intervention (HZ/su vaccine or 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.
- Pregnancy
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the participant to unacceptable risk from subsequent vaccination. In such cases, the investigator should use their clinical judgment prior to administering the next dose of the study intervention(s). Refer to Section 10.3.3.1 for the definition of pIMD.
- Participants who develop any new condition that may impair their ability to adhere to required study procedures.

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, 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:

- AEs requiring expedited reporting to IQVIA (see Appendix 3 for details regarding such events)
- Unsolicited nonserious 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-up with 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 5.4).

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.
- 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.

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 volume of approximately 30 mL of blood from each participant in the co-ad group and approximately 40 mL of blood from each participant in the Control group, will be collected during the entire study period. Refer to Table 10 for information on volumes collected for different assessments.

Table 10 Biological Samples

Sample type	Quantity	Unit	Timepoint	Group
Blood for humoral response	~10 per visit	mL	Visit 1 (Day 1) Visit 2 (Day 31) Visit 4 (Day 91)	All participants in the Co-ad group
Blood for humoral response	~10 per visit	mL	Visit 1 (Day 1) Visit 2 (Day 31) Visit 3 (Day 61) Visit 4 (Day 91)	All participants in the Control group
Urine pregnancy test	-	-	Visit 1 (Day 1) Visit 3 (Day 61)	WOCBP in the Co-ad group
Urine pregnancy test	-	-	Visit 1 (Day 1) Visit 2 (Day 31) Visit 3 (Day 61)	WOCBP in the Control group

Abbreviations: Co-ad=co-administration group; WOCBP=women of childbearing potential.

8.1.2 Laboratory Assays

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

Table 11 Laboratory Assays

Assay Type	System	Component	Method	Laboratory
Humoral immunity	Serum	RSV-A	Neutralization	GSK*
		RSV-B	Neutralization	
		HZ/su Anti-gE Ab	ELISA	

Abbreviations: Ab=antibody; ELISA=enzyme linked immunosorbent assay; gE=glycoprotein E; HZ/su=herpes zoster/subunit; RSV-A=respiratory syncytial virus subtype A; RSV-B=respiratory syncytial virus subtype B.
*GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. CLS may delegate testing to a contracted Research Organization.

Refer to Section 10.2 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 12 Immunological Read-outs

		All participants	265	HZ/su Anti-gE Ab
Blood sampling timepoint		**Subset tested**	**N of participants**	**Component**
Type of contact and timepoint	**Sampling timepoint**			
Co-ad group				
Visit 1 (Day 1)	Pre HZ/su vaccine and RSVPreF3 OA vaccine	All participants	265	RSV-A neutralization
		All participants	265	RSV-B neutralization
		All participants	265	HZ/su Anti-gE Ab
Visit 2 (Day 31)	Post RSVPreF3 OA vaccine	All participants	265	RSV-A neutralization
		All participants	265	RSV-B neutralization
Visit 4 (Day 91)	Post-dose 2 HZ/su vaccine	All participants	265	HZ/su Anti-gE Ab
Control group				
Visit 1 (Day 1)	Pre HZ/su vaccine	All participants	265	HZ/su Anti-gE Ab
Visit 2 (Day 31)	Pre RSVPreF3 OA vaccine	All participants	265	RSV-A neutralization
		All participants	265	RSV-B neutralization
Visit 3 (Day 61)	Post RSVPeF3 OA vaccine	All participants	265	RSV-A neutralization
		All participants	265	RSV-B neutralization
Visit 4 (Day 91)	Post-dose 2 HZ/su vaccine	All participants	265	HZ/su Anti-gE Ab

Abbreviations: Ab=antibody; co-ad group=co-administration group; gE=glycoprotein E; HZ/su=herpes zoster recombinant subunit; N=number; RSVPreF3 OA=respiratory syncytial virus investigational vaccine.

8.1.4 Immunological Correlates of Protection

No generally accepted immunological correlate of protection has been demonstrated so far for RSV or against herpes zoster.

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 Pregnancy Test

Before every vaccination in this study, female participants of childbearing potential must perform a urine pregnancy test on the day of and before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.

8.2.1.2 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.[12,13,14] 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.

8.2.1.3 Medical History

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

8.2.1.4 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)
- Live Zoster vaccine administration (if possible, with the date of vaccination)
- COVID-19 vaccine administration (if possible, with the date of vaccination; this information should be collected even if administration was >1 year)

8.2.1.5 Targeted Physical Examinations

History directed/targeted physical examination will be performed for each participant on Visit 1 (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.

8.2.1.6 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 8), 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 and pregnancy information.

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 done 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 (pIMDs and pregnancy) 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, myalgia, shivering/chills and gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain).

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 Other Safety Information

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). All pregnancies beginning after the administration of the first study intervention until end of study will be collected at the time points specified in the SoA (Section 1.3).

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-investigational medicinal product) will be recorded from the time a participant consents to participate in the study until EoS.

All AEs/SAEs/pIMDs/pregnancies leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study intervention until EoS.

All AEs will be collected in the timeframe showed in Table 13 and Table 14.

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 13 Timeframes for Collection and Reporting of Safety Information for the Co-ad Group

Event	Visit 1	Visit 1				Visit 2	Visit 3			Visit 4	Contact 1
	Day 1	Day 1	Day 7	Day 8[2]	Day 30	Day 31	Day 61	Day 67	Day 90	Day 91	Month 8[3]
	Pre-Dose[1]	RSV + HZ/su vacc.					HZ/su vacc.				End of Study
Administration site and systemic solicited events (eDiary)											
Unsolicited AEs											
All SAEs											
All pIMDs											
Recording of pregnancies[4]											
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; 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.

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

[2] Day 8 Remote Contact for the sentinel group only for both groups.

[3]Six months after the last study vaccination.

[4]At Visits 1 and 3 (Co-ad group), pregnancy information must be recorded prior to study intervention administration. Pregnancies that occur post first study intervention will be followed as described in Section 10.4.3.

Table 14 Timeframes for Collection and Reporting of Safety Information for the Control Group

Event	Visit 1	Visit 1				Visit 2			Visit 3			Visit 4	Contact 1
	Day 1	Day 1	Day 7	Day 8[2]	Day 30	Day 31	Day 37	Day 60	Day 61	Day 67	Day 90	Day 91	Month 8[3]
	Pre-Dose[1]	HZ/su vacc.				RSV vacc.			HZ/su vacc.				End of Study
Administration site and systemic solicited													
Unsolicited AEs													
All SAEs													
All pIMDs													
Recording of pregnancies[4]													
SAEs related to study participation or													
AEs/SAEs leading to withdrawal from the													
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.

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

[2] Day 8 Remote Contact for the sentinel group only for both groups.

[3] Six months after the last study vaccination.

[4] At Visits 1, 2, and 3 (Control group), pregnancy information must be recorded prior to study intervention administration. Pregnancies that occur post first study intervention will be followed as described in Section 10.4.3.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 13 and Table 14. 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, Pregnancies, and Other Events

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

The method of recording, evaluating, assessing intensity and causality, and outcomes 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/pregnancy.

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

After the initial AE/SAE, pIMD, or pregnancy is reported, 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, pIMDs, Pregnancies, and Other Events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/pIMD/pregnancy, it must be reported to IQVIA using the required documentation and within the timeframes mentioned in Table 15. 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/pregnancies.

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 15 Timeframes for Submitting SAE and Other Event 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
Pregnancies	24 hours**, ‡‡	Electronic‡ Expedited Adverse Events Report	24 hours*	Electronic pregnancy report

Abbreviations: 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 IQVIA.

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.

8.3.7 Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until EoS.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the female participant pregnancy and should follow the procedures outlined in Section 10.3.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication (of the mother and/or neonate) or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death)] the investigator will report according to the SAE reporting procedures described in Section 10.3.

The participant will be followed to determine the outcome of the pregnancy (e.g., until delivery of baby or for longevity). The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor or designee. See Table 15 for reporting timeframes.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

Furthermore, the investigator must report any SAE occurring as a result of a post-study pregnancy that is considered by the investigator to be reasonably related to the study intervention, to IQVIA and GSK as described in the Section 10.3.5.

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

8.3.8 Adverse Events of Special Interest

Potential immune-mediated diseases are the only adverse events of special interest (AESI) collected during this study. See Section 10.3.3.

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 assessments are described in Section 8.1.

8.10 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 I error. Global Type I error is controlled at 2.5% (1-sided). The study includes three confirmatory primary objectives. The NI margins associated to each objective are provided in Table 16.

Table 16 Study Objectives and Null Hypothesis

Objectives	Null hypothesis	Success criteria
Primary*		
To demonstrate non-inferiority of the humoral immune response to two doses of HZ/su vaccine when the first dose of HZ/su vaccine is co-administered with RSVPreF3 OA investigational vaccine, compared to two doses of HZ/su vaccine administered alone.	True Group GMC ratio between the Control group (at Day 91) divided by Co-ad group (at Day 91) for anti-gE Ab 1-month after the second HZ/su vaccine dose is above 1.5.	The upper limit of the 2 sided 95% CI of the GMC ratio between the Control group (at Day 91) versus Co-ad group (at Day 91) for anti-gE Ab 1-month after the second HZ/su vaccine dose is ≤1.5.
To demonstrate the non-inferiority of RSVPreF3 OA investigational vaccine when co-administered with the first dose of HZ/su vaccine, compared to RSVPreF3 OA investigational vaccine administered alone.	• True Group GMT ratio between Control group (at Day 61) divided by Co-ad group (at Day 31) for RSV-A neutralizing titers 1-month after the RSVPreF3 OA investigational vaccine dose is above 1.5. • True Group GMT ratio between Control group (at Day 61) divided by Co-ad group (at Day 31) in RSV-B neutralizing titers 1-month after the RSVPreF3 OA investigational vaccine dose is above 1.5.	• The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for RSV-A neutralizing titer 1-month after the RSVPreF3 OA investigational vaccine dose is ≤1.5. • The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for RSV-B neutralizing titer 1-month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.

Abbreviations: Ab=antibodies; co-ad=co-administration group; CI=confidence interval; gE=glycoprotein E; GMC=geometric mean concentration; GMT=geometric mean titer; HZ/su=herpes zoster subunit; RSV-A=respiratory syncytial virus subtype A; RSV-B=respiratory syncytial virus subtype B; RSVPreF3 OA=respiratory syncytial virus prefusion protein 3 older adult investigational vaccine.

Co-ad group: RSVPreF3 OA investigational vaccine when co administered with the first HZ/su vaccine

Control group: Administration of HZ/su vaccine (first dose), followed by RSVPreF3 OA investigational vaccine, followed by HZ/su vaccine (second dose).

*Zoster and RSV-A related endpoints will be assessed as co-primary and following the current success RSV-B will be demonstrated as sequential.

9.2 Populations for Analysis

Populations for analyses in this study are defined in Table 17.

Table 17 Analysis Sets

Analysis Set	Description
Screened set	All participants who were screened for eligibility
Enrolled set[1]	All participants who entered the study who were randomized or received study intervention or underwent a post-screening study procedure.
Exposed set	All participants who received at least one study intervention. Analysis per group is based on the study intervention administered.
RSV PPS[2]	All eligible participants: • Who received RSV vaccine as per-protocol in the control group and received all the study interventions in the Co-ad group • Who had immunogenicity results pre and post-dose for RSV neutralizing titers • Who comply with the blood draw intervals for RSV samples • Without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination up to blood sample post RSV vaccination for control group and blood sample post HZ/su vaccine dose 2 vaccination for Co-ad group • Who do not meet any of the criteria for elimination up to blood sample post RSV vaccination for control group and blood sample post HZ/su vaccine dose 2 vaccination for Co-ad group
HZ/su PPS[2]	All eligible participants: • Who received two doses of HZ/su vaccine as per-protocol in the control group and all study interventions in the Co-ad group • Who had immunogenicity results pre and post-dose for anti-gE antibody concentrations • Who comply with the blood draw intervals for zoster samples • Without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination up to blood sample post HZ/su vaccine dose 2 vaccination • Who do not meet any of the criteria for elimination up to blood sample post HZ/su vaccine dose 2 vaccination

Abbreviations: C-ad=co-administration group; HZ/su=herpes zoster/subunit; PPS=per protocol set; RSV=respiratory syncytial virus.

[1] Screen failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed to reach the target enrollment) are excluded from the Enrolled Set as they did not enter the study

[2] Contribution of participants to PPS will be defined by timepoint

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 applicable 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). This section is a summary of the planned statistical analyses of the primary and secondary immunogenicity endpoints. Supportive analyses, safety and demography summaries will be described in the SAP.

9.3.1 Primary Endpoints/Estimands Analysis

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

- Method for non-inferiority of the HZ/su vaccine in terms of enzyme linked immunosorbent assay (ELISA) Ab GMC between group ratio for gE at 1-month after the second HZ/su vaccination (i.e., at Day 91 for both Co-ad and Control groups):
  The least square point estimate and its 2-sided 95% CI for Group GMC ratio between the Control group over Co-ad group will be derived from an ANCOVA model* on $\log_{10}$ transformed concentrations.
- Method for non-inferiority of RSV investigational vaccine in terms of RSV-A neutralizing GMT between group ratio at 1-month after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 for Co-ad group, and at Day 61 for Control group):
  The least square point estimate and its 2-sided 95% CI for Group GMT ratio between Control group over 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 GMT between group ratio at 1-month after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 for Co-ad group, and at Day 61 for Control group):

The least square point estimate and its 2-sided 95% CI for Group GMT ratio between Control group over Co-ad group will be derived from an ANCOVA model* on log_{10} transformed titer.

**The model will include the treatment group and the age category (age at vaccination: 50 to 59, 60 to 69, or ≥70) as fixed effects, and the pre-vaccination 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

The following testing sequence will be used:

First sequence:

- The upper limit of the 2 sided 95% CI of the GMC ratio between the Control group (at Day 91) versus Co-ad group (at Day 91) for anti-gE Ab 1-month after the second HZ/su vaccine dose is ≤1.5.

AND

- The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for RSV-A neutralizing titer 1-month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.

Second sequence:

- The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for RSV-B neutralizing titer 1-month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.

Testing will progress in the second sequence only if the first sequence is a success, so that no further adjustment of alpha is required.

9.3.2 Secondary Endpoints/Estimands Analysis

Method for evaluation of anti-gE humoral response to HZ/su vaccine when co-administered with RSVPreF3 OA investigational vaccine or administered separately:

- Anti-gE antibody concentrations expressed as seropositivity rate with exact 95% CI at pre-vaccination and at 1-month post-second dose of HZ/su vaccine
- Anti-gE antibody concentrations expressed as Geometric Mean Concentration (GMC) with 95% CI at pre-vaccination and at 1-month post-second dose of HZ/su vaccine
- Anti-gE antibody concentrations expressed as Mean Geometric Increase (MGI) with 95% CI at pre-vaccination and at 1-month post-second dose of HZ/su vaccine. Definition for MGI is included in Table 18.
- Vaccine response rate (VRR) with exact 95% CIs at 1-month post-second dose of HZ/su vaccine. Definition for VRR is included in Table 18.

Method for evaluation of humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with the first dose of HZ/su vaccine or administered separately:

- RSV-A neutralizing titers expressed as GMT at pre-vaccination and at 1-month after the RSVPreF3 OA investigational vaccine dose

- MGI for within participants ratios of the post-dose titer (at 1-month after the RSVPreF3 OA investigational vaccine dose) over the pre-dose titer (at baseline) for RSV-A neutralizing titers
- RSV-B neutralizing titers expressed as GMT at pre-vaccination and at 1-month after the RSVPreF3 OA investigational vaccine dose
- MGI for within participants ratios of the post-dose titer (at 1-month after the RSVPreF3 OA investigational vaccine dose) over the pre-dose titer (at baseline) for RSV-B neutralizing titers

The other secondary endpoints are described in Section 3.0. Descriptive analyses of demography, immunogenicity, and safety will be detailed in the SAP.

Table 18 Definitions of Mean Geometric Increase, Vaccine Response Rate, Seropositivity

Abbreviation/Term	Definition
MGI	The geometric mean of the within participant ratios of the post-vaccination titer over the pre-vaccination titer.
VRR	For anti-gE post-second dose, is defined as the percentage of participants who have at least: A 4-fold increase post-vaccination anti-gE antibody concentration as compared to (over) the pre-vaccination anti-gE antibody concentration, for participants who are seropositive at pre-vaccination, or, A 4-fold increase post-vaccination anti-gE antibody concentration as compared to (over) the anti-gE antibody cut-off value for seropositivity (97 mIU/mL), for participants who are seronegative at pre-vaccination.
Seropositivity	Seropositivity is defined as the percentage of participants whose antibody concentration is greater than or equal to the assay cut-off value (97 mIU/mL).

Abbreviations: gE=glycoprotein E; MGI=mean geometric increase; mIU/mL=milli international units per milliliter; VRR=vaccine response rate.

9.4 Interim Analysis

9.4.1 Sequence of Analyses

The analyses will be performed in a stepwise manner.

- 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 and including Visit 4 (Day 91) are available for all participants. This analysis will be considered as final for those endpoints.
- An EoS analysis will be performed when all data up to the contact at 6 months post-last vaccination will be available for all participants.
- Any data that may become available at a later stage will be presented in additional analyses.

9.5 Sample Size Determination

The primary objective analysis will be performed on the PPS.

The target enrollment will be approximately 530 participants (approximately 265 in the Co-ad group and approximately 265 in the Control group) to obtain approximately 450 evaluable participants (approximately 225 in the Co-ad group and approximately 225 in Control group) for the evaluation of the primary objectives, assuming that approximately 15% of the enrolled participants will not be evaluable (participants withdrawn or excluded from the PPS). See Table 19.

Each objective will be evaluated with a nominal type I error of 2.5.

Table 19 Overall Power to Demonstrate Primary Non-Inferiority Objectives: Assuming 225 Evaluable Subjects in Each Group

Endpoint	Standard deviation of log_{10} concentration	Reference ratio	Non inferiority margin	Type II error	Power
HZ/su vaccine Non-inferiority* (1-sided test with alpha=2.5%)					
GMCs Anti-gE ELISA Ab	0.35	1.05	1.5	0.3%	99.7%
RSVPreF3 OA investigational vaccine Non-inferiority* (1-sided test with alpha = 2.5%)					
GMTs RSV-A neutralizing titer	0.45	1.05	1.5	4.6%	95.4%
GMTs RSV-B neutralizing titer	0.45	1.05	1.5	4.6%	95.4%
Global Power and Global Type II error				9.5%	90.5%

Abbreviations: Ab=antibody; ELISA=enzyme linked immunosorbent assay; gE=varicella zoster virus - glycoprotein E; GMC=geometric mean concentration; GMT=geometric mean titer; HZ/su=herpes zoster/subunit; RSV-A=respiratory syncytial virus subtype A; RSV-B=respiratory syncytial virus subtype B.

*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 RSVPreF3 OA investigational vaccine: non-inferiority limit = 1.5 (log10[1.5] = 0.176)

For HZ/su vaccine: non-inferiority limit = 1.5 (log10[1.5] = 0.176)

Reference Ratio= 1.05 (log10[1.05] = 0.021)

Considering a slight interference of 1.05 for the reference ratio in favor of the control group versus Co-ad group with a common population standard deviation of 0.45 for the log_{10} transformed RSV-A/RSV-B neutralizing titer and 0.35 for the log_{10} transformed HZ/su anti-gE Ab GMC, the study has at least 90.5% 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 will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs, 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), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

After reading the protocol, each investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. 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 the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor 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 Safety Review Team 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 predefined in the state location(s) to identify systematic issues that can impact participant safety and/or the reliability of study results. These predefined 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 onsite 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. 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

The neutralization assay is a functional assay that measures the ability of serum 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 layer. 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 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.[15,16] For the testing of Phase III studies, secondary standards calibrated against the international reference will be included in every run to allow conversion into international units.[17,18]

Anti-gE ELISA is a two-step ELISA based on the antibody and antigen interaction, which allows the detection and the quantification of specific IgG antibodies directed against gE in tested serum samples. Briefly, diluted serum samples are added onto a 96 polystyrene-well microplate pre-coated with gE. After a washing step, goat antibodies directed against human IgG antibodies and conjugated to HRP (a-IgG-HRP) are added and will bind to anti-gE IgG if present. After a washing step, the addition of a chromogen-substrate solution specific for HRP will provide means of detecting the anti-gE specific for the pre-coated antigen. The HRP catalyzes an enzymatic reaction which is stopped by the addition of sulfuric acid, resulting in a color change from blue to yellow. The optical density recorded is proportional to the concentration of the anti-gE antibodies present in the serum sample. Antibody concentration is expressed in mIU/mL.

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 • 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. • 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 and Solicited AE
• 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. • 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 20 and Table 21 for list of solicited site events and solicited systemic events.
  - Solicited administration site events:

Table 20 Solicited Administration Site Events

Pain
Erythema/redness
Swelling

  - Solicited systemic events:

Table 21 Solicited Systemic Events

Arthralgia
Fatigue
Fever
Headache
Myalgia
Shivering/Chills
Gastrointestinal symptoms: Nausea Vomiting Diarrhea Abdominal pain

Note: participants will be instructed to measure and record their body temperature every day any time after 12 PM. 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 20 and Table 21. 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 • For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate CRF.
b. Is life-threatening • The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • 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. • 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 • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, 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 • Is a congenital anomaly/birth defect in the offspring of a study participant.
f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).
g. Is a suspected transmission of any infectious agent via an authorized medicinal product
h. Other situations (Medically Important Events):

• 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. o 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 22. Please refer to Section 10.3.6 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 22 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: • Autoimmune / Immune-mediated myocarditis • Autoimmune / Immune-mediated pericarditis • Giant cell myocarditis
Idiopathic pulmonary fibrosis	Including but not limited to: • Idiopathic interstitial pneumonia (frequently used related terms include "Interstitial lung disease", "Pulmonary fibrosis", "Immune-mediated pneumonitis") • 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: • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) • Atrophic thyroiditis • Silent thyroiditis • 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	
Grave's or Basedow's disease	• Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy

Medical Concept	Additional Notes
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis • Vogt-Koyanagi-Harada disease
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	Including but not limited to: • Crohn’s disease • Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	

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

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

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

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

Medical Concept	Additional Notes
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: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Takayasu's arteritis

Medical Concept	Additional Notes
Medium sized and/or small vessels vasculitis	Including but not limited to: • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Behcet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis) • Erythema induratum (also known as nodular vasculitis) • Henoch-Schonlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis • Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Wegener's granulomatosis
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	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: • Kawasaki's disease • Multisystem inflammatory syndrome in adults (MIS-A) • 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 AE, SAE, pIMD, Pregnancy, and Device Deficiencies

AE, SAE, pIMD, Pregnancy Recording
• When an AE/SAE/pIMD/pregnancy/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/pIMD/pregnancy/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/pIMD. • An 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. • Designated site staff will review eDiary at Visit 2, Visit 3 (if applicable), and Visit 4, to assess participant/caregiver compliance and monitor reported events. • Investigator will collect and verify completed eDiary during discussions with the participant/participant's caregiver(s) on Visit 4.

- 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, pIMDs, Pregnancies

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.
- SAEs related to study participation or concurrent GSK medication/vaccine will be collected from the time a participant consents to participate in the study until the participant is discharged from the study.
- All other 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).
- Pregnancies will be collected from the first administration of study intervention until end of study as described in Section 10.4.3.

10.3.5.2 Assessment of Intensity and Causality

Assessment of Intensity

Table 23 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
Shivering/Chills	0	None
	1	Mild: Shivering that is easily tolerated
	2	Moderate: Shivering that interferes with normal

		activity
	3	Severe: Shivering that prevents normal activity
Gastrointestinal symptoms	0	None
	1	Mild: Gastrointestinal symptom that is easily tolerated
	2	Moderate: Gastrointestinal symptom that interferes with normal activity
	3	Severe: Gastrointestinal symptom 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 injection administration site erythema/swelling and fever will be scored by investigator as follows:

	Erythema/swelling	**Fever**
0:	≤20 mm	<38.0 °C <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 predefined 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 should specify, if AE/SAE could be causally related to a specific intervention. When a causal relationship to a specific study intervention cannot be determined, the investigator should indicate the AE/SAE to be related to all interventions.
- 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.
- 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 eCRF/Expedited Adverse Events Report, and/or, if applicable in the eDiary.

Assessment of Outcomes

The investigator will assess the outcome of all serious and nonserious 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 Pregnancy

- 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, or pIMD as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- AEs (serious or nonserious) 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.
- All SAEs and pIMDs will be followed until the event is resolved, stabilized, otherwise explained, 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 data to IQVIA within 24 hours of the investigator's awareness of the information.

Follow-up of Pregnancies

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

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

Furthermore, the investigator must report any SAE occurring as a result of a post-study pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.6.

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, pIMD, and Pregnancy Information After Removal of Write Access to the Participant's eCRFs

When additional SAE, pIMD, or pregnancy 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, Pregnancy, and Medical Device SAEs

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

- The primary mechanism for reporting an SAE or pIMD or pregnancy to IQVIA 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/pIMD/pregnancy 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/pIMD/pregnancy from a study participant or receives updated data on a previously reported SAE/pIMD/pregnancy 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 IQVIA.
- If the site during the course of the study or post-study becomes aware of any serious, nonserious AEs, or pregnancy exposure related to any GSK non-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/pIMD/pregnancy reporting can be found in SRM or other study materials.

Events Requiring Expedited Reporting to IQVIA
• Once an investigator becomes aware that an SAE/pIMD/pregnancy 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/pIMD/pregnancy. It must be completed as thoroughly as possible, with all available details of the event. • The SAE/pIMD/pregnancy report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE/pIMD/pregnancy. The investigator will always provide an assessment of causality at the time of the initial report. • Refer to the Table 15 for the details on timeframes for reporting of SAEs/pIMDs/pregnancy. • 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/pIMD. • Refer to Section below for information on back-up systems in case the electronic reporting system does not work.

SAE Reporting to the Sponsor or Designee 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. • In rare circumstances and in the absence of Fax equipment, notification by phone is acceptable with a copy of the Expedited AE Report sent by overnight mail or courier service. • Initial notification via phone does not replace the need for the investigator to complete and sign the Expedited AE Report within the designated reporting timeframes. • Contacts of the Medical Monitor for SAE reporting can be found in the SRM.

10.4 Appendix 4: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

This section defines what is considered to be a woman of childbearing potential as well as guidance on what is considered to be adequate contraception.

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    a) Documented hysterectomy.
    b) Documented bilateral salpingectomy.
    c) Documented bilateral oophorectomy.

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

3. Postmenopausal female:
    a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Table 24 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral (only if allowed by local regulations or if part of standard medical practice in the country). • Injectable.
Highly Effective Methods That Are User Independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device. • Intrauterine hormone-releasing system. • Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Male partner sterilization *Male partner sterilization prior to the female participant's entry into the study, and this male is the sole partner for that participant,* *(The information on the male sterility can come from the site personnel's review of the participant's medical records; medical examination and/or semen analysis, or medical history interview provided by her or her partner).*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: [a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

See Section 8.2.1.1 for pregnancy testing information.

10.4.3 Collection of Pregnancy Information

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor or designee within 24 hours of learning of a

participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the investigator will report according to the SAE reporting procedures described in Appendix 3.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor or designee as described in Section 10.3. While the investigator is not obligated to actively seek this information in former participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant after the first study intervention was administered must not receive any subsequent intervention (vaccinations) of any study intervention but may continue other study procedures at the discretion of the investigator.

11.0 APPENDIX 5: ABBREVIATIONS AND GLOSSARY OF TERMS

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
eG	Glycoprotein E
EoS	End of Study
EU	European Union
EUA	Emergency use authorization
F	Fahrenheit
FSFV	First subject first visit
GCP	Good Clinical Practice
GMT	Geometric mean titer
GSK	GlaxoSmithKline
HCP	Health care professional
HZ/su	Herpes zoster/subunit
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
pIMD	Potential Immune-Medicated Disease
PPS	Per Protocol Set
RSV	Respiratory syncytial virus
SAE	Serious adverse event
SADE	Serious adverse device effect
SAP	Statistical Analysis Plan
SoA	Schedule of activities
SRM	Study Reference Manual
SRT	Safety Review Team
ST	Serotype
SUSAR	Suspected Unexpected Serious Adverse Reactions
UL	Upper limit
YOA	Years of age

Table 25 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. 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 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). 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.
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. 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. 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. 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 the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control).

	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.
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 (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, 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.
Telemedicine	The use of electronic information and telecommunications technologies (both video-based and audio-only) to facilitate 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.

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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 Herpes Zoster recombinant subunit (HZ/su) vaccine in adults aged 50 years and older.

PROTOCOL NO: 219331 (RSV OA=ADJ-020)

VERSION: Original Protocol

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

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: _____

_____

_____