Protocol Amendment 1

Study ID: 219238

Official Title of Study: A Phase 3, observer-blind, randomized, placebo-controlled study to evaluate the non-inferiority of the immune response and safety of the RSVPreF3 OA investigational vaccine in adults 50-59 years of age, including adults at increased risk of respiratory syncytial virus lower respiratory tract disease, compared to older adults ≥60 years of age.

NCT number: NCT05590403

Date of Document: 30-May-2023

Clinical Study Protocol

Sponsor:

GlaxoSmithKline Biologicals SA (GSK)

Rue de l'Institut, 89
1330 Rixensart, Belgium

Primary study intervention(s)	GSK's investigational respiratory syncytial virus (RSV) vaccine BIO RSV OA=ADJ (GSK3844766A)
Other study intervention(s)	Placebo: Saline solution
eTrack study number and abbreviated title	219238 (RSV OA=ADJ-018)
EudraCT number	2022-001981-36
Date of protocol	Final: 26 July 2022
Date of protocol amendment	***Amendment 1 Final: 25 May 2023***
Title	A Phase 3, observer-blind, randomized, placebo-controlled study to evaluate the non-inferiority of the immune response and safety of the RSVPreF3 OA investigational vaccine in adults 50-59 years of age, including adults at increased risk of respiratory syncytial virus lower respiratory tract disease, compared to older adults ≥60 years of age.
Brief title	A study on the immune response and safety of a vaccine against respiratory syncytial virus given to adults 50-59 years of age, including adults at increased risk of respiratory syncytial virus lower respiratory tract disease, compared to older adults 60 years of age and above.
Sponsor signatory	***Veronica Hulstrøm, MD*** ***Clinical Project Lead*** ***RSV Older Adults***

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.3

Protocol Amendment 1 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 GSK.
- 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 comply with local bio-safety legislation.
- To ensure that all persons 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 serum samples) are retained onsite or elsewhere without the approval of GSK and the express written informed consent of the participant and/or the participant's legally acceptable representative (LAR).
- 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 their 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.

eTrack study number and abbreviated title	219238 (RSV OA=ADJ-018)
EudraCT number	2022-001981-36
Date of protocol	Final: 26 July 2022
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Investigator name

_____

Signature

_____

Date

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PPD

name, function and title

_____

Signature

_____

Date of signature

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GSK Japan study representative/Joint Vaccine Co representative name, function and title

_____

Signature

_____

Date of signature

_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)

2. Sponsor medical expert for the study

Refer to the local study contact information document.

3. Sponsor study monitor

Refer to the local study contact information document.

4. Sponsor study contact for reporting of Serious Adverse Events (SAEs)

GSK central back-up study contact for reporting SAEs: refer to Section 8.3.3.1.

Study contact for reporting SAEs: refer to the local study contact information document.

5. GSK Helpdesk for emergency unblinding

Refer to Section 6.3.5.1.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 1 (25 May 2023)

This amendment is considered substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because of significant changes in the conduct or management of the study.

Overall rationale for Amendment 1:

The purpose of this amendment is to:

Record events of atrial fibrillation (AF) as Adverse Events of Special Interest (AESIs) CCI [redacted]

CCI [redacted]

Other updates are described in the table below:

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
2.3.1. Risk assessment	The description has been updated as per the current GSK guidelines for the protocols.	In parallel with the RSVpreF3 OA clinical development program, another RSV vaccine development program was initiated by GSK, with the objective to prevent RSV-associated lower respiratory tract illness in neonates and infants during their first 6 months of life, through immunization of pregnant women with a single dose of investigational RSV maternal vaccine candidate. This section was updated to include most up to date information regarding this topic, as per GSK's current format.
3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS 4.3. Justification for dose 8.1.2. Laboratory assays 8.1.3. Immunological read-outs 9.3.1. Primary endpoints/estimands analysis 9.5. Sample size determination 10.2. Appendix 2: Clinical laboratory tests	The terminology of "neutralizing antibody/ies" titer has been changed to "neutralization" titer.	For alignment with the CSR and other current protocols.
1.3. Schedule of activities (SoA) 6.8. Concomitant therapy 8.3.1. Time period and frequency for collecting AE, SAE and other safety information 8.3.2. Method of detecting AEs and SAEs, pregnancies, and other events 8.3.3. Regulatory reporting requirements for SAEs, pregnancies, and other events 8.3.3.1.Contact information for reporting SAEs, AESIs (including pIMDs and AF) and pregnancies 8.3.4. Treatment of AEs 10.3.5. Adverse events of special interest (AESIs) 10.3.5.2. Atrial fibrillation (AF) 10.3.8. Recording and follow-up of AEs, SAEs, AESIs (including pIMDs and AF) and pregnancies	pIMDs and AF adverse events meeting the AEs or serious adverse events (SAEs) definitions will be considered as adverse events of special interest (AESI) in this study and additional information on these events is to be reported in the AF follow-up questionnaire in electronic case report form (eCRF).	AESIs were defined to include pIMDs and AF. CCI [redacted]

Section # and title	Description of change	Brief rationale
10.3.8.1. Time period for collecting and recording AEs, SAEs, AESIs (including pIMDs and AF) and pregnancies 10.3.8.2. Follow-up of AEs, SAEs, AESIs (including pIMDs and AF), pregnancies or any other events of interest 10.3.8.2.1. Follow-up during the study 10.3.8.2.2. Follow-up after the participant is discharged from the study 10.3.8.3. Updating of SAE, AESIs (including pIMD and AF), and pregnancy information after removal of write access to the participant's eCRF 10.3.10. Reporting of SAEs, AESIs (including pIMDs and AF), pregnancies and other events 10.7.1. List of abbreviations 10.7.2. Glossary of terms		
4.3. Justification for dose	The terminology for respiratory syncytial virus, RSVPreF3-binding IgG has been clarified.	This nomenclature more precisely reflects what is indeed measured by the neutralization assay and the enzyme-linked immunosorbent assay (ELISA) respectively.
6.3.5.1. Emergency unblinding	The section has been updated to reflect that GSK's Global Safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.	For alignment with current protocol template.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

GSK is developing an RSVPreF3 OA investigational vaccine against RSV-associated (subtypes A and B) disease in adults ≥60 YOA. The aim of this study is to demonstrate the non-inferiority (NI) of the immune response and evaluate safety of RSVPreF3 OA investigational vaccine in adults 50-59 YOA, including those who are at increased risk of RSV-lower respiratory tract disease (LRTD), versus adults ≥60 YOA, where vaccine efficacy against RSV-LRTD is being assessed in another clinical study.

Objectives, endpoints and estimands: Refer to Section 3.

1.2. Schema

Refer to Figure 1 for a schematic presentation of the study design.

1.3. Schedule of activities (SoA)

Table 1 Schedule of activities (Amended: 25 May 2023)

Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Notes
Timepoint	**Day 1**	**Day 31**	**Month 6**	**Month 12**	
Informed consent	●				Freely given and written informed consent must be obtained from each study participant prior to participation in the study. The participant's informed consent may be obtained prior to Visit 1. See Section 10.1.3
Distribution of participant card	○				See Section 8.3.5
Check inclusion/exclusion criteria	●				See Section 5.1 and Section 5.2
Check with participants if he/she will appoint a caregiver, and distribute information letter to caregiver, when applicable	○	○	○		See Section 4.1.3 and Section 10.1.3
Screening conclusion	●				See Section 5.4
Baseline and demography assessments					
Collect demographic data	●				See Section 8.2.1.1
Measure/record height and weight	●				See Section 8.2.1.2
Record medical history	●				See Section 8.2.1.3
Record history of vaccine administration	●				Any vaccination administered up to 1 year before administration of the study intervention should be recorded in the eCRF. Administration of *Shingrix* and COVID-19 vaccines at any timepoint (even if longer than 1 year before the study intervention administration) should be recorded in the eCRF. See Section 8.2.1.4
Physical examination/vital signs	●	○ [a]	○ [a]	○ [a]	See Section 8.2.1.5
Record smoking status and smoking exposure history (including electronic smoking devices)	●				See Section 8.2.1.6. Refer to Glossary of terms for definitions of current and former smoker.
Clinical specimens for laboratory assays					
Blood sampling for antibody determination in all participants (~10 mL)	● [b]	●	●	●	See Section 8.1.1
Blood sampling for CMI response in a subset (~25 mL)	● [b]	●	●	●	See Section 8.1.1

Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Notes
Timepoint	**Day 1**	**Day 31**	**Month 6**	**Month 12**	
Study intervention					
Check criteria for temporary delay for enrollment and study intervention administration	○				See Section 5.5
Urine pregnancy test (only for women of childbearing potential in Cohort 1)	●[b]				See Section 8.2.1.7
Study group and intervention number allocation	○				See Section 6.3.2 and Section 6.3.3
Record body temperature before study intervention administration	●				The route for measuring temperature can be oral or axillary (see Section 8.2.1.8). Fever is defined as temperature ≥38.0°C/100.4°F regardless of the location of measurement.
Study intervention administration (including 30-minutes post-study intervention administration observation)	●				See Section 6.1
Record administered study intervention number	●				
Safety assessments					
Distribute diary cards	○				A paper diary will be distributed to all study participants at Visit 1 (day of study intervention administration). All participants will record solicited events after study intervention administration and for 3 subsequent days (Days 1-4), unsolicited AEs, and concomitant medications/products after study intervention administration and for 29 subsequent days (Days 1-30). See Section 10.3.8
Return of diary cards		○			See Section 10.3.8
Record solicited administration site and systemic events (Days 1–4 post-study intervention administration)	●	●			See Section 10.3.8 and Table 11
Record unsolicited AEs (Days 1-30 post-study intervention administration) ***in the participants***[c]	●	●			See Section 10.3.8 and Table 11
Record concomitant medications/vaccinations	●	●	●	●	See Section 6.8
Record any intercurrent medical conditions	●	●	●	●	See Section 9.2.1 and Table 11
Record all SAEs and pIMDs[c]	●	●	●		See Section 10.3.8 and Table 11
Record AEs/SAEs leading to withdrawal from the study and pregnancies	●	●	●	●	See Section 10.3.8 and Table 11

Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Notes
Timepoint	**Day 1**	**Day 31**	**Month 6**	**Month 12**	
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to administration of the study intervention) up to study end. See Section 10.3.8 and Table 11
Record SAEs and pIMDs related to study intervention administration and fatal SAEs[c]	●	●	●	●	SAEs and pIMDs related to study intervention administration and fatal SAEs should be collected after study intervention administration (Day 1) up to study end. See Section 10.3.8 and Table 11
Study Conclusion				●	See Section 4.4

Note: The double-line borders indicate the analyses which will be performed on all data (i.e., data that are as clean as possible) obtained up to this timepoints.
AE=Adverse event; ***AESI= Adverse event of specific interest;*** CMI=Cell-mediated immunity; COVID-19=Coronavirus disease 2019; eCRF=Electronic case report form; pIMD=Potential immune-mediated disease; SAE=Serious adverse event.
● 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
a. If deemed necessary by the investigator.
b. The blood sample and urine sample for pregnancy test should be taken on the same day, prior to study intervention administration. If the study intervention administration is delayed by any reason, in the event samples have been taken, the samples will need to be collected again on the day of study intervention administration and the first blood sample will be destroyed.
c. Atrial fibrillation (AF) will be considered as AESI in this study and will be additionally reported in the AF follow-up questionnaire (electronic or paper) in eCRF. The collection of AF will be performed following the AE/SAE reporting periods. For AF that were reported before the implementation of this Protocol Amendment 1, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.
Note: Visit 2, Visit 3 and Visit 4 should be done on site. Under special circumstances (e.g., pandemic), study visits can be done at home, or biological samples can be taken at a different location (see Section 8).

Table 2 Intervals between study visits

Interval	Planned visit interval	Allowed interval range
Visit 1→Visit 2	30 days	30-42 days
Visit 1→Visit 3	180 days	180-210 days
Visit 1→Visit 4	365 days	350-380 days

2. INTRODUCTION

2.1. Study rationale

GSK is developing an RSVPreF3 OA investigational vaccine against RSV-associated (subtypes A and B) disease in adults ≥60 YOA because of increased risk of RSV-LRTD. However, some younger patient groups also have an increased risk of RSV-LRTD. The aim of this observer-blind study is to demonstrate the NI of the immune response and to evaluate safety of the RSVPreF3 OA investigational vaccine in adults 50-59 YOA, including those who are at increased risk of RSV-LRTD, versus adults ≥60 YOA, where vaccine efficacy against RSV-LRTD is being assessed in another clinical study.

2.2. Background

RSV is an RNA virus of which 2 antigenically distinct subtypes exist, referred to as RSV-A and RSV-B [Borchers, 2013]. RSV is a highly contagious human pathogen that causes respiratory tract infections in people of all ages. In temperate climates throughout the world, RSV predictably causes fall-winter epidemics. In (sub) tropical regions, viral activity is more endemic, and outbreaks are less temporally focused.

RSV is one of the important viral pathogens identified in adults with acute respiratory infections and is increasingly recognized as a cause of serious illness in high-risk adults, including those with chronic lung and heart disease. In a prospective cohort study over 4 RSV seasons in healthy elderly patients (≥65 YOA) and high-risk adults (≥21 YOA) with chronic heart or lung disease, RSV infection developed annually in 3% to 7% of healthy elderly patients and in 4% to 10% of high-risk adults [Falsey, 2005; Shi, 2021]. Healthy elderly patients with RSV infection required fewer visits to the doctor's office compared to those with influenza. Utilization of health care services among high-risk adults with either RSV infection or influenza was similar. RSV infection in the elderly and high-risk adults has a disease burden similar to that of a non-pandemic influenza A in a population with a high rate of influenza vaccination [Falsey, 2005].

In different populations of patients with chronic morbidities both the prevalence and incidence of RSV infections is increased, leading to an increase in need for medical care and hospitalization in high income countries. A major US study reported incidence of RSV-related hospitalizations among different types of high-risk patients of different age groups, in 2 different settings (New York City and Rochester). Adults with COPD had 3.2–13.4 times higher hospitalization rates than those without COPD. Adults with asthma had 2.0-3.6 times higher estimated hospitalization rates than those without asthma. Adults with diabetes had 2.4–11.4 times higher hospitalization rates than those without diabetes. Adults with CAD had estimated RSV hospitalization rates 3.7–7.0 times higher than those without CAD. Estimated IRRs for CHF were the largest; adults with CHF had 4.0-33.2 times higher hospitalization rates than those without CHF. Estimated IRRs for CHF were highest in the youngest age group and declined with increasing age. [Branche, 2022]. Different European, Asian and US studies have reported an exacerbation of either COPD, asthma, interstitial pulmonary fibrosis or cystic fibrosis ranging from 2.2% to 17% [Htar, 2020; Branche, 2022; Shi, 2021]. Patients with chronic renal disease as well as those with chronic liver disease have impaired immune functions

due to their disease pathogenesis, which is associated, in general, with increased susceptibility to infections [Betjes, 2013; Irvine, 2019].

Please refer to the current IB for information regarding pre-clinical studies, and clinical studies of RSVPreF3 OA investigational vaccine.

2.3. Benefit/Risk assessment

2.3.1. Risk assessment (Amended: 25 May 2023)

Detailed information about the known and expected benefits and potential risks (syncope, hypersensitivity, pIMD) and reasonably expected AEs of RSVPreF3 OA investigational vaccine can be found in the IB and Development Safety Update Report.

Potential/Identified Risk	Mitigation Strategy
RSVPreF3 OA investigational vaccine	
pIMDs are considered a potential risk, as for all vaccines containing an adjuvant system. Refer to Section 10.3.5.1 for details.	
Hypersensitivity reactions (including anaphylaxis).	All participants will remain under observation at the clinical center for at least 30 minutes after study intervention administration. Participants with a history of hypersensitivity or severe allergic reaction to any component of the vaccine as well as a known latex hypersensitivity are excluded from study enrollment.
Study procedures	
Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, erythema/redness, and swelling.	Physician can implement the measures that they consider necessary.
Pain, redness, irritation, and bruising may occur at the site where blood is drawn.	Physician can implement the measures that they consider necessary.
Syncope (fainting) can occur following or even before any blood draw or study intervention administration as a psychogenic response to the needle insertion.	Participants who mention experiencing previous episodes of fainting or dizziness before, during or after a blood draw or previous vaccination, will be asked to lie down during the intervention and remain under observation at the clinical center until deemed necessary by site personnel. Appropriate medical treatment must be readily available during this period.

For details of study procedures, dose, and study design justification, refer to Section 1.3 and Section 4.2.

In parallel with the RSVPreF3 OA clinical development program, another RSV vaccine development program was initiated by GSK, with the objective to prevent RSV-associated lower respiratory tract illness in neonates and infants during their first 6 months of life, through immunization of pregnant women with a single dose of the investigational RSV maternal vaccine candidate. The maternal vaccine contains 120 µg of the RSVPreF3 antigen, as does the RSVPreF3 OA vaccine, however it does not include any adjuvant.

In 2020, GSK initiated a Phase 3, double-blind, 2:1-randomized, placebo-controlled study (RSV MAT-009; NCT04605159) in 24 countries to assess the safety and efficacy of the maternal vaccine candidate (RSVPreF3 Mat) administered to 18–49-year-old women in the late second or third trimester of pregnancy.

CCI

The vaccine candidate for older adults (OA) contains the same RSV antigen as the RSV maternal vaccine candidate but the RSV OA vaccine is combined with GSK's established AS01E adjuvant to boost the immune response in the OA population.

The RSV OA vaccine trials in participants >60 YoA are closely monitored for safety with all available safety data reviewed internally. In addition, the Phase 3 RSV OA=ADJ-006 clinical study is monitored by an IDMC on an ongoing basis. The IDMC has not raised any concern for safety in the OA 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 YOA and above. This age cut-off has been chosen since on the one hand there is a high unmet medical need in patients with chronic comorbidities and that as of 50 YOA there is a strong increase in the percentage of people with chronic comorbidities while on the other hand for women the incidence of spontaneous pregnancies is only about 4 in 100 000 women in this age group [Salihu, 2003]. 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 not benefit directly from participating in this study. For those receiving the RSVPreF3 OA investigational vaccine, in a pre-specified efficacy interim analysis of an ongoing Phase 3 trial in adults aged 60 years and above, the primary endpoint was exceeded with no unexpected safety concerns observed (refer to IB).

An indirect benefit is that the information obtained in this study will aid the development of an RSV OA vaccine, which is intended to prevent disease associated with RSV infection in older adults and adults at increased risk of RSV-LRTD.

Another benefit for all study participants may include gaining information about their general health status through the medical evaluations/assessments associated with this study (i.e., physical examination).

2.3.3. Overall Benefit/Risk conclusion

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

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 3 Study objectives, endpoints and estimands (Amended: 25 May 2023)

Objectives	Endpoints and estimands
Primary*	
• To demonstrate the NI** of the humoral immune response in healthy participants 50-59 YOA compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• RSV-A neutralization titers expressed as group GMT ratio (OA-RSV/Adults-HA-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration***. • RSV-A neutralization titers expressed as group SRR difference (OA-RSV - Adults-HA-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration compared to baseline***.
• To demonstrate the NI** of the humoral immune response in healthy participants 50-59 YOA compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• RSV-B neutralization titers expressed as group GMT ratio (OA-RSV/Adults-HA-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration***. • RSV-B neutralization titers expressed as group SRR difference (OA-RSV - Adults-HA-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration compared to baseline***.
• To demonstrate the NI** of the humoral immune response in participants 50-59 YOA at increased risk of RSV-LRTD compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• RSV-A neutralization titers expressed as group GMT ratio (OA-RSV/Adults-AIR-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration***. • RSV-A neutralization titers expressed as group SRR difference (OA-RSV - Adults-AIR-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration compared to baseline***.

Objectives	Endpoints and estimands
• To demonstrate the NI** of the humoral immune response in participants 50-59 YOA at increased risk of RSV-LRTD compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• RSV-B neutralization titers expressed as group GMT ratio (OA-RSV/Adults-AIR-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration***. • RSV-B neutralization-titers expressed as group SRR difference (OA-RSV - Adults-AIR-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration compared to baseline***.
Secondary - Safety	
• To evaluate the safety and reactogenicity after the RSVPreF3 OA investigational vaccine administration.	• Percentage of participants reporting each solicited administration site event with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days). • Percentage of participants reporting each solicited systemic event with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days). • Percentage of participants reporting unsolicited AEs within 30 days after study intervention administration (i.e., the day of study intervention administration and 29 subsequent days). • Percentage of participants reporting any SAEs and pIMDs after study intervention administration (Day 1) up to Month 6. • Percentage of participants reporting SAEs and pIMDs related to study intervention administration after study intervention administration (Day 1) up to study end (Month 12). • Percentage of participants reporting any fatal SAEs after study intervention administration (Day 1) up to study end (Month 12).
Secondary - Immunogenicity	
• To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine until 12 months post-study intervention administration.	• RSV-A and RSV-B neutralization-titers expressed as GMT, at pre-study intervention administration, 1 month, 6 months and at 12 months after study intervention administration.
• To evaluate the CMI response after RSVPreF3 OA investigational vaccine administration until 12 months post-study intervention administration.	• CMI response expressed as group geometric mean of the frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least 1 cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, at pre-study intervention administration, 1 month, 6 months and at 12 months after study intervention administration, in a subset of participants.

Objectives	Endpoints and estimands
Tertiary *(Note that tertiary objectives, endpoints, and estimands are optional and might be assessed only if needed; therefore, not all testing might be performed and reported)*	
CCI [redacted]	

AE=Adverse event; AIR=At increased risk; CD=Cluster of differentiation; CD40L=CD40 ligand; CMI=Cell-mediated immunity; GMT=Geometric mean titer; HA=Healthy adults; IFN=Interferon; IL=Interleukin; LRTD=Lower respiratory tract disease; NI=Non-inferiority; OA=Older adults; pIMD=Potential immune-mediated disease; RSV=Respiratory syncytial virus; SAE=Serious adverse event; SRR=Seroresponse rate; TNF=Tumor necrosis factor; YOA=Years of Age.
* Refer to Section 9.3.1 for the testing sequence of primary objectives.
** NI criteria are defined in Section 9.1.
*** Co-primary endpoints. Refer to Section 9.1 for statistical hypotheses.

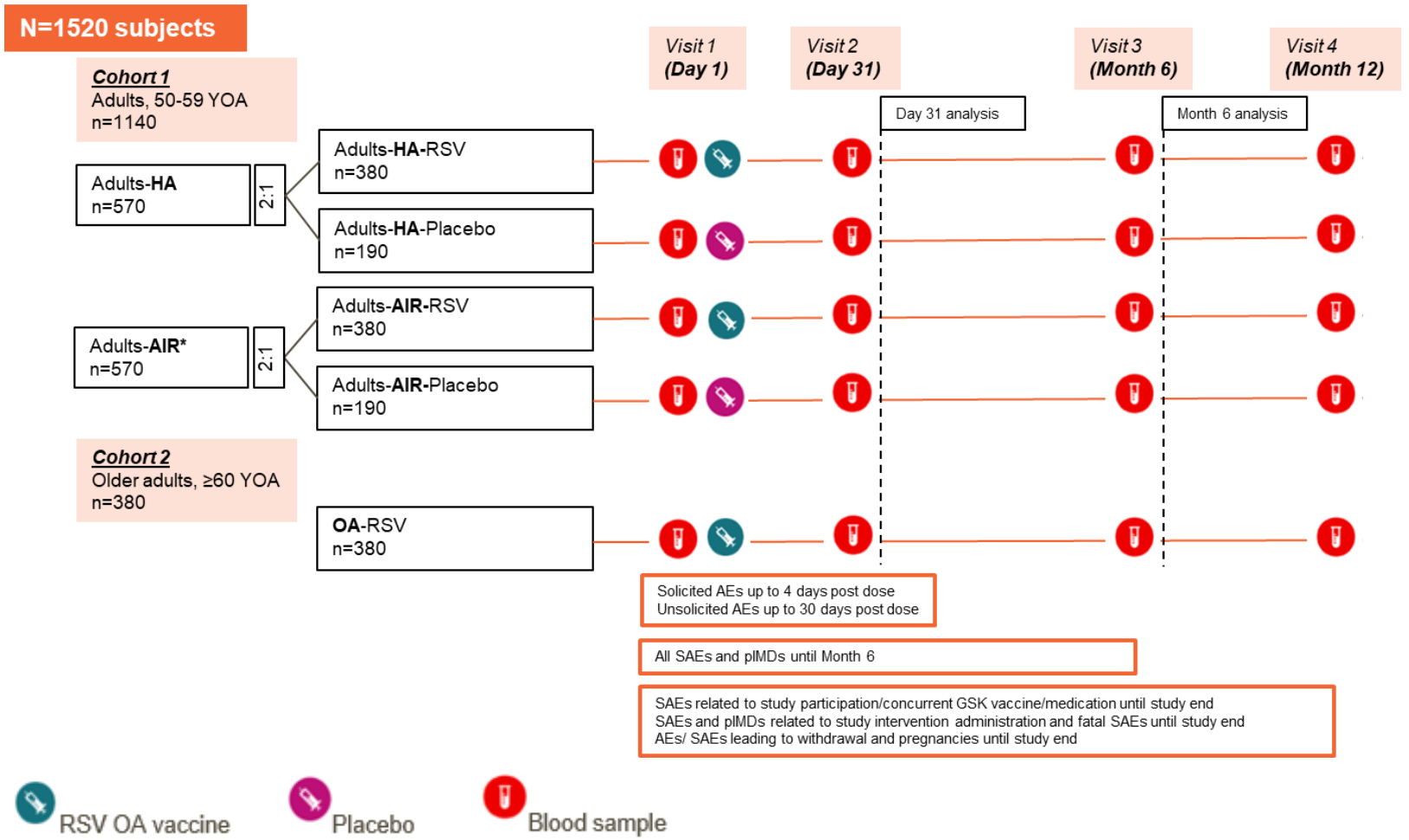
Details related to attributes of estimand covering intercurrent events, population and treatment definition are provided in the Section 9.

4. STUDY DESIGN

4.1. Overall design

The study design overview is presented in Figure 1.

Figure 1 Study design overview



AE=Adverse event; AIR=At increased risk; GSK=GlaxoSmithKline Biologicals SA; HA=Healthy adults; n=Number; OA=Older adults; pIMD=Potential immune-mediated disease; RSV=Respiratory syncytial virus; SAE=Serious adverse event; YOA=Years of age.
* Participants with underlying medical conditions such as chronic pulmonary and cardiovascular diseases, diabetes mellitus types 1 and 2, and chronic liver and renal diseases

- **Type of study**: self-contained.
- **Experimental design**: Phase 3, observer-blind, randomized, placebo-controlled study with 2 cohorts (see Figure 1):
  - Cohort 1 (adults 50-59 YOA), with 2 sub-cohorts (Adults-HA and Adults-AIR) and 4 parallel groups:
    - Adults-HA-RSV Group
    - Adults-HA-Placebo Group
    - Adults-AIR-RSV Group
    - Adults-AIR-Placebo Group
  - Cohort 2 (adults ≥60 YOA) with a single group (OA-RSV Group)
- **Duration of the study**: approximately 12 months for all participants.
- **Primary completion date**: Day 31 (1 month after the administration of study intervention).
- **Control**: placebo saline solution.
- **Blinding**: observer-blind for Cohort 1, and open-label for Cohort 2. The study will be conducted in an observer-blind manner for Cohort 1 from study start-up to Day 31 analysis, beyond which the study will be considered single-blind (see Section 9.4.1 and Section 6.3.5 for details).
- **Data collection**: standardized eCRF. Solicited events and unsolicited AEs will be collected by the participant using a pDiary. New concomitant medications/vaccinations will be collected in the diary card as of the day of study intervention administration and for 29 subsequent days (Day 1 to Day 30). As of Day 30, the details are collected in source documents prior to entering them in the eCRF until study end.
- **Safety monitoring:** the study will be conducted with oversight by the project SRT. Please refer to Section 10.1.5 for the SRT structure.
- **Vaccination schedule**: Participants will receive a single dose of study intervention (either RSVPreF3 OA investigational vaccine or placebo) at Visit 1 (Day 1).
- **Study groups**: Refer to Figure 1 and Table 4 for an overview of the study groups.

Table 4 Study cohorts, groups, intervention and blinding

Study cohort	Groups	Number of participants	Age (Min-Max)	Study intervention	Blinding
Cohort 1					
Adults-HA	Adults-HA-RSV	380	50–59 YOA	RSVPreF3 OA investigational vaccine	The study will be conducted in an observer-blind manner for Cohort 1 from study start up to Day 31 analysis*
	Adults-HA-Placebo	190	50–59 YOA	Placebo	
Adults-AIR	Adults-AIR-RSV	380	50–59 YOA	RSVPreF3 OA investigational vaccine	
	Adults-AIR-Placebo	190	50–59 YOA	Placebo	
Cohort 2					
	OA-RSV	380	≥60 YOA	RSVPreF3 OA investigational vaccine	Open-label

AIR=At increased risk; CSR=Clinical Study Report; HA=Healthy adults; Max=Maximum; Min=Minimum; OA=Older adults; RSV=Respiratory syncytial virus; YOA=Years of age.
* Beyond Day 31 analysis the study will be considered single-blind. The GSK central study team will be unblinded to the data at the time of Day 31 analysis to prepare the CSR of the Day 31 analysis. The study participants will remain blinded until the study end. For details regarding the sequence of analysis, refer to Section 9.4.1.

4.1.1. Overview of the recruitment plan

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

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

The procedures for participants identification/recruitment must be approved by the IEC/IRB together with the material intended for participants identification/recruitment and participants use.

4.1.2. Enrollment rules

Cohort 1

- Enrollment rules will be applied to ensure equal representation of participants in the healthy adults (Adults-HA) and at increased risk (Adults-AIR) sub-cohorts in Cohort 1:
  - Approximately 50% of healthy participants (Adults-HA-RSV Group and Adults-HA-Placebo Group).
  - Approximately 50% of participants at increased risk of RSV-LRTD (Adults-AIR-RSV Group and Adults-AIR-Placebo Group)

- Since the target population in the Adults-AIR Sub-cohort is heterogenous, enrollment will be done to ensure adequate representation of the different diseases (see Section 5.1.1.2). It is therefore intended to enroll:
  - Approximately 25% of participants with chronic pulmonary diseases
  - Approximately 25% of participants with chronic cardiovascular diseases
  - Approximately 25% of participants with diabetes mellitus types 1 and 2
  - The remaining 25% can be distributed freely across the above 3 disease categories as well as include participants with chronic renal or liver disease.

Cohort 2

- Enrollment rules will also be applied to ensure adequate representation by age category within Cohort 2:
  - Approximately 40% of participants 60-69 YOA
  - Approximately 30% of participants 70-79 YOA
  - Approximately 10% of participants ≥80 YOA
  - The remaining 20% can be distributed freely across the 3 age categories.

Both cohorts

- When the target number of participants is reached in a particular disease or age category, further enrollment of participants in that category will be stopped. If needed, the maximum number of participants in a particular disease or age category may be adapted during the study.

For details on the enrollment rules, refer to the SPM.

4.1.3. Caregiver support

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

A caregiver can be appointed by the participant at any time during the study, when the participant feels it is necessary. Each caregiver should receive the caregiver information letter before providing support to the study participant. Ideally, a single caregiver should be appointed by the participant but, in some situations, it may happen that several caregivers will support a study participant throughout the conduct of the study. This should be recorded in the source documents.

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) the site staff should inform the participant of the possibility to appoint a caregiver. Then at

the subsequent study visits 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.

4.2. Scientific rationale for study design

RSV is associated with serious illness in OA and high-risk adults, including those with chronic lung and heart disease or other co-morbidities that may lead to increased risk of RSV-LRTD. The efficacy of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV-LRTD in OA ≥60 YOA has been shown in the Phase 3 clinical study RSV OA=ADJ-006 (refer to IB). The current study is designed as a Phase 3, observer-blind, placebo-controlled study to demonstrate the NI of the immune response and evaluate safety of RSVPreF3 OA investigational vaccine in adults 50-59 YOA, including those who are at increased risk of RSV-LRTD, compared to adults ≥60 YOA.

The inclusion of a group of healthy adults (50-59 YOA) will document the immunogenicity in adults and in the population of OA, since immunogenicity might be impacted by disease and/or age in both those groups.

There are 2 cohorts:

- Cohort 1, with adults 50-59 YOA
  - Sub-cohort Adults-HA with the following groups
    - Adults-HA-RSV and
    - Adults-HA-Placebo

    Participants in the Adults-HA-RSV Group will receive a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1).

    Participants in the Adults-HA-Placebo Group will receive a single injection of placebo at Visit 1 (Day 1).
  - Sub-cohort Adults-AIR with the following groups:
    - Adults-AIR-RSV and
    - Adults-AIR-Placebo

    Participants in the Adults-AIR-RSV Group will receive a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1).

    Participants in the Adults-AIR-Placebo Group will receive a single injection of placebo at Visit 1 (Day 1).
- Cohort 2, with adults ≥60 YOA
  - OA-RSV Group

    Participants in the OA-RSV Group will receive a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1).

4.2.1. Rationale for the use of placebo

As there is currently no licensed RSV vaccine available, placebo groups (receiving saline solution) will be used as control for the safety/reactogenicity assessments.

4.2.2. Rationale for study blinding

Given the difference in reconstitution and visual appearance of the RSVPreF3 OA investigational vaccine and the saline solution used as placebo, double blinding is not possible, and the study will be conducted in an observer-blind manner for Cohort 1 (until Day 31 analysis). As all participants in Cohort 2 will receive the same study intervention (RSVPreF3 OA investigational vaccine), the study will be conducted in an open-label manner for Cohort 2. Please refer to Glossary of terms for the definition of observer-blind and open-label.

Further information on blinding and unblinding is provided in Section 6.3.5.

4.3. Justification for dose (Amended: 25 May 2023)

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 formulation of 120 µg RSVPreF3/AS01$_E$ were selected for further evaluation in the Phase 3 clinical program. The RSV OA=ADJ-002 study was designed to assess the immunogenicity of a 2-dose AS01$_E$ adjuvanted or unadjuvanted RSVPreF3 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*, 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 ***neutralization geometric mean titers*** (GMTs) and RSVPreF3***-binding*** IgG geometric mean concentrations, peaked 1 month after the first dose, and the second dose did not increase the levels observed after the first dose.

The results from study RSV OA=ADJ-002 demonstrated statistically significant superiority of the 120 µg formulations in terms of RSV A ***neutralization*** titers over at least 1 of the 30 µg and 60 µg formulations with the same adjuvant content or unadjuvanted. ***An increase in the RSVPreF3-binding IgG GMCs and fold increase over baseline was also observed with increase in antigen dose from 30 µg to 120 µg.*** The data demonstrated an immunologic benefit of any AS01$_E$ or AS01$_B$ formulations over unadjuvanted formulations in terms of frequency of RSVPreF3specific CD4+ T cells expressing at least 2 markers. Importantly, the CD4+ T cells frequencies induced by the AS01-containing formulations in OA were close or similar to the frequencies observed in young adults. This was not observed following the administration of 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, supported the selection of a 120 µg based formulation. The results also showed that all the AS01-adjuvanted formulations evaluated are considered to have a clinically acceptable safety profile. The AS01-adjuvanted formulation with the lowest reactogenicity profile, i.e., the $AS01_E$-based formulation, was selected. The immunological response observed after 1 vaccine dose of the $AS01_E$-based formulation is considered adequate for a RSVPreF3 OA candidate vaccine.

The RSVPreF3 OA investigational vaccine has not been given in its present form to adults 50-59 YOA.

4.4. End of Study definition

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

EoS: LSLV (Visit 4 at Month 12) or Date of the last testing/reading released of the Human Biological Samples, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV.

5. STUDY POPULATION

Adherence to the inclusion and exclusion criteria specified in the protocol is essential. Deviations from these criteria are not allowed because they can jeopardize the scientific integrity, regulatory acceptability of the study or safety of the participant.

5.1. Inclusion criteria

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

- Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the diary cards, attend study site visits, ability to access and utilize a phone or other electronic communications).

  Note: for participants in case of physical incapacity that would preclude the self-completion of the diary cards, 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 completing diaries or make decisions on behalf of the participant. Refer to Glossary of terms for the definition of caregiver.

- Written or witnessed informed consent obtained from the participant prior to performance of any study-specific procedure.

5.1.1. Specific inclusion criteria for all participants in Cohort 1

- A male or female participant 50-59 YOA at the time of the 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 10.4.1.1.1 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 until study end for this study, and
  - has a negative pregnancy test on the day of study intervention administration.

  Refer to Section 10.4.1 for definitions of woman of childbearing potential and adequate contraception.

5.1.1.1. Specific inclusion criteria for participants in the Adults-HA Sub-cohort

- Healthy participants as established by medical history and clinical examination before entering into the study.
- Participants with chronic stable medical conditions with or without specific treatment, such as hypertension, hypercholesterolemia, or hypothyroidism, and who are not at increased risk for RSV-LRTD (see Section 5.1.1.2), are allowed to participate in this study if considered by the investigator as medically stable (no changes in the treatment or disease severity in the past 3 months).

5.1.1.2. Specific inclusion criteria for participants in the Adults-AIR Sub-cohort

Participants should be diagnosed with at least 1 of the following medical conditions and have a stable condition (no changes in the treatment or disease severity in the past 3 months):

- Chronic pulmonary disease resulting in activity restricting symptoms or use of long-term medication:
  - Chronic obstructive pulmonary disease (COPD)
    - Global Initiative for Chronic Obstructive Lung Disease (GOLD) Grade 2-4 (see Section 10.5.1)
  - Asthma
    - Patient on regular medication (excluding exercise asthma)
  - Cystic fibrosis
  - Other chronic respiratory diseases: lung fibrosis, restrictive lung disease, interstitial lung disease, emphysema or bronchiectasis
- Chronic cardiovascular disease
  - Chronic heart failure (CHF):

    - A minimum of class II symptoms according to New York Heart Association classification of heart failure (see Section 10.5.2)
  - Pre-existing coronary artery disease (CAD not otherwise specified)
    - Physician diagnosis of CAD based on electrocardiogram, exercise stress test, nuclear stress test, cardiac computed tomography scan or cardiac angiogram (more than the presence of hypercholesterolemia)
  - Cardiac arrhythmia
    - Patient on treatment for cardiac arrhythmia
- Diabetes mellitus: types 1 and 2
- Other diseases at increased risk for RSV-LRTD disease
  - Chronic kidney disease
    - G2-G3 disease (Glomerular Filtration Rate between 30 and 90 ml/min/1.73 m^2 – see section 10.5.3)
  - Chronic liver disease

5.1.2. Specific inclusion criteria for Cohort 2 (OA-RSV Group)

- A male or female participant ≥60 YOA at the time of the study intervention administration.
- Participants with chronic stable medical conditions with or without specific treatment, such as diabetes, hypertension or cardiac disease are allowed to participate in this study if considered by the investigator as medically stable (no changes in the treatment or disease severity in the past 3 months).
- 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.

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

- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., current malignancy, human immunodeficiency virus) or immunosuppressive/cytotoxic therapy (e.g., medication used during cancer chemotherapy, organ transplantation, or to treat autoimmune disorders), based on medical history and physical examination (no laboratory testing required).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention.
- Hypersensitivity to latex.

- Unstable chronic illness.
- Any history of dementia or any medical condition that moderately or severely impairs cognition.

  Note: If deemed necessary for clinical evaluation, the investigator can use tools such as Mini-Mental State Exam, Mini-Cog or Montreal Cognitive Assessment (to determine cognition levels of the participant).
- Recurrent or uncontrolled neurological disorders or seizures. Participants with medically controlled active or 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 diary cards, attend study site visits). Study participants may decide to assign a caregiver to help them complete the study procedures. For details see Section 4.1.3.
- Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study (e.g., life-threatening disease).
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine, or medical device) other than the study intervention during the period beginning 30 days before the dose of study intervention (Day -29 to Day 1), or planned use during the study period (up to Visit 4, Month 12).
- Planned or actual administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after the dose of study intervention administration, with the exception of inactivated and subunit influenza vaccines or COVID-19 vaccines (fully licensed or with EUA) which can be administered up to 14 days before or from 14 days after the study intervention administration.

  Note: In case an emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly.
- Previous vaccination with an RSV vaccine, including investigational RSV vaccines.
- Chronic administration of immune-modifying drugs (defined as more than 14 consecutive days in total) and/or administration of long-acting immune-modifying treatments or planned administration at any time up to the end of the study.
  - Up to 3 months prior to the study intervention administration:
    - For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent. Inhaled and topical steroids are allowed.

- Administration of immunoglobulins and/or any blood products or plasma derivatives.

– Up to 6 months prior to study intervention administration: long-acting immune-modifying drugs including among others immunotherapy (e.g., TNF-inhibitors), monoclonal antibodies, antitumoral medication.

5.2.3. Prior/Concurrent clinical study experience

- Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or invasive medical device).

  Refer to Glossary of terms for the definition of 'invasive medical device'.

5.2.4. Other exclusions

5.2.4.1. Other exclusions for all participants

- 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 period that will prohibit participating in the study until study end.
- Participation of any study personnel or their immediate dependents, family, or household members.

5.2.4.2. Other exclusions for Cohort 1

- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions.

5.3. Lifestyle considerations

No lifestyle restrictions are applicable for this study.

5.4. Screening failures

A screening failure is an individual who consents to participate in this study but is not entered in the study.

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

5.5. Criteria for temporarily delaying enrollment/study intervention administration

Enrollment/study intervention administration may be postponed until the transient conditions cited below are resolved, and prior to the end of the study enrollment period:

- Acute disease and/or fever at the time of enrollment and/or study intervention administration. Refer to the SoA (Table 1) for definition of fever and location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- Participants with symptoms suggestive of active 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 COVID-19 positive contacts may be dosed at least 14 days after the exposure, provided that the participant remains symptom-free, and at the discretion of the investigator.
- In case of administration of inactivated and subunit influenza vaccines or COVID-19 vaccines (fully licensed or with EUA): postponement of study intervention administration within given protocol timelines and prior to the end of the study enrollment period, to allow respect of at least 14 days interval between flu/COVID-19 vaccination and study intervention administration.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Refer to the Glossary of terms for the definition of study intervention.

6.1. Study intervention(s) administered

Study interventions are mentioned in Table 5.

Table 5 Study interventions administered

Study intervention name:	**RSVPreF3 OA investigational vaccine**		**Placebo**
Study intervention formulation:	RSVPreF3 (120 µg)	AS01E: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injections q.s. 0.5 mL	Sodium chloride (NaCl) (0.9%); Water for injections
Presentation:	Powder for suspension for injection; Vial	Suspension for suspension for injection; Vial	Solution for injection; Syringe
Type:	Study		Control
Product category:	Biological		NA
Route of administration:	IM		IM
Administration site:			
• **Location**	Deltoid		Deltoid
• **Laterality****	Non-dominant arm		Non-dominant arm
Number of doses to be administered:	1		1
Volume to be administered by dose*:**	0.5 mL		Approximately 0.7 mL****
Packaging and labeling:	Refer to the SPM for more details		Refer to the SPM for more details
Manufacturer:	GSK		GSK

GSK=GlaxoSmithKline Biologicals SA; IM=Intramuscular; MPL=Monophosphoryl lipid A; NA=Not applicable; OA=Older adults; SPM=Study Procedures Manual.
* QS-21: *Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
** The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the study intervention in the non-dominant arm, an injection in the dominant arm may be performed
*** Refer to the SPM for the volume after reconstitution
**** The volume of the saline pre-filled syringe may be between 0.6 mL and 0.8 mL. The full volume is to be injected.

Study participants must be observed closely for at least 30 minutes after the administration of the study intervention(s). Appropriate medical treatment must be readily available during the observation period in case of anaphylaxis, syncope.

6.2. Preparation, handling, storage, and accountability

The study intervention(s) must be stored in a secured place within the temperature range specified on the study intervention's label. The storage temperature should be continuously monitored and recorded with a calibrated (if not validated) temperature monitoring device(s).

Only authorized study personnel should be allowed access to the study intervention(s). Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the SPM for more details on storage and handling of the study intervention(s).

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Participant identification

Participant identification numbers will be assigned sequentially to the individuals who have consented to participate in the study. Each study center will be allocated a range of participant identification numbers.

6.3.2. Randomization to study intervention

- Participants in Cohort 1, Adults-HA Sub-cohort will be randomly assigned to the Adults-HA-RSV Group and Adults-HA-Placebo Group in a 2:1 ratio at Visit 1 (Day 1) to receive the RSVPreF3 OA investigational vaccine or placebo, respectively.
- Participants in Cohort 1, Adults-AIR Sub-cohort will be randomly assigned to the Adults-AIR-RSV Group and Adults-AIR-Placebo Group in a 2:1 ratio at Visit 1 (Day 1) to receive the RSVPreF3 OA investigational vaccine or placebo, respectively.
- All participants in Cohort 2 (OA-RSV Group) will be assigned to receive the RSVPreF3 OA investigational vaccine.

The randomization of supplies within blocks will be performed at GSK, using MAtEx, a program developed for use in SAS (Cary, NC, US) by GSK. Entire blocks will be shipped to the study centers/warehouse(s).

To allow GSK to take advantage of greater rates of recruitment in this multi-center study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

6.3.3. Intervention allocation to the participant

An automated internet-based system (SBIR) will be used for randomization and for identification of intervention material. The system's randomization algorithm will use a stratification by healthy/at increased risk status and CMI subset (participant included in the CMI subset or not) and a minimization procedure accounting for the study and center within each stratum. Minimization factors will have equal weight in the minimization algorithm.

Refer to Section 4.1.2 for details of the enrollment rules.

Once a participant identification number is allocated, the randomization system will determine study group and will provide the study intervention number to be used for the dose of study intervention.

When SBIR is not available, please refer to the SBIR user guide or SPM for specific instructions.

Refer to the SPM for additional information about the study intervention number allocation.

6.3.4. Allocation of participants to CMI assay subsets

The subsets are detailed below.

Cohort	Sub-cohort	Group	Number of participants
Cohort 1	Adults-HA	Adults-HA-RSV	~100
		Adults-HA-Placebo	~50
	Adults-AIR	Adults-AIR-RSV	~100
		Adults-AIR-Placebo	~50
Cohort 2	OA ≥60 YOA	OA-RSV	50
Total			**~350**

AIR=At increased risk; HA=Healthy adults; OA=Older adults; YOA=Years of age

Participants contributing to the CMI subset will be recruited from a selected number of countries and selected number of sites. In the selected sites, the investigator will allocate the first participants in each cohort/sub-cohort to the CMI subset until the allocated target is reached.

6.3.5. Blinding and unblinding

Data from Cohort 1 will be collected in an observer-blind manner. The participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment. To do so, study intervention(s) will be prepared and administered by qualified study personnel who will not participate in the evaluation and review of any study endpoint (i.e., reactogenicity, safety).

Refer to SPM regarding details of the tasks that can be performed by the unblinded study personnel.

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

The study will be conducted in an observer-blind manner for Cohort 1 from study start-up to Day 31 analysis, beyond which the study will be considered single-blind. The study participants in Cohort 1 will remain blinded up to study end, however, the investigators will receive a copy of the CSR with results of the Day 31 analysis on immunogenicity, reactogenicity and safety data. As a consequence, the investigators could become unblinded to some specific participants through summary results. The individual data listings and participant treatment assignments will not be provided to the investigators until after the conclusion of the study (completion of Visit 4, Month 12 [study end]).

Note that the GSK central study team (CRDL, Statistician, Safety Representative, etc.) will be unblinded to the study intervention assignment at the time of Day 31 analysis in order to prepare the CSR of the Day 31 analysis.

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

6.3.5.1. Emergency unblinding (Amended: 25 May 2023)

Unblinding a participant's individual study intervention number should occur ONLY in case of a medical emergency when this information is essential for the clinical management or welfare of the participant.

In case of emergency, the investigator can have unrestricted, immediate and direct access to the participant's study intervention information via an automated internet-based system (e.g., SBIR). The investigator may contact a GSK Helpdesk (refer to Table 6) if help is needed to access the participant's study intervention information (i.e., if the investigator is unable to access SBIR).

A physician other than the investigator (e.g., an emergency room physician) or participant/participant's caregiver or family member may also request emergency access to the participant's study intervention information either via the investigator or investigator's back-up (preferred option) or via the GSK Helpdesk (back-up option). The participant card provides contact information for the investigator(s), their back-up and GSK Helpdesk.

GSK's Global Safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

Table 6 Contact information for emergency unblinding

GSK Helpdesk
Available 24/24 hours and 7/7 days

The Helpdesk is available by phone, fax and email
Toll-free number:

Country	Toll-free phone number
Germany, Spain	00 800 4344 1111
Canada	1 833 541 0263
Japan	00 531 320 109
Mexico	800 123 3102
US	1 844 446 3133

Phone (for countries where the toll-free number is not available): +32 2 656 68 04
Fax: +32 2 401 25 75
Email: rix.ugrdehelpdesk@gsk.com

6.3.5.2. Unblinding prior to regulatory reporting of SAEs

GSK Global Safety staff may unblind the intervention assignment for any participant with a SUSAR. GSK Global Safety is responsible for unblinding the study intervention assignment within the timeframes defined for expedited reporting of SAEs (refer to Section 10.3.10.1). For SAEs requiring expedited reporting to 1 or more regulatory agencies, a copy of the report containing participant's intervention assignment may be sent to investigators in accordance with local regulations and/or GSK policy. GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study intervention(s), prior to regulatory reporting.

GSK policy requires unblinding of any unexpected SAE which is attributable/suspected to be attributable to the study interventions, prior to regulatory reporting. VCSP is responsible for unblinding the study intervention assignment within the timeframes defined for expedited reporting of SAEs (refer to Section 10.3.10.1).

In addition, GSK VCSP staff may unblind the intervention assignment for any participant with a SUSAR or a SAE that is fatal or life-threatening. For SAEs requiring expedited reporting to 1 or more regulatory agencies, a copy of the report containing participant's intervention assignment may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study intervention compliance

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

6.5. Dose modification

Section is not applicable.

6.6. Continued access to study intervention after the end of the study

There is no plan to provide continued access to the study intervention following the end of the study.

The investigator will ask each participant if they are interested in a booster study/long-term evaluation study. If a participant is not interested in joining the booster study/long-term evaluation study the reason for refusal will be documented, when available, in the participant's eCRF.

6.7. Treatment of overdose

Not applicable for this study.

6.8. Concomitant therapy (Amended: 25 May 2023)

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

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

- All concomitant medication including vaccines/products, except vitamins and dietary supplements, administered during the 30-day period after the dose of study intervention (Day 1 to Day 30).
- All concomitant medication leading to elimination from the analysis, including products/vaccines. Please refer to the Section 5.2.2 for further details.
- All concomitant medication which may explain/cause/be used to treat an SAE/pIMD including vaccines/products, as defined in Section 8.3.1 and Section 10.3.8. These must also be recorded in the Expedited Adverse Event Report.
- ***For all AF AESIs (including serious and non-serious), concomitant drugs which could be associated with development or worsening of AF must be reported in the AF follow-up questionnaire.***
- Any prophylactic medication (e.g., analgesics, antipyretics) administered on the day of study intervention administration (Day 1) in the absence of ANY symptom and in anticipation of a reaction to the study intervention administration.

Refer to Table 7 for an overview of the timing for recording of concomitant medication during the study.

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

Table 7 Timing of collection of concomitant medication to be recorded (Amended: 25 May 2023)

	Dose 1 Day 1	Day 30	Study conclusion (Visit 4 at Month 12)
All concomitant medication including vaccines/products, except vitamins and dietary supplements			
All concomitant medication including products/vaccines leading to elimination from the analysis			
All concomitant medication including vaccines/products which may explain/cause/be used to treat an SAE/ pIMD/***AF****)			
Any prophylactic medication			

AF: Atrial Fibrillation; p***IMD***=Potential immune-mediated disease; SAE=Serious adverse event.
Note: The collection period for the concomitant medications to be recorded in eCRF is indicated in gray.
AESI= Adverse event of specific interest
**** For all AF AESIs (including serious and non-serious), concomitant drugs which could be associated with development or worsening of AF must be reported in the AF follow-up questionnaire.***

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Not applicable.

7.2. Participant discontinuation/withdrawal from the study

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 them since the date of withdrawal/last contact.

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

Investigators 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 GSK (refer to Section 10.3.10.1 for the details)
- Unsolicited non-serious AEs
- Solicited AE
- 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 the participant has withdrawn consent and the reason for withdrawal was provided, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE/AESI until the event is resolved (see Section 10.3.8.2).

7.3. Lost to follow-up

Participants will be considered 'lost to follow-up' if they fail to return for scheduled visits and cannot be contacted by the study site.

Please refer to the SPM for a description of actions to be taken before considering the participant lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

In case of doubts of immediate safety concerns regarding the inclusion of a possible participant, inclusion should be postponed until a decision can be made.

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

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

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

The SPM provides the investigator and site personnel with detailed administrative and technical information that does not impact participant safety.

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Follow-up visits (Visit 2, 3 and/or 4) may be conducted at the participant's home (by the site staff or by a home care service system), if appropriate. If home visits are not possible, telephone calls or other means of virtual contacts may be used.
- Diary cards may be transmitted from and to the site by electronic means if allowed by local regulations and or conventional mail or collected at home.
- Biological samples may be collected at a different location* other than the study site or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.

* It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 pandemic (version 2, 27 March 2020) for more details.

Impact on the PPS for immunogenicity will be determined on a case-by-case basis.

8.1. Immunogenicity assessments

Biological samples (Table 8) 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.

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

8.1.1. Biological samples

Table 8 Biological samples

Sample type	Quantity	Unit	Timepoint	Subset name*
Blood for humoral response	~10	mL	Visit 1 (Day 1) Visit 2 (Day 31) Visit 3 (Month 6) Visit 4 (Month 12)	All participants
Blood for CMI	~25	mL	Visit 1 (Day 1) Visit 2 (Day 31) Visit 3 (Month 6) Visit 4 (Month 12)	CMI subset
Urine for pregnancy test	—	—	Visit 1 (Day 1)	Women of Childbearing Potential in Cohort 1

CMI=Cell-mediated immunity.
* Refer to Section 6.3.4 for subset description.

An overall volume of 40 mL will be collected from all study participants during the entire study period. Additionally, 100 mL will be collected from the participants enrolled in the CMI subset during the entire study period. Refer to Table 10 and SoA (Table 1) for information on volumes collected for different assessments.

8.1.2. Laboratory assays

All laboratory testing (Table 9) will be performed at GSK laboratory or in a laboratory designated by GSK.

Table 9 Laboratory assays (Amended: 25 May 2023)

Assay type	System	Component	Challenge	Method	Laboratory
Humoral Immunity (Antibody determination)	Serum	RSV-A ***neutralization*** titer		Neutralization	GSK*
	Serum	RSV-B ***neutralization*** titer		Neutralization	GSK*
CMI	PBMC	CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17 secreting CD4+ and CD8+ T cells	Peptide pool covering RSVPreF3	ICS	GSK*

CD=Cluster of differentiation; CD40L=CD40 ligand; CLS=Clinical laboratory sciences; CMI=Cell-mediated immunity; CRO=Contract research organization; GSK=GlaxoSmithKline Biologicals SA; ICS=Intracellular cytokine staining; IFN=Interferon; IL=Interleukin; PBMC=Peripheral blood mononuclear cell; RSV=Respiratory syncytial virus; TNF=Tumor necrosis factor.
* GSK laboratory refers to the CLS in Rixensart, Belgium; Wavre, Belgium. CLS may delegate testing to a contracted CRO.

Additional testing on serum and frozen PBMC samples to characterize the immune response to RSV/to the investigational RSV OA vaccine/vaccine components may be performed if deemed necessary for accurate interpretation of the data and/or should such test(s) become available in the GSK' laboratory or a laboratory designated by GSK.

Please 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

Immunological read-outs are described in Table 10.

Table 10 Immunological read-outs (Amended: 25 May 2023)

Blood sampling time point		Subset name	No. of participants	Component
Type of contact and time point	Sampling time point			
Humoral immunity (on serum samples)				
Visit 1 (Day 1)	Pre-Adm	All participants	~1520	RSV-A ***neutralization titer*** RSV-B ***neutralization titer***
Visit 2 (Day 31)	Day 31	All participants	~1520	RSV-A ***neutralization titer*** RSV-B ***neutralization titer***
Visit 3 (Month 6)	Month 6	All participants	~1520	RSV-A ***neutralization titer*** RSV-B ***neutralization titer***
Visit 4 (Month 12)	Month 12	All participants	~1520	RSV-A ***neutralization titer*** RSV-B ***neutralization titer***
CMI (on PBMC samples)				
Visit 1 (Day 1)	Pre-Adm	CMI subset	~350	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells
Visit 2 (Day 31)	Day 31	CMI subset	~350	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells
Visit 3 (Month 6)	Month 6	CMI subset	~350	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells
Visit 4 (Month 12)	Month 12	CMI subset	~350	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells

CD=Cluster of differentiation; CD40L=CD40 ligand; CMI=Cell-mediated immunity; IL=Interleukin; IFN=Interferon; Pre-Adm=Pre-study intervention administration; RSV=Respiratory syncytial virus; TNF=Tumor necrosis factor; PBMC=Peripheral blood mononuclear cell.

8.1.4. Immunological correlates of protection

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

8.2. Safety assessments

The investigator(s) and their 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.

8.2.1. Pre-intervention administration procedures

8.2.1.1. Collection of demographic data

Record demographic data such as year of birth, age at the time of study intervention administration, sex, race* and ethnicity* in the participant's eCRF.

* Differences in the safety and efficacy of certain medical products, including vaccines [Haralambieva, 2013; Pérez-Losada, 2009; Kollmann, 2013] have been observed in racially and ethnically distinct subgroups. These differences may be attributable to intrinsic factors (e.g., genetics, metabolism, elimination), extrinsic factors (e.g., diet, environmental exposure, sociocultural issues), or interactions between these factors. Therefore, both geographic ancestry (race) and ethnicity will be collected for all study participants.

8.2.1.2. Measure/record height and weight

Measure the participant's height and weight and record the values in the eCRF.

8.2.1.3. Medical history (Amended: 25 May 2023)

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

A pre-defined list of current co-morbidities [Quan, 2011] to be recorded will be available in the eCRF ***(In addition to the chronic diseases listed in Section 5.1, additional information on rheumatologic diseases, hemiplegia and paraplegia will be collected).***

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.

Any vaccine administered up to 1 year before study vaccine administration should be recorded in the eCRF with date of vaccination. For history of influenza vaccination, information about the vaccine formulation (e.g., adjuvanted or non-adjuvanted or high-dose) should be recorded.

Administration of *Shingrix* and any COVID-19 vaccine at any timepoint (even if longer than 1 year before the study vaccine administration) should be recorded in the eCRF. The date of vaccinations should be collected and recorded in the eCRF.

8.2.1.5. Physical examination/vital signs

- At minimum, temperature, vital signs (e.g., heart rate, respiratory rate and blood pressure) must be collected.
- Vital signs are to be taken after at least 10 minutes of rest and before blood collection for laboratory tests and will consist of systolic/diastolic blood pressure, heart rate and respiratory rate by counting the number of breaths for 1 minute.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Collected information needs to be recorded in the eCRF.
- 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 5.5 for the list of criteria for temporary delay of study intervention administration.
- Physical examination at the study visits after the study intervention administration visit (Visit 2, Visit 3 and/or Visit 4), will be performed only if the participant indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.

8.2.1.6. Smoking status and smoking exposure history

The smoking status will be collected in the eCRF, differentiating tobacco use (cigarettes, cigars, cigarillos, pipes, etc.) and use of electronic smoking devices (e-cigarettes). Refer to Glossary of terms for the definitions of current and former smoker.

Smoking exposure history should be recorded as number of years for both current and former smokers. When applicable, the number of years of exposure should be collected separately for tobacco and electronic smoking devices.

All data will be recorded in the participant's eCRF.

8.2.1.7. Pregnancy test (only for women of childbearing potential in Cohort 1)

Female participants of childbearing potential in Cohort 1 must perform a urine pregnancy test before the administration of the dose of study intervention. Pregnancy testing must be performed 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.

Refer to Section 10.4.3.1 for the information on study continuation for participants who become pregnant during the study.

8.2.1.8. Pre-study intervention administration body temperature

The body temperature of each participant needs to be measured prior to study intervention administration and recorded in the eCRF. The route for measuring temperature can be oral or axillary. If the participant has fever (defined as temperature ≥38.0°C/100.4°F regardless of the location of measurement) on the day of study intervention administration, the visit will be rescheduled (refer to Section 5.5 for details).

8.3. AEs, SAEs and other safety reporting

8.3.1. Time period and frequency for collecting AE, SAE and other safety information (Amended: 25 May 2023)

An overview of the protocol-required reporting periods for AEs, SAEs, and AESIs (including pIMDs and AF) is given in Table 11.

Table 11 Timeframes for collecting and reporting of safety information (Amended: 25 May 2023)

	Pre-Adm* D1	Adm D1	D4#	D30	6 months post-dose	Study conclusion 12 months post-dose
Solicited administration site and systemic events		■				
Unsolicited AEs†		■	■	■		
All SAEs†		■	■	■	■	
All pIMDs		■	■	■	■	
SAEs related to study participation** or concurrent GSK medication/vaccine	■	■	■	■	■	■
Pregnancy		■	■	■	■	■
AEs/SAEs leading to withdrawal from the study		■	■	■	■	■
SAEs and pIMDs related to study intervention administration and fatal SAEs†		■	■	■	■	■
Intercurrent medical conditions***		■	■	■	■	■

Adm=Study intervention administration; AE=Adverse event; D=Day; GSK=GlaxoSmithKline Biologicals SA; pIMD=Potential immune-mediated disease; Pre-Adm=Pre-study intervention administration; SAE=Serious adverse event.
* Corresponds to the day when informed consent is obtained (Day 1, prior to study intervention administration).
# Day 4 is not a visit/contact at site.

** Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests such as blood sampling) or related to a GSK product will be recorded from the time a participant consents to participate in the study

*** Intercurrent medical conditions: 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.

† ***AF will be considered as AESI in this study and will be additionally reported in the AF follow-up questionnaire in eCRF.***

AF reporting will follow the same reporting periods as for unsolicited AEs and SAEs. Non-serious AF with an onset during the 30-day period following study vaccine administration will be collected. The reporting of AF meeting SAE definition (serious AF) will be performed according to the SAE reporting period. Fatal AF and Serious AF judged as related to study vaccination will be reported according to the fatal SAE and related SAE reporting period, respectively. For AF that were reported before the implementation of this Protocol Amendment 1, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

The investigator or designee will record and immediately report all SAEs in enrolled participants to the sponsor or designee 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 Section 10.3.10. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 11. Investigators are not obligated to actively seek AEs or SAEs from former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and if the investigator considers the event to be reasonably related to the study intervention, the investigator will promptly notify the study contact for reporting SAEs mentioned in the Table 13.

8.3.2. Method of detecting AEs and SAEs, pregnancies, and other events (Amended: 25 May 2023)

Detection and recording of AEs/SAEs/***AESI (including*** pIMDs ***and AF)***/pregnancies are detailed in Section 10.3.8.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.9.

Open-ended and non-leading verbal questioning of participants is the preferred method of acquiring information related to an AE/SAE/***AESI (including pIMDs and AF)***/pregnancy.

8.3.3. Regulatory reporting requirements for SAEs, pregnancies, and other events (Amended: 25 May 2023)

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/ ***AESI (including pIMDs and AF)***/pregnancy, it must be reported to GSK using the required documentation and within the timeframes mentioned in Table 12. This is essential for GSK to meet legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/ ***AESI (including pIMDs and AF)***, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.9.2.

Local regulatory requirements and sponsor policy for preparation of an investigator safety report of SUSAR must be followed. These reports will be forwarded to investigators as necessary.

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

Please refer to Section 10.3.10 for further details regarding the reporting of SAEs/ ***AESI (including pIMDs and AF)***/pregnancies.

Table 12 Timeframes for submitting SAEs, pregnancy and other events reports to GSK

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
Pregnancies	24 hours*	electronic pregnancy report	24 hours*	electronic pregnancy report
pIMDs	24 hours**, ‡‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Serious AF†	***24 hours****	***Electronic expedited AEs Report + AF follow-up questionnaire***	***24 hours****	***Electronic expedited AEs Report + AF follow-up questionnaire***

GSK=GlaxoSmithKline Biologicals SA; pIMD=Potential immune-mediated disease; SAE=Serious adverse event.
* 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.
‡‡ For each SAE/pIMD, the investigator(s) must document in the medical notes that they have reviewed the SAE/pIMD and have provided an assessment of causality.
† Only AF meeting SAE definition will be reported in electronic Expedited AE Report and in the specific AF follow-up questionnaire. Non-serious AF will be reported in the non-serious adverse event eCRF screen and in the AF follow-up questionnaire. For AF that were reported before the implementation of this Protocol Amendment 1, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

8.3.3.1. Contact information for reporting SAEs, AESIs *(including* pIMDs *and AF)* and pregnancies (Amended: 25 May 2023)

Table 13 Contact information for reporting SAEs, AESI *(including* pIMDs *and AF)* and pregnancies (Amended: 25 May 2023)

Study contact for questions regarding SAEs, *AESIs (including* pIMDs *and AF),* pregnancies Refer to the local study contact information document
Back-up study contact for reporting SAEs, *AESIs (including* pIMDs *and AF)*, pregnancies Available 24/24 hours and 7/7 days: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: ogm28723@gsk.com US sites only: Fax: 1 610 787 7053 Canadian sites only: Fax: 1 866 903 4718

8.3.4. Treatment of AEs (Amended: 25 May 2023)

Any medication, vaccine or products administered for the treatment of an SAE/***pIMD*** should be recorded in the Expedited Adverse Event Report of the participant's ***eCRF*** **screen** (refer to Section 10.3.10.1). ***For the AF, this information will be captured in the Expedited Adverse Events Report and in the AF follow-up questionnaire in eCRF.***

8.3.5. 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 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(s) or their back-up.

8.4. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Biomarkers

Not applicable for this study.

8.7. Immunogenicity assessments

Immunogenicity is described in Section 8.1.

8.8. Health outcomes

Not applicable for this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

Statistical hypotheses are associated to the confirmatory primary NI objectives, which will be tested according to the graphical procedure detailed in Section 9.3.1. Global type I error is controlled at 2.5% (1-sided).

Table 14 Study objectives and null hypothesis

Objectives	Null hypothesis
Primary	
• To demonstrate the NI of the humoral immune response in healthy participants 50-59 YOA compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• **Null hypothesis 1 (H1):** The anti-RSV-A GMT ratio (OA-RSV Group over Adults-HA-RSV Group) is >1.5 or the SRR difference (OA-RSV Group – Adults-HA-RSV Group) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favor of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.
• To demonstrate the NI of the humoral immune response in healthy participants 50-59 YOA compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• **Null hypothesis 2 (H2):** The anti-RSV-B GMT ratio (OA-RSV Group over Adults-HA-RSV Group) is >1.5 or the SRR difference (OA-RSV Group – Adults-HA-RSV Group) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favor of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.
• To demonstrate the NI of the humoral immune response in participants 50-59 YOA at increased risk of RSV-LRTD compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• **Null hypothesis 3 (H3):** The anti-RSV-A GMT ratio (OA-RSV Group over Adults-AIR-RSV Group) is >1.5 or the SRR difference (OA-RSV Group – Adults-AIR-RSV Group) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favor of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.

Objectives	Null hypothesis
• To demonstrate the NI of the humoral immune response in participants 50-59 YOA at increased risk of RSV-LRTD compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• **Null hypothesis 4 (H4):** The anti-RSV-B GMT ratio (OA-RSV Group over Adults-AIR-RSV Group) is >1.5 or the SRR difference (OA-RSV Group – Adults-AIR-RSV Group) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favor of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.

AIR=At increased risk; GMT=Geometric mean titer; H1=Null hypothesis 1; H2=Null hypothesis 2; H3=Null hypothesis 3; H4= Null hypothesis 4; HA=Healthy adults; LRTD=Lower respiratory tract disease; NI=Non-inferiority; OA=Older adults; RSV=Respiratory syncytial virus; SRR=Seroresponse rate; YOA=Years of age.

9.2. Analysis sets

Analysis sets are presented in Table 15.

Table 15 Analysis sets

Analysis set	Description
Screened Set	All participants who were screened for eligibility.
Enrolled Set	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). NOTE: screening 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.
Exposed Set	All participants who received the study intervention. Analysis per group is based on the administered intervention.
Per-Protocol Set*	All eligible participants who received the study intervention as per protocol, had immunogenicity results pre- and post-dose, complied with blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. Analysis per group is based on the administered intervention.

* Contribution of participants to PPS will be defined by timepoint.

9.2.1. Criteria for elimination from analysis

If a participant meets 1 of the criteria mentioned in the Section 5.2.1 (medical conditions) or Section 5.2.2 (concomitant therapy), they may be eliminated from per-protocol analysis.

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 SAP will be developed and finalized before FSFV. This section is a summary of the planned statistical analyses of the confirmatory primary endpoints. Descriptive analyses of demography, immunogenicity, and safety will be detailed in the SAP.

9.3.1. Primary endpoints/estimands analysis

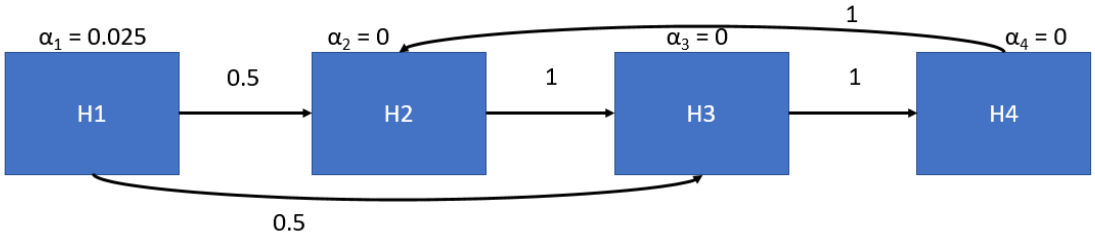
Considering the sampling timepoint at 1 month post-study intervention administration, the 2-sided 95% and 97.5% Cis for group GMT ratios (OA-RSV Group over Adults-HA-RSV Group and OA-RSV Group over Adults-AIR-RSV Group) will be derived from an ANCOVA model on log_{10}-transformed titers for each neutralization ***assay***. The model will include the group (OA-RSV Group, Adults-HA-RSV Group and Adults-AIR-RSV Group) and the baseline log_{10}-transformed titer as covariate.

The SRR is defined as the proportion of participants having a fold increase in ***neutralization*** titers (1 month post-study intervention administration over pre-study intervention administration) ≥4. The 2-sided 95% and 97.5% Cis for group SRR difference (OA-RSV Group minus Adults-HA-RSV Group and OA-RSV Group minus Adults-AIR-RSV Group) will be derived using the method of Miettinen and Nurminen Miettinen, 1985] **(Amended: 25 May 2023)**.

Missing data will not be replaced.

NI for each primary objective will be claimed to be successful if the upper limit of the 2-sided CI for the GMT ratio will be ≤1.5 and the upper limit of the 2-sided CI for the SRR difference will be ≤0.10, according to the significance level provided by the graphical testing procedure.

The following graphical testing procedure will be applied to control the global type I error at 2.5% (1-sided) [Bretz, 2009].



Refer to Table 14 where H1/H2/H3/H4 labels are assigned.

The initial allocation of α among the null hypotheses is (0.025, 0, 0, 0), while the propagation rules are specified by the transition matrix:

$$\begin{pmatrix} 0 & 0.5 & 0.5 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \end{pmatrix}$$

The primary analysis set will be the PPS.

9.4. Interim analyses

All analyses will be conducted on final data, as clean as possible.

9.4.1. Sequence of analyses

The analyses will be performed stepwise:

- **Day 31 (PCA)**: A first analysis will be performed on all immunogenicity, reactogenicity and safety data available and as clean as possible, when data for at least primary and secondary endpoints up to Visit 2 (Day 31) are available for all participants. This analysis will be considered as final for those endpoints

  The GSK central study team (CRDL, Statistician, Safety Representative, etc.) will be unblinded to the details of the treatment assignments at the time of the Day 31 analysis in order to prepare the CSR of the Day 31 analysis. Refer to Section 6.3.5 for details of blinding and unblinding procedures.

- **Month 6**: A second analysis will be performed on all immunogenicity and safety data available and as clean as possible, when data for at least secondary endpoints up to Visit 3 (Month 6) are available for all participants. This analysis will be considered as final for those endpoints.

- An **end of study** analysis will be performed when all data for at least secondary endpoints up to study conclusion (Visit 4, Month 12) will be available for all participants.

- If the data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed.

9.4.2. Statistical considerations for interim analysis

No statistical adjustment for interim analysis is required.

9.5. Sample size determination

The target sample size for the study is approximately 1520 participants: 380 participants each in the Adults-HA-RSV Group and Adults-AIR-RSV Group, 190 participants each in the Adults-HA-Placebo Group and Adults-AIR-Placebo Group and 380 participants in the OA-RSV Group.

The sample size in the groups receiving the investigational vaccine is driven by the statistical power to prove the primary NI objectives.

Assuming 342 evaluable participants in each group receiving the investigational vaccine, the power to demonstrate the primary NI objectives following the graphical testing procedure in Section 9.3.1 is presented in Table 16. Power was estimated by 10 000 simulations, using SAS 9.4:

- Individual RSV-A and RSV-B ***neutralization*** titers at baseline and at 1 month post-study intervention administration were modeled by a multivariate log-normal distribution, means and variance-covariance matrix based on historical data from other RSV OA vaccine clinical trials. The Adults-AIR-RSV Group was assumed to have the same multivariate log-normal distribution of the OA-RSV Group (i.e., same

means and variance-covariance matrix), while the Adults-HA-RSV Group was assumed to have a 1.25-fold higher mean at 1 month post-study intervention administration for both ***neutralization titers*** **(Amended: 25 May 2023)**.

- Raw p-values were obtained from shifted 1-sided t-tests (for group GMT ratios) and using the method of Miettinen and Nurminen (for group SRR difference). The p-value associated to each NI objective is the maximum between the p-values from the GMT ratio and from the SRR difference (co-primary endpoints).
- P-values associated to each NI objective were compared with the corresponding alpha, as propagated by the graphical testing procedure, to identify which NI objectives were successfully demonstrated at each simulation.

Table 16 Power of primary NI objectives

Objective	Power
NI in the Adults-HA-RSV Group for the RSV-A strain	>99%
NI in the Adults-HA-RSV Group for the RSV-B strain	>99%
NI in the Adults-AIR-RSV Group for the RSV-A strain	93.6%
NI in the Adults-AIR-RSV Group for the RSV-B strain	82.8%
All	**82.7%**

All=power to demonstrate all primary NI objectives simultaneously; AIR=At increased risk; HA=Healthy adults; NI=Non-inferiority; RSV=Respiratory syncytial virus.

A 10% attrition rate is accounted from enrolled to evaluable participants.

Participants who withdraw from the study will not be replaced.

10. 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:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH 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 for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE(s) or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. 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 study and for 1 year after completion of the study.

10.1.3. Informed consent process

The investigator(s) or their representative(s) must fully explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary.

Freely given and written/witnessed informed consent must be obtained from each participant, as appropriate, prior to participation in the study.

The content of the ICF must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written or witnessed 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 re-consented if a new version of the ICF(s) or an ICF addendum is released during their participation in the study.

A copy of the ICF(s) must be provided to the participants.

10.1.4. Data protection

Participants will be assigned a unique identifier by the investigator. Any participant records or datasets transferred to the sponsor 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, in accordance with the Data Privacy Notice that will be sent to the site staff.

The participants must be informed that:

- Their personal study-related data will be used by the sponsor in accordance with local data protection law.
- Their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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.

10.1.5. Committees structure

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 initiation of the study in that country. This includes IRBs/IECs for review and approval of the protocol and subsequent amendments, ICF and any other documentation.

Safety oversight will be provided by a blinded SRT composed of GSK RSV OA project team members.

10.1.6. 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 study registers.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

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

10.1.7. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents, including source documents (see Glossary of terms for the exact definition of essential and source documents). The document storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential study documents may be added or removed where justified (in advance of study initiation) based on their importance and relevance to the study. When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies (see Glossary of terms for the exact definition of certified copies).

All participant data related to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants (see Glossary of terms for the exact definition of source documents) that supports information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies for such review and inspection.

The sponsor 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).

Study monitors will perform ongoing source data verification to confirm that data entered in the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be fully explained if necessary (e.g., via an audit trail). The safety and rights of participants must be protected, and the study conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

QTLs will be pre-defined in the Quality Plan to identify systematic issues that can impact participant safety and/or the reliability of study results. These pre-defined parameters will

be monitored during the study. Important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

Study records and source documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 25 years from issuance of the final CSR/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source documents

Source documents provide evidence to establish the existence of the participant and substantiate the integrity of collected data. The investigator should maintain a record of the location(s) of their source documents.

Data transcribed into the eCRF from source documents must be consistent with those source documents; any discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data and documents can be found in the Glossary of terms.

10.1.9. Study and site start and closure

Start of study is defined as FSFV.

First act of recruitment

The first act of recruitment is the first site initiated.

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 enough notice in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor 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.

10.1.10. Publication policy

GSK aims to submit the results of the study for publication in searchable, peer reviewed scientific literature within 18 months from the LSLV for interventional studies and follows the guidance from the ICMJE.

10.2. Appendix 2: Clinical laboratory tests

RSV-A and RSV-B neutralization assays (Amended: 25 May 2023)

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

Virus neutralization is performed by incubating a fixed amount of RSV-A strain (Long, ATCC No. VR-26) or RSV-B strain (18537, ATCC No. VR-1580) with serial dilutions of the test serum. The serum-virus mixture is then transferred onto a layer of Vero cells (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, 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 ***neutralization*** titer is expressed in Estimated Dilution 60 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 [Barbas, 1992; Bates, 2014]. ***The ED60 neutralization titers will also be converted in concentration in International Units per milliliter (IU/mL).*** Secondary standards calibrated against the international reference (NIBSC 16/284) [McDonald, 2018; McDonald, 2020] are included in every run to allow conversion into international units per millimeters.

Intracellular cytokine staining

The ICS is used to assess RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least 1 cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17 (secondary endpoint).

As previously described [Moris, 2011], thawed PBMCs are stimulated in vitro in the presence of anti-CD28 and anti-CD49d antibodies either with pools of 15-mer peptides overlapping by 11 amino acids and spanning the sequence of the RSVPreF3 protein, or with medium. After 2 hours of incubation at 37ºC, Brefeldin A is added to inhibit cytokine secretion during an additional overnight incubation at 37ºC. Cells are subsequently harvested, stained for surface markers (CD4+ and CD8+) and then fixed. Fixed cells are then permeabilized and stained with labeled antibodies specific for the following immune markers:

- CD3+: phenotyping T cells;
- CD40L (CD154), expressed on activated CD4+ T cells, [Chattopadhyay, 2005; Frentsch, 2005; Samten, 2000; Stubbe, 2006];
- IL-2: key for the development, survival and function of T cells [Boyman, 2012];
- TNF-α: anti-viral/intracellular factor, pro-inflammatory cytokine, cytotoxicity [Sedger, 2014];
- IFN-γ: anti-viral factor, associated with the Th1-like profile [Schoenborn, 2007];
- 4-1BB (CD137), expressed on activated CD4+ and CD8+ T cells [Wölfl, 2008];
- IL-13: associated with the Th2-like profile [Bao, 2015];
- IL-17: associated with the Th17-like profile [Korn, 2009].

After staining with the markers above, the cellular samples are analyzed by flow-cytometry allowing to determine the frequency of CD4+ and/or CD8+ T cells expressing the marker(s) of interest per million of CD4+ and/or CD8+ T cells.

10.3. Appendix 3: AEs: definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of an AE

An AE is any untoward medical occurrence (an unfavorable/unintended sign – including an abnormal laboratory finding), symptom, or disease (new or exacerbated) in a clinical study participant that is temporally associated with the study intervention. The AE may or may not be considered related to the study intervention.

10.3.1.1. Events Meeting the AE Definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after administration of the study intervention even though they may have been present before study start.
- Signs, symptoms, or the clinical sequelae of a suspected drug, disease or other interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study intervention or a concurrent medication.
- Signs or symptoms temporally associated with administration of the study intervention.
- Signs, symptoms that require medical attention (e.g., hospital stays, physician visits and emergency room visits).
- Pre- or post-intervention events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited AEs are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.

10.3.1.2. Events NOT Meeting the AE Definition

- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pre-existing conditions or signs and/or symptoms present in a participant before the study intervention. These events 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.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

10.3.2. Definition of an SAE

An SAE is any untoward medical occurrence that:	
a.	Results in death.
b.	Is life-threatening Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
c.	Requires hospitalization or prolongation of existing hospitalization Note: In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
d.	Results in disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e.	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.	Other situations Medical or scientific judgment must be exercised in deciding whether reporting is appropriate in other situations. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition should be considered serious. Examples of such events are invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; and convulsions that do not result in hospitalization.

10.3.3. Solicited events

h. Solicited administration site events

The following administration site events will be solicited (Table 17):

Table 17 Solicited administration site events

Pain at administration site
Redness at administration site
Swelling at administration site

i. Solicited systemic events

The following systemic events will be solicited (Table 18):

Table 18 Solicited systemic events

Fever
Headache
Myalgia (muscle pain)
Arthralgia (joint pain)
Fatigue (tiredness)

Note: Participants will be instructed to measure and record the temperature in the evening. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the diary card.

10.3.4. Unsolicited AEs

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 A***E***s must have been communicated by a participant who has signed the informed consent. Unsolicited A***E***s include both serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or an emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

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

10.3.5. Adverse events of special interest (AESIs) (Amended: 25 May 2023)

Adverse events of special interest (AESIs) collected during this study include potential immune-mediated diseases (pIMDs) and Atrial Fibrillation (AF).

10.3.5.1. *Potential immune-mediated diseases* (pIMDs)

pIMDs are 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 19. Please refer to the Section 10.3.8.1 for reporting details.

The investigator(s) must exercise their 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.

Table 19 List of 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”
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:

Medical Concept	Additional Notes
	• 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
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

Medical Concept	Additional Notes
	• Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • 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	
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	Includes the following: • Acute necrotizing myelitis

Medical Concept	Additional Notes
other inflammatory demyelinating variants	• 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)
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	
Autoimmune / Immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis

Medical Concept	Additional Notes
	• 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	
Lichen planus	• Includes liquen planopilaris
Localized Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
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
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)

Medical Concept	Additional Notes
	• 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	
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	

10.3.5.2. Atrial fibrillation (AF)

AEs of AF are considered as AESI in this study.

When there is enough evidence to make the above diagnosis, the AE must be reported as AESI. Symptoms, signs or conditions which might (or might not) represent AF, should be recorded and reported as AEs but not as AESI until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

For each case of AF reported in the AE or SAE section in the eCRF, additional information will be collected in a specific 'AF follow-up questionnaire' eCRF screen.

10.3.6. 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 Section 10.3.1 and Section 10.3.2).

The investigator(s) must exercise their medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

10.3.7. Events or outcomes not qualifying as AEs or SAEs

10.3.7.1. Pregnancy

Female participants who become pregnant after administration of the study intervention may continue the study at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any abnormal pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an SAE. Please refer to Section 10.3.2 for definition of SAE.

10.3.8. Recording and follow-up of AEs, SAEs, *AESIs (including* pIMDs *and AF)* and pregnancies (Amended: 25 May 2023)

The participants will be instructed to contact the investigator immediately should they experience any signs or symptoms they perceive as serious.

When an AE/SAE***/AESIs (including pIMDs and AF)*** occurs, it is the investigator's responsibility to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator will then record all relevant information regarding an AE/SAE***/AESIs (including pIMDs and AF)*** on the eCRF. The investigator may not send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers will be blinded on copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event, based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE***/AESIs (including pIMDs and AF)*** instead of individual signs/symptoms.

A pDiary will be used in this study to capture solicited administration site or systemic events. The pDiary will be distributed to all participants at Visit 1. The participant should be trained on how and when to complete the pDiary. If a participant is unable or not willing to complete the pDiary him/herself, he/she may be helped by a caregiver (refer to Glossary of terms for the definition of caregiver).

Anyone who measures administration site or systemic events and who will record the event in the pDiary, e.g., the study caregiver, should have received a caregiver information letter explaining the role of the caregiver prior to completing the pDiary. This training must be documented in the participant's source record.

If any individual other than the participant is making entries in the pDiary, their identity must be documented in the participant's source record.

Collect and verify completed pDiary during discussions with the participant on Visit 2.

Any unreturned pDiary will be sought from the participant through telephone call(s) or any other convenient procedure.

The investigator or delegate will transcribe the required information into the eCRF in English.

10.3.8.1. Time period for collecting and recording AEs, SAEs, *AESIs (including pIMDs and AF)* and pregnancies (Amended: 25 May 2023)

Refer to Table 11 for an overview of the protocol required reporting periods for AEs, SAEs, pIMDs and pregnancies.

All solicited administration site and systemic events with onset during the 4 days following administration of the study intervention, and all unsolicited AEs that occur during the 30 days following administration of the study intervention must be recorded into the appropriate section of the eCRF, irrespective of their intensity.

Non-serious AF with an onset during the 30-day period following study vaccine administration will be collected.

The time period for collecting and recording all SAEs and pIMDs will begin at the first receipt of study intervention and will end 6 months after study intervention administration. ***AF reporting will follow the same reporting periods as for AEs and SAEs (Table 11).***

All AEs/SAEs***/AESIs (including pIMDs and AF)*** leading to withdrawal from the study and pregnancies will be collected and recorded from the time of the first receipt of study intervention until the participant is discharged from the study. SAEs related to study participation or to a concurrent GSK medication/vaccine will be collected from the time consent is obtained until the participant is discharged from the study. All pIMDs related to study participation will be collected until study end.

10.3.8.2. Follow-up of AEs, SAEs, *AESIs (including* pIMDs and AF), pregnancies or any other events of interest (Amended: 25 May 2023)

After the initial AE/SAE/***AESI (including*** pIMD***s and AF)***/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, ***AESIs (including*** pIMDs ***and AF)*** (as defined in Section 10.3.5.1) will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

10.3.8.2.1. Follow-up during the study (Amended: 25 May 2023)

AEs/***AESIs (including*** pIMDs ***and AF)*** documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study or the participant is lost to follow-up.

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

10.3.8.2.2. Follow-up after the participant is discharged from the study (Amended: 25 May 2023)

The investigator will provide any new or updated relevant information to GSK on a previously reported SAE/pIMD using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable. ***For AF cases, the investigator will provide any new or updated relevant information on previously reported AF to GSK using a paper/electronic Expedited Adverse Events Report and the AF follow-up questionnaire 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.

10.3.8.2.3. 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 GSK using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the 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 10.3.10.

10.3.8.3. Updating of SAE, *AESIs (including* pIMD and AF), and pregnancy information after removal of write access to the participant's eCRF (Amended: 25 May 2023)

When additional SAE, ***AESI (including*** pIMD ***and AF),*** 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 the Study contact for reporting SAEs (refer to Section 8.3.3.1 or to GSK Global Safety department within the defined reporting timeframes specified in the Table 12).

10.3.9. Assessment of intensity and causality

10.3.9.1. Assessment of intensity

The intensity of the following solicited AEs will be assessed as described in Table 20:

Table 20 Intensity scales for solicited events in participants ≥50 YOA

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.
Redness at administration site		Greatest surface diameter in mm
Swelling at administration site		Greatest surface diameter in mm
Temperature*		Temperature in °C/°F
Headache	0	None/Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue (tiredness)	0	None/Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia (muscle pain)	0	None/Normal
	1	Mild: Myalgia present but does not interfere with activity
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia (joint pain)	0	None/Normal
	1	Mild: Arthralgia present but does not interfere with activity
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

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

The maximum intensity of administration site redness/swelling, and fever will be scored at GSK as follows:

Intensity grade	Redness/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 investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgment.

The intensity should be assigned to 1 of the following categories:

1 (mild)	=	An AE which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (In adults, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy).

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

10.3.9.2. Assessment of causality

The investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgment.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The investigator will also consult the IB while making their assessment.

Causality should be assessed by the investigator using the following question:

Is there a reasonable possibility that the unsolicited AE may have been caused by the study intervention?

YES	:	There is a reasonable possibility that the study intervention contributed to the AE.
NO	:	There is no reasonable possibility that the AE is causally related to the administration of the study intervention. There are other, more likely causes and administration of the study intervention is not suspected to have contributed to the AE.

If an event meets the criteria to be determined 'serious' (see Section 10.3.2), additional examinations/tests will be performed by the investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.

- Lack of efficacy of the study intervention, if applicable.
- An error in study intervention administration.
- Other cause (specify).

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to GSK.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator(s) may change their opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.9.3. Medically attended visits

For each solicited and unsolicited AE the participant experiences, the participant will be asked if they 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.

10.3.9.4. Assessment of outcomes

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

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

10.3.10. Reporting of SAEs, *AESIs (including* pIMDs *and AF)*, pregnancies and other events (Amended: 25 May 2023)

10.3.10.1. Events requiring expedited reporting to GSK (Amended: 25 May 2023)

Once an investigator becomes aware that an SAE has occurred in enrolled participant, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS, even if the investigator does not have complete information on the SAE. It must be completed as thoroughly as possible, with all available details of the event.

The SAE report must be updated WITHIN 24 HOURS of the receipt of updated information on the SAE. The investigator will always provide an assessment of causality at the time of the initial report.

Refer to the Table 12 for the details on timeframes for reporting of SAEs/***AESIs (including*** pIMDs ***and AF)***/pregnancies.

The investigator will be required to confirm the review of SAE causality within 72 hours of submission of the SAE.

Refer to Section 10.3.10.2 for information on back-up systems in case the electronic reporting system does not work.

10.3.10.2. Back-up system in case the electronic reporting system does not work

If the electronic reporting system does not work, the investigator (or designee) must fax or email a completed, dated and signed paper Expedited Adverse Events Report to the study contact for reporting SAEs (refer to Sponsor Information) or to GSK VCSP department within 24 hours of becoming aware of the SAE.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report within 24 hours after the electronic reporting system is working again. The information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.4. Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1. Definitions

10.4.1.1. Woman of childbearing potential (WOCBP)

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

10.4.1.1.1. Women not considered as women of childbearing potential

- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral oophorectomy
  - Documented bilateral salpingectomy

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

- Postmenopausal female

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use a non-hormonal, highly effective contraception method if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception guidance

- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 21).

Table 21 Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent* *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Injectable
• Oral (only if allowed by local regulations or if part of standard medical practice in the country)
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion or ligation
Vasectomized partner *(A vasectomized partner is a highly effective contraception 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 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 drug. 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.)*

* 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 subjects in clinical studies.

10.4.3. Collection of pregnancy information

10.4.3.1. Female participants who become pregnant

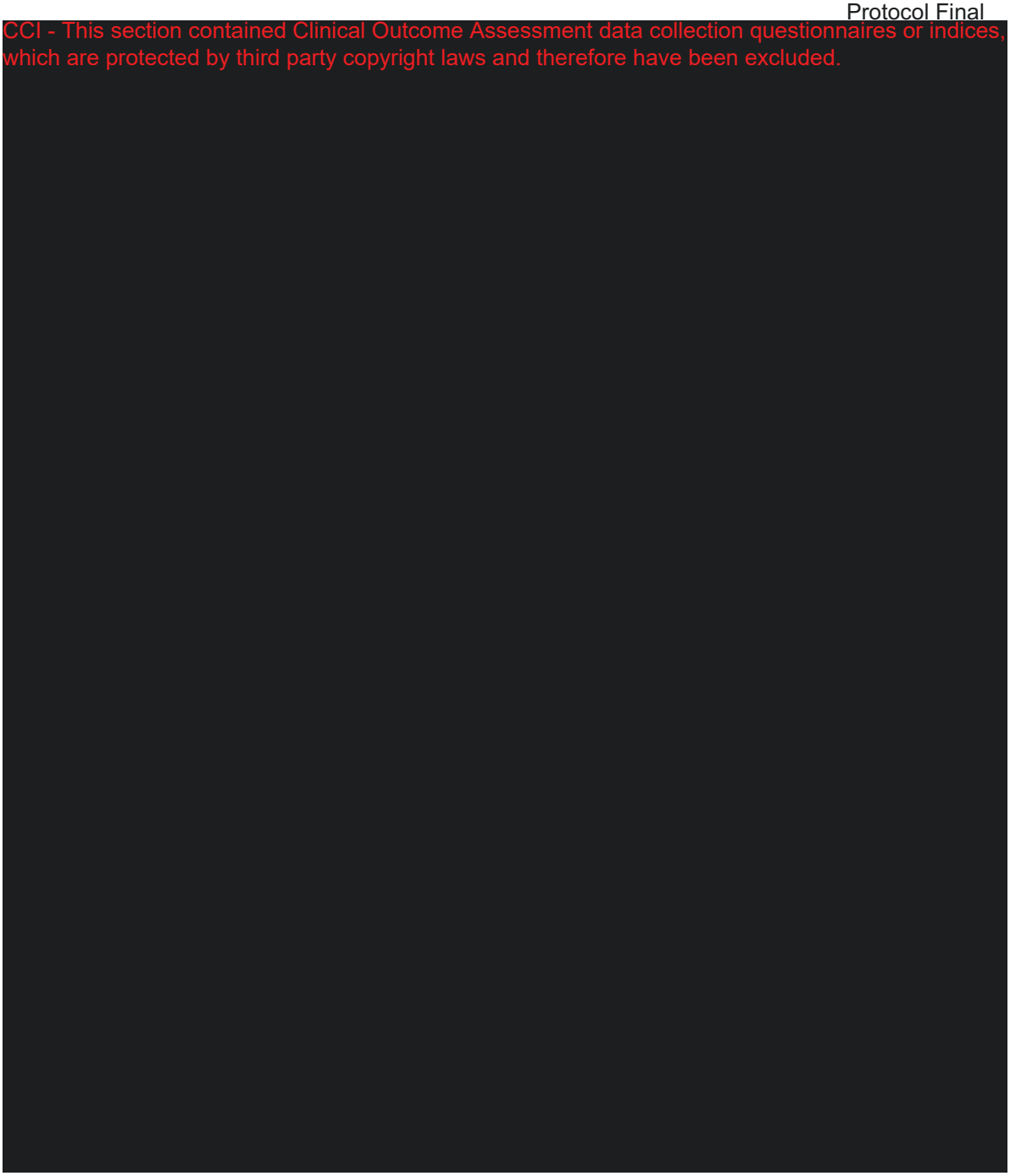
Refer to Sections 8.3.1, 8.3.2, 10.3.8.1, 10.3.8.2 and 10.3.8.3 for further information on detection, recording, reporting and follow-up of pregnancies.

Any female participant who becomes pregnant during the study may continue other study procedures at the discretion of the investigator.

10.5. Appendix 5: Grading scales for chronic diseases in scope of the AIR population

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



10.6. Appendix 6: Country-specific requirements

10.6.1. Germany

Explanatory statement concerning Gender Distribution (Article 7, paragraph 2 (12) of the German GCP ORDER).

For this study, there is no intention to conduct specific analyses investigating the relationship between gender and the safety, immunogenicity and efficacy of the investigational RSV OA vaccine. Recruitment will include both males and females. To not expose pregnant women and their fetuses/children to an investigational vaccine, females enrolled in this study will either be of non-childbearing potential (i.e., hysterectomy, bilateral oophorectomy, bilateral salpingectomy or post-menopause), or if she is of childbearing potential, she must have a negative pregnancy test and use appropriate methods of contraception for the study duration (refer to the study protocol, Section 5.1 "Inclusion criteria" and Section 5.2 "Exclusion criteria"). Women who are pregnant, planning to become pregnant or breastfeeding are excluded from this study.

Remote Source Data Verification during exceptional situations in Germany

Frequent instream monitoring of safety data by the central study team at GSK is required for this study. Instream review of study data items and processes should be considered during exceptional situations/circumstances, such as with pandemics like COVID-19, focusing on key data points, patient assessments and processes that are critical to ensure the rights, safety and well-being of study participants and the integrity of the study and data. Prior to any rSDV activity a written agreement by the Investigator will be obtained. The agreement includes the extent and the method of rSDV activities. Monitoring Plan and Study-Specific Risk Register will be updated to include rSDV activities and CRAs will be guided for the conduct of rSDV.

Option 1 Transfer of redacted Source Documentation

Process for transfer and review of redacted source documentation provided by the site:

- The CRA instructs study site on the source data needed for the remote SDV activities.
- The CRA instructs site staff they must pseudonymize the requested documentation, do a quality check that anonymized (redacted) areas cannot be read, and then delivers the documentation to the CRA in an encrypted form of communication (the site should have a documented process).
- The minimum requirements regarding quality of the copies will be agreed with the site upfront:
  - For the scanning of paper documents resolution will be a minimum of 300 dpi.
  - For the scanning of photographs and images resolution will be 600 dpi minimum.
  - Color scanners must be able to produce copies that match the original.

  - A4 format as final size without loss of information.
  - Documents will be saved as PDF.
  - In order to maintain quality standards, a captured image will not be subjected to non- uniform scaling (i.e., sizing) or re-sampling to a lower resolution.

- Redacted source document scans will be sent to the CRA via email using 1 of the following secure options:

a. TLS connection:

   TLS connections are intended to support significant mail flow between GSK and external partners in a secure manner.

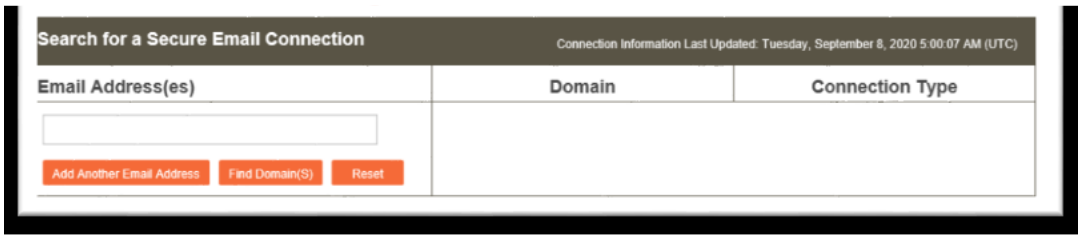
b. GSK Secure

   In cases where only a handful of users are communicating or the volume of emails is low, the use of GSK secure, the GSK ad-hoc message encryption solution is recommended.

c. Password protected PDF attachment

   A password protected scan (PDF) will be attached to an email. The password to open the attachment will be send in a separate email.

- The CRA may use the secure email website to assess whether the sites email address is secure (i.e., encrypted).



- Prior to starting remote SDV the CRA ensures that the provided documents are complete and does not contain any personal information.
  - In case the CRA detects any personal information that has not been redacted, the CRA informs the study site and deletes the files (incl. the Recycle bin).
  - A Data Breach must be reported Data Breach Web Report Form.
- Use of an external PC screen is recommended. The CRA will not generate any copies from the source data received.
- Source data verification/review will be conducted according to the process outlined in the GSK Monitoring SOP.
- After completion of SDV activities, the CRA deletes all copies/images of participant data received from the site. This includes the deletion of the recycle bin and any temporary files.
- A statement confirming that all documents were destroyed will be provided by the CRA via email to the site.

- Details of what was monitored remotely will be documented in the appropriate section of the Monitoring Visit Report.

Option 2 – Review of Subject Source Documentation remotely

Process for use of Webcams, WebEx, MS Teams for viewing participant source remotely:

- The CRA ensures that the site personnel sharing information with GSK have authority to do so.
- Remote SDV activities will be performed exclusively by the assigned site monitor.
- Prior to conducting any remote SDV activities the CRA ensures that a written informed consent, covering the proposed SDV activities, has been signed by the study patient.
- For CRAs using GSK laptops, only use GSK approved video conferencing tools (e.g., MS Teams or GSK WebEx). Live image transmission is fully encrypted and protected for authorized user. By using these systems, it will be assured that data will be viewed only but not transmitted/stored.
- FSP/Local CRO CRAs not using GSK laptops, only MS Teams via Remote Access Application may be used for meetings between the CRA and the site. WebEx is not permitted from non-GSK laptops. Other tools like FaceTime, WhatsApp or Zoom are not permitted since they do not have sufficient encryption features. GSK does not have enterprise contract/privacy agreement with these providers.
- Prior to the remote monitoring visit, the CRA instructs study site on the specific data needed for the remote SDV.
- Source data verification will be conducted according to the process outlined in the Monitoring SOP.
- The use of a headset is required, do not use computer audio.
- The CRA does not capture screens or take pictures of screens to ensure we are not transferring content outside of clinical sites.
- WebEx or Teams do not store or have access to any data, GSK staff is not allowed to make or store any screenshots or save any data which has been shared.
- Details of what was monitored remotely will be documented in the appropriate section of the Monitoring Visit Report.
- In case of technical malfunctions or if the security of the transmission is no longer ensured, we will pause rSDV activities. GSK Issue Management Procedures will be initiated.

10.6.2. Japan

Regulatory and Ethical Considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27 March 1997)" and Pharmaceuticals and Medical Devices Act.

The statement "To assume responsibility for the proper conduct of the study at this site." on the Protocol Investigator Agreement Page means the investigator's responsibility defined by Japanese GCP.

GSK will submit the clinical trial notification to the regulatory authorities in accordance with Pharmaceuticals and Medical Devices Act before conclusion of any contract for the conduct of the study with study sites.

Study Period

Study Period is included in Exhibit 1.

Study Administrative Structure

Sponsor information is included in Exhibit 1. List of Medical Institutions and Investigators is included in Exhibit 2.

Unapproved Medical Device

If unapproved medical devices are used in the study, further details will be added in Exhibit 3. In case no unapproved medical devices are used, Exhibit 3 will not be attached.

10.7. Appendix 7: Abbreviations and glossary of terms

10.7.1. List of abbreviations (Amended: 25 May 2023)

AE:	Adverse event
AESI:	Adverse events of special interest
AF	***Atrial Fibrillation***
AIR:	At increased risk
ANCOVA:	Analysis of covariance
AS01$_B$:	Adjuvant system containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21)
AS01$_E$:	Adjuvant system containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)
CAD:	Coronary artery disease
CD:	Cluster of differentiation
CHF:	Chronic heart failure
CI:	Confidence interval
CIOMS:	Council for International Organizations of Medical Sciences
CKD:	Chronic kidney disease
CKD-EPI:	Chronic Kidney Disease Epidemiology Collaboration
CLS:	Clinical laboratory sciences
CMI:	Cell-mediated immunity
COPD:	Chronic obstructive pulmonary disease
COVID-19:	Coronavirus disease 2019
CRA:	Clinical research associate
CRDL:	Clinical research and development lead
CRO:	Contract research organization

CSR:	Clinical study report
DPI:	Dots per inch
eCRF:	Electronic case report form
EoS:	End of study
ES:	Exposed Set
EUA:	Emergency use authorization
FEV:	Forced expiratory volume
FSFV:	First subject first visit
FSH:	Follicle stimulating hormone
GCP:	Good Clinical Practice
GFR:	Glomerular filtration rate
GMT:	Geometric mean titer
GOLD:	Global Initiative for Chronic Obstructive Lung Disease
GSK:	GlaxoSmithKline Biologicals SA
HA:	Healthy adults
HIPAA:	Health Insurance Portability and Accountability Act
HRT:	Hormonal replacement therapy
IB:	Investigator's brochure
ICF:	Informed consent form
ICH:	International Council on Harmonization
ICMJE:	International Committee of Medical Journal Editors
ICS:	Intracellular cytokine staining
IDMC:	Independent data monitoring committee
IEC:	Independent Ethics Committee
IFN:	Interferon

IL:	Interleukin
IM:	Intramuscular
IRB:	Institutional Review Board
IRR:	Incidence rate ratio
LAR:	Legally acceptable representative
LML:	Local medical lead
LRTD:	Lower respiratory tract disease
LSLV:	Last subject last visit
MAtEx:	MATerial EXcellence
MDRD:	Modification of Diet in Renal Disease
MedDRA:	Medical Dictionary for Regulatory Activities
MET:	Metabolic equivalent of task
NI:	Non-inferiority
OA:	Older adults
PBMC:	Peripheral blood mononuclear cells
PCA:	Primary Completion Achieved
PDF:	Portable document format
pDiary:	Paper diary
pIMD:	Potential immune-mediated disease
PPS:	Per-Protocol Set
QS-21:	*Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
QTL:	Quality tolerance limit
RNA:	Ribonucleic acid
rSDV:	Remote source data verification

RSV:	Respiratory syncytial virus
SAE:	Serious adverse event
SAP:	Statistical analysis plan
SAS:	Statistical analysis system
SBIR:	Source data Base for Internet Randomization
SDV:	Source document verification
SoA:	Schedule of activities
SOP:	Standard operating procedure
SPM:	Study Procedures Manual
SRR:	Seroresponse rate
SRT:	Safety review team
SUSAR:	Suspected unexpected serious adverse reaction
TLS:	Transport layer security
TNF:	Tumor necrosis factor
US:	United States
VCSP:	Vaccines Clinical Safety and Pharmacovigilance
WOCBP:	Woman of childbearing potential
YOA:	Years of age

10.7.2. Glossary of terms (Amended: 25 May 2023)

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.
Adverse event of special interest	***An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.***
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an observer-blind study, the participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment. The study will be conducted in an observer-blind manner for Cohort 1 from study start-up to Day 31 analysis at Day 31, beyond which the study will be considered single-blind. This means that the investigator and/or his staff will be aware of the intervention assignment, but the participant will not. In an open-label study, no blind is used. Both the investigator and the participant know the identity of the

intervention assigned. The study will be conducted in an open-label manner for Cohort 2.

Caregiver:

A 'caregiver' is someone who

- lives in the close surroundings of a participant and has a continuous caring role or
- has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home).

In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol specified 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.

Certified copy:

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Current smoker:

A person who is currently smoking or who has stopped smoking within 6 months before study start.

Eligible:

Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.

Enrolled participant:

All participants who entered the study (who were randomized or received study intervention or underwent a post-screening procedure)

NOTE: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled Analysis Set as they did not enter the study.

Refer to the Section 9.2 for the definition of 'Enrolled Set' applicable to the study.

Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
eTrack:	GSK's tracking tool for clinical studies.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
Former smoker:	A person who stopped smoking for at least 6 months at the time of study start.
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:	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.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Invasive medical device:	An invasive medical device is a device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.
Investigational vaccine:	A pharmaceutical form of an active ingredient being tested in a clinical study, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonym: Investigational Medicinal Product
Investigator:	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified

	individual or party to perform those study-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
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical study was concluded according to the pre-specified protocol or was terminated.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Protocol amendment:	The ICH defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Screened participant	All participants who were screened for eligibility.
Self-contained study:	Study with objectives not linked to the data of another study.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified follow-up period following study intervention administration.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g. hospital records, clinical and office charts, laboratory

	notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, laboratories and at medico-technical departments involved in the clinical study).
Study intervention:	Any investigational or marketed product(s) or placebo intended to be administered to a participant during the study.
Study monitor:	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
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.

10.8. Appendix 8: Protocol Amendment history

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

DOCUMENT HISTORY	
Document	Date of Issue
Original Protocol	26 July 2022
Amendment 1	***25 May 2023***

Detailed description of the current Protocol amendment

Sponsor signatory	~~Mathieu Peeters, MD~~ ~~Clinical & Epidemiology Project Lead~~ ~~Vx Clinical Sciences~~ ***Veronica Hulstrøm, MD*** ***Clinical Project Lead*** ***RSV Older Adults***

Section 1.3. Schedule of Activities

Table 1: Schedule of activities (Safety Assessments)

Type of contact	Visit 1	Visit 2	Visit 3	Visit 4	Notes
Timepoint	**Day 1**	**Day 31**	**Month 6**	**Month 12**	
Safety assessments					
Distribute diary cards	○				A paper diary will be distributed to all study participants at Visit 1 (day of study intervention administration). All participants will record solicited events after study intervention administration and for 3 subsequent days (Days 1-4), unsolicited AEs, and concomitant medications/products after study intervention administration and for 29 subsequent days (Days 1-30). See Section 10.3.8
Return of diary cards		○			See Section 10.3.8
Record solicited administration site and systemic events (Days 1–4 post-study intervention administration)	●	●			See Section 10.3.8 and Table 11
Record unsolicited AEs (Days 1-30 post-study intervention administration) ***in the participants***[c]	●	●			See Section 10.3.8 and Table 11
Record concomitant medications/vaccinations	●	●	●	●	See Section 6.8
Record any intercurrent medical conditions	●	●	●	●	See Section 9.2.1 and Table 11
Record all SAEs and pIMDs[c]	●	●	●		See Section 10.3.8 and Table 11
Record AEs/SAEs leading to withdrawal from the study and pregnancies	●	●	●	●	See Section 10.3.8 and Table 11
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine	●	●	●	●	SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to administration of the study intervention) up to study end. See Section 10.3.8 and Table 11
Record SAEs and pIMDs related to study intervention administration and fatal SAEs[c]	●	●	●	●	SAEs and pIMDs related to study intervention administration and fatal SAEs should be collected after study intervention administration (Day 1) up to study end. See Section 10.3.8 and Table 11
Study Conclusion				●	See Section 4.4

Note: The double-line borders indicate the analyses which will be performed on all data (i.e., data that are as clean as possible) obtained up to this timepoints.

AE=Adverse event; ***AESI= Adverse event of specific interest;*** CMI=Cell-mediated immunity; COVID-19=Coronavirus disease 2019; eCRF=Electronic case report form; pIMD=Potential immune-mediated disease; SAE=Serious adverse event.

● 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

If deemed necessary by the investigator.

The blood sample and urine sample for pregnancy test should be taken on the same day, prior to study intervention administration. If the study intervention administration is delayed by any reason, in the event samples have been

taken, the samples will need to be collected again on the day of study intervention administration and the first blood sample will be destroyed.

Atrial fibrillation (AF) will be considered as AESI in this study and will be additionally reported in the AF follow-up questionnaire (electronic or paper) in eCRF. The collection of AF will be performed following the AE/SAE reporting periods. For AF that were reported before the implementation of this Protocol Amendment 1, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

Note: Visit 2, Visit 3 and Visit 4 should be done on site. Under special circumstances (e.g., pandemic), study visits can be done at home, or biological samples can be taken at a different location (see Section 8).

Section 2.3.1. Risk assessment

CCI

[redacted]

~~The vaccine candidate for OA contains the same RSV antigen as the RSV maternal candidate vaccine but it is combined with GSK's established AS01 adjuvant to boost the immune response in the older adult population.~~

~~The RSV OA vaccine trials in participants 60 YOA and older are closely monitored for safety with all available safety data reviewed internally. In addition, the Phase 3 RSV OA=ADJ-006 clinical study is monitored by an IDMC on an ongoing basis. The IDMC met most recently on 08 June 2022 and did not raise any concerns in the OA population. But the RSV OA vaccine has not been studied in pregnant women.~~

CCI

[redacted]

CCI

The vaccine candidate for older adults (OA) contains the same RSV antigen as the RSV maternal vaccine candidate but the RSV OA vaccine is combined with GSK's established AS01E adjuvant to boost the immune response in the OA population.

The RSV OA vaccine trials in participants >60 YoA are closely monitored for safety with all available safety data reviewed internally. In addition, the Phase 3 RSV OA=ADJ-006 clinical study is monitored by an IDMC on an ongoing basis. The IDMC has not raised any concern for safety in the OA 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 YOA and above. This age cut-off has been chosen since on the one hand there is a high unmet medical need in patients with chronic comorbidities and that as of 50 YOA there is a strong increase in the percentage of people with chronic comorbidities while on the other hand for women the incidence of spontaneous pregnancies is only about 4 in 100 000 women in this age group [Salihu, 2003]. 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.

Section 3. Objectives, endpoints, and estimands

Table 3. Study objectives, endpoints and estimands

Within the table, every instance of "neutralization ~~antibody~~ titers" has been changed to "neutralization titers".

Objectives	Endpoints and estimands
Primary*	
• To demonstrate the NI** of the humoral immune response in healthy participants 50-59 YOA compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• RSV-A neutralization antibody titers expressed as group GMT ratio (OA-RSV/Adults-HA-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration***. • RSV-A neutralization antibody titers expressed as group SRR difference (OA-RSV - Adults-HA-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration compared to baseline***.
• To demonstrate the NI** of the humoral immune response in healthy participants 50-59 YOA compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• RSV-B neutralization ~~antibody~~ titers expressed as group GMT ratio (OA-RSV/Adults-HA-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration***. • RSV-B neutralization ~~antibody~~ titers expressed as group SRR difference (OA-RSV - Adults-HA-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration compared to baseline***.
• To demonstrate the NI** of the humoral immune response in participants 50-59 YOA at increased risk of RSV-LRTD compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• RSV-A neutralization antibody titers expressed as group GMT ratio (OA-RSV/Adults-AIR-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration***. • RSV-A neutralization antibody titers expressed as group SRR difference (OA-RSV - Adults-AIR-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration compared to baseline***.
• To demonstrate the NI** of the humoral immune response in participants 50-59 YOA at increased risk of RSV-LRTD compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• RSV-B neutralization ~~antibody~~ titers expressed as group GMT ratio (OA-RSV/Adults-AIR-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration***. • RSV-B neutralization ~~antibody~~ titers expressed as group SRR difference (OA-RSV - Adults-AIR-RSV), 1 month after the RSVPreF3 OA investigational vaccine administration compared to baseline***.
Secondary - Safety	
• To evaluate the safety and reactogenicity after the RSVPreF3 OA investigational vaccine administration.	• Percentage of participants reporting each solicited administration site event with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days). • Percentage of participants reporting each solicited systemic event with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days). • Percentage of participants reporting unsolicited AEs within 30 days after study intervention administration (i.e., the day of study intervention administration and 29 subsequent days). • Percentage of participants reporting any SAEs and pIMDs after study intervention administration (Day 1) up to Month 6. • Percentage of participants reporting SAEs and pIMDs related to study intervention administration after study intervention administration (Day 1) up to study end (Month 12).

Objectives	Endpoints and estimands
	• Percentage of participants reporting any fatal SAEs after study intervention administration (Day 1) up to study end (Month 12).
Secondary - Immunogenicity	
• To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine until 12 months post-study intervention administration.	• RSV-A and RSV-B neutralization ~~antibody~~ titers expressed as GMT, at pre-study intervention administration, 1 month, 6 months and at 12 months after study intervention administration.
• To evaluate the CMI response after RSVPreF3 OA investigational vaccine administration until 12 months post-study intervention administration.	• CMI response expressed as group geometric mean of the frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least 1 cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17, at pre-study intervention administration, 1 month, 6 months and at 12 months after study intervention administration, in a subset of participants.
Tertiary *(Note that tertiary objectives, endpoints, and estimands are optional and might be assessed only if needed; therefore, not all testing might be performed and reported)*	
CCI [redacted]	

Section 4.3. Justification for dose

Based on the results up to 1 month post-Dose 2 from study RSV OA=ADJ-002, a single dose regimen (0.5 mL) and the formulation of 120 µg RSVPreF3/AS01$_E$ were selected for further evaluation in the Phase 3 clinical program. The RSV OA=ADJ-002 study was designed to assess the immunogenicity of a 2-dose AS01$_E$ adjuvanted or unadjuvanted RSVPreF3 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 COPD investigational vaccine~~, it was expected that immunological responses would reach higher levels 1 month post-Dose 2 as compared with 1 month post-Dose 1. However, the RSV OA=ADJ-002 results demonstrated that the second dose given 2 months after the first dose had no added value

in terms of humoral and/or cellular immune responses. The humoral response, both in terms of RSV A ~~neutralizing antibody~~ ***neutralization geometric mean titers (***GMTs***)*** and RSVPreF3***-binding*** IgG geometric mean concentrations, peaked 1 month after the first dose, and the second dose did not increase the levels observed after the 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~~ ***neutralization*** titers over at least 1 of the 30 µg and 60 µg formulations with the same adjuvant content or unadjuvanted. ***An increase in the RSVPreF3-binding IgG GMCs and fold increase over baseline was also observed with increase in antigen dose from 30 µg to 120 µg.*** The data demonstrated an immunologic benefit of any $AS01_E$ or $AS01_B$ formulations over unadjuvanted formulations in terms of frequency of RSVPreF3specific CD4+ T cells expressing at least 2 markers. Importantly, the CD4+ T cells frequencies induced by the AS01-containing formulations in OA were close or similar to the frequencies observed in young adults. This was not observed following the administration of 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, supported the selection of a 120 µg based formulation. The results also showed that all the AS01-adjuvanted formulations evaluated are considered to have a clinically acceptable safety profile. The AS01-adjuvanted formulation with the lowest reactogenicity profile, i.e., the $AS01_E$-based formulation, was selected. The immunological response observed after 1 vaccine dose of the $AS01_E$-based formulation is considered adequate for a RSVPreF3 OA candidate vaccine.

The RSVPreF3 OA investigational vaccine has not been given in its present form to adults 50-59 YOA.

Section 6.3.5.1. Emergency unblinding

GSK's Global Safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

Section 6.8 Concomitant therapy

- ***For all AF AESIs (including serious and non-serious), concomitant drugs which could be associated with development or worsening of AF must be reported in the AF follow-up questionnaire.***

Table 7. Timing of collection of concomitant medication to be recorded

	Dose 1 Day 1	**Day 30**	**Study conclusion (Visit 4 at Month 12)**
All concomitant medication including vaccines/products, except vitamins and dietary supplements			
All concomitant medication including products/vaccines leading to elimination from the analysis			
All concomitant medication including vaccines/products which may explain/cause/be used to treat an SAE/ pIMD/***AF****)			
Any prophylactic medication			

AF: Atrial Fibrillation; p***IMD***=Potential immune-mediated disease; SAE=Serious adverse event.
Note: The collection period for the concomitant medications to be recorded in eCRF is indicated in gray.
AESI= Adverse event of specific interest
**** For all AF AESIs (including serious and non-serious), concomitant drugs which could be associated with development or worsening of AF must be reported in the AF follow-up questionnaire.***

Section 8.1.2. Laboratory assays

Table 9. Laboratory assays

Assay type	**System**	**Component**	**Challenge**	**Method**	**Laboratory**
Humoral Immunity (Antibody determination)	Serum	RSV-A ~~antibody~~ ***neutralization***		Neutralization	GSK*
	Serum	RSV-B ~~antibody~~ ***neutralization***		Neutralization	GSK*
CMI	PBMC	CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17 secreting CD4+ and CD8+ T cells	Peptide pool covering RSVPreF3	ICS	GSK*

Section 8.1.3. Immunological read-outs

Table 10. Immunological read-outs

Blood sampling time point		**Subset name**	**No. of participants**	**Component**
Type of contact and time point	**Sampling time point**			
Humoral immunity (on serum samples)				
Visit 1 (Day 1)	Pre-Adm	All participants	~1520	RSV-A ~~neutralizing antibody~~ ***neutralization titer*** RSV-B ~~neutralizing antibody~~ ***neutralization titer***
Visit 2 (Day 31)	Day 31	All participants	~1520	RSV-A ~~neutralizing antibody~~ ***neutralization titer*** RSV-B ~~neutralizing antibody~~ ***neutralization titer***
Visit 3 (Month 6)	Month 6	All participants	~1520	RSV-A ~~neutralizing antibody~~ ***neutralization titer*** RSV-B ~~neutralizing antibody~~ ***neutralization titer***
Visit 4 (Month 12)	Month 12	All participants	~1520	RSV-A ~~neutralizing antibody~~ ***neutralization titer***

Blood sampling time point		Subset name	No. of participants	Component
Type of contact and time point	Sampling time point			
				RSV-B ~~neutralizing antibody~~ ***neutralization titer***
CMI (on PBMC samples)				
Visit 1 (Day 1)	Pre-Adm	CMI subset	~350	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells
Visit 2 (Day 31)	Day 31	CMI subset	~350	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells
Visit 3 (Month 6)	Month 6	CMI subset	~350	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells
Visit 4 (Month 12)	Month 12	CMI subset	~350	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells

Section 8.2.1.3. Medical history

A pre-defined list of current co-morbidities [Quan, 2011] to be recorded will be available in the eCRF ***(In addition to the chronic diseases listed in Section 5.1, additional information on rheumatologic diseases, hemiplegia and paraplegia will be collected).***

Section 8.3.1. Time period and frequency for collecting AE, SAE and other safety information

An overview of the protocol-required reporting periods for AEs, SAEs, and AESIs (including pIMDs and AF) is given in Table 11.

Table 11. Timeframes for collecting and reporting of safety information

	Pre-Adm* D1	Adm D1	Adm D4#	D30	6 months post-dose	Study conclusion 12 months post-dose
SAEs and pIMDs related to study intervention administration and fatal SAEs†						

† AF will be considered as AESI in this study and will be additionally reported in the AF follow-up questionnaire in eCRF.

AF reporting will follow the same reporting periods as for unsolicited AEs and SAEs. Non-serious AF with an onset during the 30-day period following study vaccine administration will be collected. The reporting of AF meeting SAE definition (serious AF) will be performed according to the SAE reporting period. Fatal AF and Serious AF judged as related to study vaccination will be reported according to the fatal SAE and related SAE reporting period, respectively. For AF that were reported before the implementation of this Protocol Amendment 1, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

Section 8.3.2. Method of detecting AEs and SAEs, pregnancies, and other events

Detection and recording of AEs/SAEs/***AESI (including*** pIMDs ***and AF)***/pregnancies are detailed in Section 10.3.8.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.9.

Open-ended and non-leading verbal questioning of participants is the preferred method of acquiring information related to an AE/SAE/***AESI (including*** pIMD***s and AF)***/pregnancy.

Section 8.3.3. Regulatory reporting requirements for SAEs, pregnancies, and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/***AESI (including*** pIMD***s and AF)***/pregnancy, it must be reported to GSK using the required documentation and within the timeframes mentioned in Table 12. This is essential for GSK to meet legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/***AESI (including*** pIMDs ***and AF)***, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.9.2.

Please refer to Section 10.3.10 for further details regarding the reporting of SAEs/***AESI (including*** pIMDs ***and AF)***/pregnancies.

Table 12. Timeframes for submitting SAEs, pregnancy and other events reports to GSK

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
Pregnancies	24 hours*	electronic pregnancy report	24 hours*	electronic pregnancy report
pIMDs	24 hours**, ‡‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Serious AF†	***24 hours****	***Electronic expedited AEs Report + AF follow-up questionnaire***	***24 hours****	***Electronic expedited AEs Report + AF follow-up questionnaire***

GSK=GlaxoSmithKline Biologicals SA; pIMD=Potential immune-mediated disease; SAE=Serious adverse event.
* 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.
‡‡ For each SAE/pIMD, the investigator(s) must document in the medical notes that they have reviewed the SAE/pIMD and have provided an assessment of causality.
† Only AF meeting SAE definition will be reported in electronic Expedited AE Report and in the specific AF follow-up questionnaire. Non-serious AF will be reported in the non-serious adverse event eCRF screen and in the AF follow-up questionnaire. For AF that were reported before the implementation of this Protocol Amendment 1, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

Section 8.3.3.1. Contact information for reporting SAEs, AESIs ***(including pIMDs and AF)*** and pregnancies

Table 13. Contact information for reporting SAEs, AESIs ***(including*** pIMDs ***and AF)*** and pregnancies

Study contact for questions regarding SAEs, *AESIs (including* pIMDs *and AF)*, pregnancies Refer to the local study contact information document
Back-up study contact for reporting SAEs, *AESI (including* pIMDs *and AF)*, pregnancies Available 24/24 hours and 7/7 days: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +32 2 656 51 16 or +32 2 656 80 09 Email address: ogm28723@gsk.com ~~(primary) and PV.ICSRManagement@gsk.com (in CC)~~ ~~Fax: 1 610 787 7053~~ US sites only: Fax: 1 610 787 7053 Canadian sites only: Fax: 1 866 903 4718

Section 8.3.4. Treatment of AEs

Any medication, vaccine or products administered for the treatment of an SAE/***pIMD*** should be recorded in the Expedited Adverse Event Report of the participant's ***eCRF*** **screen** (refer to Section 10.3.10.1). ***For the AF, this information will be captured in the Expedited Adverse Events Report and in the AF follow-up questionnaire in eCRF.***

Section 9.5. Sample size determination

- Individual RSV-A and RSV-B ~~neutralizing antibody~~ ***neutralization*** titers at baseline and at 1 month post-study intervention administration were modeled by a multivariate log-normal distribution, means and variance-covariance matrix based on historical data from other RSV OA vaccine clinical trials. The Adults-AIR-RSV Group was assumed to have the same multivariate log-normal distribution of the OA-RSV Group (i.e., same means and variance-covariance matrix), while the Adults-HA-RSV Group was assumed to have a 1.25-fold higher mean at 1 month post-study intervention administration for both ~~neutralizing antibodies~~ ***neutralization titers***.

Section 10.2. Appendix 2: Clinical laboratory tests

RSV-A and RSV-B neutralization assays

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

Virus neutralization is performed by incubating a fixed amount of RSV-A strain (Long, ATCC No. VR-26) or RSV-B strain (18537, ATCC No. VR-1580) with serial dilutions of the test serum. The serum-virus mixture is then transferred onto a monolayer of Vero cells (African Green Monkey, kidney, Cercopitheus aethiops, ATCC CCL 81) and incubated for 2 days to allow infection of the Vero cells by non-neutralized virus and the formation of plaques in the cell monolayer. Following a fixation step, RSV-infected cells are detected using a primary antibody directed against RSV (Polyclonal anti-RSV-A/B IgG) and a secondary antibody conjugated to horse-radish peroxidase, allowing the visualization of plaques after coloration with TrueBlue peroxidase substrate. Viral plaques are counted using an automated microscope coupled to an image analyzer (Scanlab system with a Reading software or equivalent). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at each serum dilution and the number of plaques in the virus control wells (no serum added). The serum ~~neutralizing antibody~~ ***neutralization*** titer is expressed in Estimated Dilution 60 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 [Barbas, 1992; Bates, 2014]. ***The ED60 neutralization titers will also be converted in concentration in International Units per milliliter (IU/mL).*** Secondary standards calibrated against the international reference (NIBSC 16/284) [McDonald, 2018; McDonald, 2020] are included in every run to allow conversion into international units per millimeters.

Section 10.3.5. ***Adverse events of special interest (***AESIs***)***

~~pIMDs are the only AESIs collected for this study.~~

Adverse events of special interest (AESIs) collected during this study include potential immune-mediated diseases (pIMDs) and Atrial Fibrillation (AF).

Section 10.3.5.1. ***Potential immune-mediated diseases*** (pIMDs)

Section 10.3.5.2. ***Atrial fibrillation (AF)***

AEs of AF are considered as AESI in this study.

When there is enough evidence to make the above diagnosis, the AE must be reported as AESI. Symptoms, signs or conditions which might (or might not) represent AF, should be recorded and reported as AEs but not as AESI until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

For each case of AF reported in the AE or SAE section in the eCRF, additional information will be collected in a specific 'AF follow-up questionnaire' eCRF screen.

Section 10.3.8. Recording and follow-up of AEs, SAEs, ***AESIs (including*** pIMDs ***and AF)*** and pregnancies

When an AE/SAE***/AESIs (including pIMDs and AF)*** occurs, it is the investigator's responsibility to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator will then record all relevant information regarding an AE/SAE***/AESIs (including pIMDs and AF)*** on the eCRF. The investigator may not send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF.

There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers will be blinded on copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event, based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE***/AESIs (including pIMDs and AF)*** instead of individual signs/symptoms.

Section 10.3.8.1. Time period for collecting and recording AEs, SAEs, ***AESIs (including*** pIMDs ***and AF)*** and pregnancies

All solicited administration site and systemic events with onset during the 4 days following administration of the study intervention, and all unsolicited AEs that occur during the 30 days following administration of the study intervention must be recorded into the appropriate section of the eCRF, irrespective of their intensity.

Non-serious AF with an onset during the 30-day period following study vaccine administration will be collected.

The time period for collecting and recording all SAEs and pIMDs will begin at the first receipt of study intervention and will end 6 months after study intervention administration. ***AF reporting will follow the same reporting periods as for AEs and SAEs (Table 11).***

All AEs/SAEs***/AESIs (including pIMDs and AF)*** leading to withdrawal from the study and pregnancies will be collected and recorded from the time of the first receipt of study intervention until the participant is discharged from the study. SAEs related to study participation or to a concurrent GSK medication/vaccine will be collected from the time consent is obtained until the participant is discharged from the study. All pIMDs related to study participation will be collected until study end.

Section 10.3.8.2. Follow-up of AEs, SAEs, ***AESIs (including*** pIMDs ***and AF)***, pregnancies or any other events of interest

After the initial AE/SAE/***AESI (including*** pIMD***s and AF)***/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, ***AESIs (including*** pIMDs ***and AF)*** (as defined in Section 10.3.5.1) will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Section 10.3.8.2.1. Follow-up during the study

AEs/***AESIs (including*** pIMDs ***and AF)*** 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.

Section 10.3.8.2.2. Follow-up after the participant is discharged from the study

The investigator will provide any new or updated relevant information to GSK on a previously reported SAE/pIMD using a paper/electronic Expedited Adverse Events Report and/or pregnancy report as applicable. ***For AF cases, the investigator will provide any new or updated relevant information on previously reported AF to GSK using a paper/electronic Expedited Adverse Events Report and the AF follow-up questionnaire 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.

Section 10.3.8.3. Updating of SAE, ***AESIs (including*** pIMD ***and AF***), and pregnancy information after removal of write access to the participant's eCRF

When additional SAE, ***AESI (including*** pIMD ***and AF),*** 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 the Study contact for reporting SAEs (refer to Section 8.3.3.1 or to GSK Global Safety department within the defined reporting timeframes specified in the Table 12).

Section 10.3.10. Reporting of SAEs, ***AESIs (including*** pIMDs ***and AF)***, pregnancies and other events

Section 10.3.10.1. Events requiring expedited reporting to GSK

Refer to the Table 12 for the details on timeframes for reporting of SAEs/***AESIs (including*** pIMDs ***and AF)***/pregnancies.

Section 10.7.1. List of abbreviations

AF	***Atrial Fibrillation***

Section 10.7.2. Glossary of terms

Adverse event of special interest	***An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.***

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