Protocol Amendment 1

Study ID: 218350

Official Title of Study: A Phase III, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of an RSVPreF3 OA investigational vaccine when co-administered with FLU aQIV (inactivated influenza vaccine – adjuvanted) in adults aged 65 years and above.

NCT number: NCT05568797

Date of Document: 16-Dec-2022

Clinical Study Protocol

Sponsor:
GlaxoSmithKline Biologicals SA (GSK)
Rue de l'Institut, 89
1330 Rixensart, Belgium

Primary study interventions and numbers	GlaxoSmithKline Biologicals SA (GSK)'s investigational respiratory syncytial virus (RSV) vaccine BIO RSV OA=ADJ (GSK3844766A)
Other study interventions	Seqirus, Inc.'s inactivated quadrivalent, adjuvanted influenza vaccine
eTrack study number and abbreviated title	218350 (RSV OA=ADJ-017)
EudraCT number	2022-000623-21
Date of protocol	Final: 24 March 2022
Date of protocol amendment	Amendment 1 Final: 13 December 2022
Title	A Phase III, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of an RSVPreF3 OA investigational vaccine when co-administered with FLU aQIV (inactivated influenza vaccine – adjuvanted) in adults aged 65 years and above.
Brief title	A study on the immune response and safety of a vaccine against respiratory syncytial virus (RSV) when given alone or co-administered with an adjuvanted vaccine against influenza in adults aged 65 years and above.

Based on GlaxoSmithKline Biologicals SA Protocol WS v17.2

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and abbreviated title	218350 (RSV OA=ADJ-017)
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Sponsor signatory	Mathieu Peeters, MD Clinical Project Lead RSV Older Adults
Signature	_____
Date	_____

Note: Not applicable if an alternative signature process (e.g., electronic signature or email approval) is used to get the sponsor approval.

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

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

eTrack study number and abbreviated title	218350 (RSV OA=ADJ-017)
EudraCT number	2022-000623-21
Date of protocol	Final: 24 March 2022
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Title	A Phase III, open-label, randomized, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of an RSVPreF3 OA investigational vaccine when co-administered with FLU aQIV (inactivated influenza vaccine – adjuvanted) in adults aged 65 years and above.
Investigator name	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA (GSK)
89, rue de l'Institut
1300 Rixensart, Belgium

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

This section is not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	13 December 2022
Original Protocol	24 March 2022

Type of Protocol Amendment	Numbering	Type of changes
Global	Amendment 1	New changes for all

Amendment 1 (13 December 2022)

This amendment is considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall rationale for Amendment 1:

The purpose of this amendment was to promote from secondary objective to primary objective the non-inferiority of RSV-B neutralizing antibody titers, as measured by GMT, when RSVPreF3 OA is co-administered with FLU aQIV, compared to RSVPreF3 OA alone. In addition, the SAE definition of anomalies in offspring was added, laboratory blinding procedures were updated, and minor editorial changes were made for clarity but are not included in this summary table.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Section 1.3; Table 2 (Schedule of Activities for the Control group)	Separation of study group allocation from intervention number allocation, which were both listed together in Visit 1.	To clarify that intervention number allocation takes place in both Visit 1 and Visit 2 and study group allocation takes place in Visit 1 only.
Section 3; Table 5 (Objectives, Endpoints and Estimands)	Promotion of RSV-B neutralizing antibody assessment to a primary endpoint/objective.	Updated as per recommendation by Center for Biologics Evaluation and Research (CBER).
Section 6.3.5 (Blinding and unblinding)	Laboratory blinding	To maintain study blinding during laboratory analysis as per recommendation by CBER.

Section # and title	Description of change	Brief rationale
Section 9.1: Statistical hypotheses; Table 18	RSV-B neutralizing antibody assessment was added to the primary endpoints in Table 18.	To align with the update of the primary objectives.
Section 9.2: Analysis set; Table 19	The Per Protocol set (PPS) was updated with participant eligibility criteria.	Section updated for clarity and in accordance with the statistical analysis plan (SAP).
Section 9.3.1: Primary endpoints/estimands analysis	To include the success Criteria of NI in terms of RSV-B neutralizing antibody.	In accordance with the update in the primary objectives.
Section 9.5: Sample size determination; Table 21	Update of sample size determination to reflect the addition of RSV-B neutralizing antibody as a primary endpoint.	In accordance with the update in the primary objectives.
Section 10.3.2 (Definition of an SAE)	Addition of an SAE criterion.	To update the definition of an SAE to include anomalies in the offspring of a study participant as per Medicines and Healthcare Products Regulatory Agency (MHRA) feedback.
Section 10.3.8.1; Table 26 (Assessment of intensity)	To correct protocol template error in the Intensity scales for solicited events.	Correction of “Fatigue” Grade 0 parameter From “Normal” to “None” in Table 26.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

GlaxoSmithKline Biologicals (GSK) is developing a new respiratory syncytial virus (RSV) PreFusion protein 3 (PreF3) Older Adult (OA) investigational vaccine (RSVPreF3 OA) against RSV-associated (subtypes A and B) disease in adults ≥60 years of age (YOA). The vaccine development is currently in Phase III, and immunogenicity, safety, and reactogenicity of the candidate vaccine when co-administered with other vaccines are being investigated.

The present study will assess the immunogenicity, safety and reactogenicity of the RSVPreF3 OA investigational vaccine when co-administered with the adjuvanted quadrivalent influenza vaccine, FLU aQIV, in adults aged ≥65 YOA. FLU aQIV (marketed as *Fluad Tetra, FLUAD QUADRIVALENT* and *Fluad Quad*) is an inactivated, adjuvanted influenza vaccine marketed by Seqirus, Inc., and contains 2 influenza A-like strains (H1N1 and H3N2) and 2 influenza B-like strains (one from the Yamagata lineage and one from the Victoria lineage). It is indicated for the active immunization of individuals ≥65 YOA against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

Previous studies with the RSVPreF3 OA candidate vaccine have assessed the immune response at 1 month after vaccination. CCI [redacted]

Objectives and endpoints: Refer to Table 5.

1.2. Schema

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

1.3. Schedule of Activities (SoA)

Study visits should preferably be done on site. If deemed necessary, study visits during the follow-up phases can be done at home or at the long-term care facility (LTCF), as per local regulation. CCI [redacted]

Table 1 Schedule of Activities for the Co-Ad group

Type of contact	Visit 1	Visit 2*	Contact 1	Notes
Timepoints	Day 1	Day 31	Month 6**	
Obtain informed consent	●			See Section 10.1.3 for details
Distribution of Participant card	○			See Section 8.3.5 for details
Check inclusion/exclusion criteria	●			See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Check with participant if he/she will appoint a caregiver and distribute caregiver information letter, when applicable	○	○		See Sections 4.1.3 and 10.1.3 for details
Baseline and demographic assessments				
Collect demographic data	●			See Section 8.2.1.1 for more information
Record medical and vaccination history	●			See Section 8.2.1.2 for more information
Perform history-directed physical examination	○			See Section 8.2.1.3 for more information
Laboratory assessment				
Blood sampling from all participants for antibody determination (~10 mL)	●***	●⇑		See Section 8.1.1 for more information
Study interventions				
Check contraindications, warnings and precautions to study intervention administration	○			See Sections 7.1.1 and 8.2.1.4 for more information
Check criteria for temporary delay for enrollment and study intervention administration	○			See Section 5.5 for more information
Randomization	●			See Section 6.3 for more information
Study group and intervention number allocation	○			See Section 6.3.2, 6.3.3 and 6.3.4 for more information
Record body temperature before study intervention administration#	●			The location for measuring temperature can be oral or axillary
Study intervention administration (RSVPreF3 OA investigational vaccine + FLU aQIV) (including 30-minute post-dosing observation)	●			See Section 6.1 for more information
Recording of administered study intervention number	●			

Type of contact Timepoints	Visit 1 Day 1	Visit 2* Day 31	Contact 1 Month 6**	Notes
Safety assessments				
Setup of eDiary	○			See Section 10.3.7 for more information
Training on use of eDiary	○			See Section 10.3.7 for more information
Recording of solicited events in eDiary (Days 1 - 7 post-dosing)	Δ			See Section 10.3.3 and 10.3.7 for more information
Recording of ongoing solicited events in eDiary if applicable (Days 8 - 30 post-dosing)	Δ			See Section 10.3.3 and 10.3.7 for more information
Review eDiary		○∫		See Section 10.3.7 for more information
Collect eDiary or assist participant to delete application		○		See Section 10.3.7 for more information
Recording of unsolicited AEs (Days 1 - 30 post-dosing)	●	●		See Sections 10.3.4 and 10.3.7 for more information
Recording of concomitant medications/vaccinations	●	●	●	See Section 6.8 for more information
Recording of intercurrent medical conditions	●	●	●	See Section 9.2.1 for more information
Recording of SAEs and pIMDs	●	●	●	See Section 10.3.7 for more information
Recording of AEs/SAEs leading to withdrawal from the study	●	●	●	See Section 10.3.7 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine§	●	●	●	See Section 10.3.7 for more information
Contact for safety follow-up			●	See Sections 8.2.2 and 10.3.7.2 for more information
Study conclusion			●	See Section 4.4 for more information

AE = adverse event; **Co-Ad** = co-administration; **eCRF** = electronic case report form; **pIMD** = potential immune-mediated disease; **RSVPreF3 OA** = respiratory syncytial virus PreFusion protein 3 older adult; **SAE** = serious adverse event

Note: The double-line borders indicate the analyses that will be performed on all data obtained up to these timepoints (refer to Section 9.4).

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

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

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

Grey is used to indicate a study procedure that is not applicable.

*Visit 2 should preferably be done on site. However, if deemed necessary, local regulations allow, and quality of study procedures is maintained, this study visit can be replaced by a home visit conducted by authorized staff. Any information from the participant required according to study procedures and not collected during the home visit can be obtained by means of a phone call conducted by the site staff.

**Six months after study interventions administration. For this contact, multiple formats (e.g., email, text message, fax, or phone call) can be proposed by the study site. Refer to Section 8.2.2.1 for more information.

***Sample collected at Day 1 will be used as baseline for RSV and FLU vaccination.

⇑Sample collected at Day 31 will be used for the post-vaccination RSV vaccine- and FLU vaccine-related testing.

#The route for measuring temperature can be oral or axillary. Fever is defined as temperature ≥38.0°C, regardless of the location of measurement.

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

§SAEs related to study participation or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to study vaccine administration) up to study end.

Table 2 Schedule of Activities for the Control group (Amended: 13 December 2022)

Type of contact	Visit 1	Visit 2	CCI	Visit 4*	Contact 1	Notes
Timepoints	**Day 1**	**Day 31**		**Day 61**	**Month 7****	
Obtain informed consent	●					See Section 10.1.3 for details
Distribution of Participant card	○					See Section 8.3.5 for details
Check inclusion/exclusion criteria	●					See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Check with participant if he/she will appoint a caregiver and distribute caregiver information letter, when applicable	○	○		○		See Sections 4.1.3 and 10.1.3 for details
Baseline and demographic assessments						
Collect demographic data	●					See Section 8.2.1.1 for more information
Record medical and vaccination history	●					See Section 8.2.1.2 for more information
Perform history-directed physical examination	○					See Section 8.2.1.3 for more information
Laboratory assessment						
Blood sampling from all participants for antibody determination (~10 mL)	●***	●⇑		●		See Section 8.1.1 for more information
Blood sampling for anti-RSV antibody determination, from subset (~10 mL)						See Section 8.1.1 for more information
CCI		●		●		See Section 8.1.1 for more information
Study interventions						
Check contraindications, warnings and precautions to study intervention administration	○	○				See Sections 7.1.1 and 8.2.1.4 for more information
Check criteria for temporary delay for enrollment and/or study intervention administration	○	○				See Section 5.5 for more information
Randomization	●					See Section 6.3 for more information
Study group allocation	○					See Section 6.3.2, 6.3.3 and 6.3.4 for more information
Intervention number allocation	○	○				***See Section 6.3.2, 6.3.3 and 6.3.4 for more information***
Record body temperature before study intervention administration#	●	●				The location for measuring temperature can be oral or axillary

Type of contact	Visit 1	Visit 2	CCI	Visit 4*	Contact 1	Notes
Timepoints	**Day 1**	**Day 31**		**Day 61**	**Month 7****	
Study intervention administration (FLU aQIV) (including 30-minute post-dosing observation)	●					See Section 6.1 for more information
Study intervention administration (RSVPreF3 OA investigational vaccine) (including 30-minute post-dosing observation)		●				See Section 6.1 for more information
Recording of administered study intervention number	●	●				
Safety assessments						
Setup of eDiary	○	○†				See Section 10.3.7 for more information
Training on use of eDiary	○	○‡				See Section 10.3.7 for more information
Recording of solicited events in eDiary (Days 1 - 7 post-dosing)	Δ	Δ				See Section 10.3.3 and 10.3.7 for more information
Recording of ongoing solicited events in eDiary if applicable (Days 8 - 30 post-dosing)	Δ	Δ				See Section 10.3.3 and 10.3.7 for more information
Review eDiary		○∫		○∫		See Section 10.3.7 for more information
Collect eDiary or assist participant to delete application				○		See Section 10.3.7 for more information
Recording of unsolicited AEs (Days 1 - 30 post-dosing)	●	●		●		See Sections 10.3.4 and 10.3.7 for more information
Recording of concomitant medications/vaccinations	●	●		●	●	See Section 6.8 for more information
Recording of intercurrent medical conditions	●	●		●	●	See Section 9.2.1 for more information
Recording of SAEs and pIMDs	●	●		●	●	See Section 10.3.7 for more information
Recording of AEs/SAEs leading to withdrawal from the study	●	●		●	●	See Section 10.3.7 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine§	●	●		●	●	See Section 10.3.7 for more information
Contact for safety follow-up					●	See Sections 8.2.2 and 10.3.7.2 for more information
Study conclusion					●	See Section 4.4 for more information

AE = adverse event; CCI ; **eCRF** = electronic case report form; **pIMD** = potential immune-mediated disease; **RSV** = respiratory syncytial virus; **SAE** = serious adverse event

Note: The double-line borders indicate the analyses that will be performed on all data obtained up to these timepoints (refer to Section 9.4).

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

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

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

Grey is used to indicate a study procedure that is not applicable.

CCI

*Visit 4 should preferably be done on site. However, if deemed necessary, local regulations allow, and quality of study procedures is maintained, this study visit can be replaced by a home visit conducted by authorized staff. Any information from the participant required according to study procedures and not collected during the home visit can be obtained by means of a phone call conducted by the site staff.

**Six months after study interventions administration. For this contact, multiple formats (e.g., email, text message, fax, or phone call) can be proposed by the study site. Refer to Section 8.2.2.1 for more information.

***Sample collected at Day 1 will be used as baseline for the FLU vaccination in the Control group.

⇑ Sample collected at Day 31 will be used for the post-vaccination FLU vaccine-related testing. This sample will also be used as baseline for the RSV vaccination in the Control group. Sample collected at Day 61 will be used for the post-vaccination RSV vaccine-related testing.

#The route for measuring temperature can be oral or axillary. Fever is defined as temperature ≥38.0°C, regardless of the location of measurement.

†Participants will be asked to bring back their eDiary at Visit 2 (Day 31) for the site to activate the second solicited symptom recording period.

‡Training on use of eDiary at Visit 2 (Day 31) only applicable if there is a change in eDiary audience (e.g., from participant to caregiver).

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

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

Table 3 Intervals between study visits (Co-Ad group)

Interval	Planned Visit Interval	Allowed Interval Range
Visit 1 (Day 1) → Visit 2 (Day 31)	30 days	30 – 37 days
Visit 1 (Day 1) → Contact 1 (Month 6)	180 days	180 – 210 days

Co-Ad = co-administration

Table 4 Intervals between study visits (Control group)

Interval	Planned Visit Interval	Allowed Interval Range
Visit 1 (Day 1) → Visit 2 (Day 31)	30 days	30 – 37 days
Visit 2 (Day 31) → Visit 3 (Day 45)	14 days	12 – 16 days
Visit 2 (Day 31) → Visit 4 (Day 61)	30 days	30 – 37 days
Visit 2 (Day 31) → Contact 1 (Month 7)	180 days	180 – 210 days

2. INTRODUCTION

2.1. Study rationale

GSK is developing a new respiratory syncytial virus (RSV) PreFusion protein 3 (PreF3) Older Adult (OA) investigational vaccine (RSVPreF3 OA) against RSV-associated (subtypes A and B) disease in adults ≥60 years of age (YOA). The vaccine development is currently in Phase III, and immunogenicity, safety, and reactogenicity of the candidate vaccine when co-administered with other vaccines are being investigated.

The present study will assess the immunogenicity, safety and reactogenicity of the RSVPreF3 OA investigational vaccine when co-administered with the adjuvanted quadrivalent influenza vaccine, FLU aQIV, in adults aged ≥65 YOA. FLU aQIV (marketed as *Fluad Tetra, FLUAD QUADRIVALENT* and *Fluad Quad*) is an inactivated, adjuvanted influenza vaccine marketed by Seqirus, Inc., and contains 2 influenza A-like strains (H1N1 and H3N2) and 2 influenza B-like strains (one from the Yamagata lineage and one from the Victoria lineage). It is indicated for the active immunization of individuals ≥65 YOA against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

Previous studies with the RSVPreF3 OA candidate vaccine have assessed the immune response at 1 month after vaccination. CCI [redacted]

2.2. Background

RSV is a ribonucleic acid (RNA) virus with 2 antigenically distinct subgroups, referred to as RSV A and RSV B [Borchers, 2013]. RSV is a highly contagious human pathogen that causes respiratory tract infections in individuals of all age groups. Symptomatic RSV re-infections are common and continue throughout adulthood [Simoes, 1999; Krilov, 2011]. These re-infections generally go undiagnosed because they manifest as common acute upper respiratory tract infections [Graham, 2011]. However, in more vulnerable

individuals (e.g., immunocompromised individuals or older adults), re-infections can also lead to severe disease.

In temperate climates, RSV predictably causes fall-winter epidemics [Noyola, 2008]. In (sub) tropical regions, viral activity is more endemic, and outbreaks are less temporally focused [Borchers, 2013].

According to the Centers for Disease Control and Prevention (CDC) [CDC, 2018], RSV leads to an average of 177 000 hospitalizations and 14 000 deaths among OA in the United States (US) each year. As the global population ages, the morbidity and mortality from respiratory infections appear to be steadily increasing [Binder, 2017]. In the US, the burden of the disease has been shown to be significant and data indicate that RSV is comparable to influenza (in an influenza-vaccinated population) in terms of number of infections, hospitalizations, and deaths. Based on epidemiological data collected prospectively in 2008-2010 in 14 countries worldwide (including North America, Europe, and East Asia), the average percentage of documented RSV infections in OA with influenza-like illness is 7.4%, with values between 0% and 17.1% across countries [Falsey, 2014].

Similarly, a recent worldwide systematic review and meta-analysis assessed the global burden of RSV-associated acute respiratory infection (ARI) in OA. The estimated number of RSV-ARI cases was found to be 1.5 million with an incidence of 6.7 cases/1000 person-years in industrialized countries. In 2015, approximately 1.5 million episodes of RSV-ARI occurred in OA in industrialized countries, and approximately 14.5% of these episodes involved a hospital admission [Nam, 2019].

To date, no licensed vaccine or prophylactic treatment is available for RSV. Currently available treatment for RSV infection is limited to supportive care. Natural infection is known to induce only partial protective immunity [Simoes, 1999; Krilov, 2011]. Therefore, re-infections occur frequently throughout an individual's lifetime, rendering the development of a long-lasting efficacious vaccine challenging. RSV re-infections in OA can result in severe RSV disease despite the presence of robust serum RSV neutralizing antibody (NAb) titers [Cherukuri, 2013].

Taking into consideration the pre-existing immunity and immunosenescence of the target population, the composition of GSK's new investigational vaccine (RSVPreF3 OA) has been built primarily to have the potential to boost/induce durable RSV neutralizing antibody responses and restore/elicit RSV-specific CD4+ T cell responses to specific RSV epitopes. GSK intends to develop this vaccine to protect OA against RSV-associated (subtypes A and B) lower respiratory tract infection (LRTI) during several seasons.

Please refer to the current Investigator's Brochure (IB) for information regarding pre-clinical and clinical studies of the RSVPreF3 OA investigational vaccine**.**

2.3. Benefit/Risk assessment

2.3.1. Risk Assessment

Detailed information about the known and expected benefits and risks and expected adverse events (AE) of the RSVPreF3 OA investigational vaccine can be found in the IB, and the development safety update report (DSUR).

Potential/Identified Risk	Mitigation Strategy
RSV 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.
Syncope and hypersensitivity reactions (including anaphylaxis).	All participants will remain under observation at the clinical center for at least 30 minutes after vaccination.
Study procedures	
IM vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, erythema/redness, and swelling.	As a mitigation strategy, physicians can implement the measures that they consider necessary.
Pain and bruising may occur at the site where blood is drawn.	As a mitigation strategy, physicians can implement the measures that they consider necessary.
Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle insertion.	Participants who mention experiencing previous episodes of fainting or dizziness before, during or after a blood draw, will remain under observation at the clinical center until deemed necessary by site personnel. Appropriate medical treatment must be readily available during this period

IM = intramuscular; **pIMD** = potential immune-mediated diseases; **RSV** = respiratory syncytial virus

For expected adverse reactions associated with FLU aQIV, please refer to the Summary of Product Characteristics (SmPC).

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

2.3.2. Benefit Assessment

The participants may not directly benefit from vaccination with the RSVPreF3 OA investigational vaccine because vaccine efficacy has not been established yet. Hence it is not known whether the RSVPreF3 OA investigational vaccine is effective in protecting against RSV disease.

An indirect benefit is that the information obtained in this study will aid the development of an RSV investigational vaccine, which is intended to prevent disease associated with RSV infection in OA.

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).

All participants will receive a seasonal FLU vaccine as part of the study. Participants may, therefore, have the benefit of being protected against circulating strains of influenza during the active influenza season.

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.

The benefits of FLU aQIV appear to outweigh its potential risks. The established favorable benefit-risk profile for FLU aQIV remains unchanged for the active immunization of individuals as of 65 YOA against influenza disease caused by influenza type A and type B viruses contained in the vaccine.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 5 Study objectives, endpoints and estimands (Amended: 13 December 2022)

Objectives	Endpoints and Estimands
Primary	
• To demonstrate the non-inferiority of the FLU vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to the FLU vaccine administered alone.	• HI antibody titers for each of the FLU vaccine strains expressed as group GMT ratio, one month after the FLU vaccine dose.
• To demonstrate the non-inferiority of the RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine compared to the RSVPreF3 OA investigational vaccine administered alone.	• RSV-A neutralization antibody titers expressed as group GMT ratio, one month after the RSVPreF3 OA investigational vaccine dose.
• ***To demonstrate the non-inferiority of the RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine compared to the RSVPreF3 OA investigational vaccine administered alone.***	• ***RSV-B neutralization antibody titers expressed as group GMT ratio, one month after the RSVPreF3 OA investigational vaccine dose.***
Secondary	
• To evaluate the non-inferiority of the FLU vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to the FLU vaccine administered alone.	• HI seroconversion status for each of the FLU vaccine strains expressed as SCR, one month after the FLU vaccine dose.
• To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine or administered alone.	• RSV-A neutralization antibody titers expressed as MGI at one month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralizing antibody titers expressed as MGI at one month after the RSVPreF3 OA investigational vaccine dose.
• To evaluate the humoral immune response to the FLU vaccine when co-administered with the	• HI antibody titers for each of the FLU vaccine strains expressed as GMT, at Day 1 and Day 31.

Objectives	Endpoints and Estimands
RSVPreF3 OA investigational vaccine or administered alone.	• HI seroconversion status for each of the FLU vaccine strains expressed as SCR, from Day 1 to Day 31. • HI seroprotection status for each of the FLU vaccine strains expressed as SPR, at Day 1 and Day 31. • HI antibody titers for each of the FLU vaccine strains expressed as MGI, one month after the FLU vaccine dose.
• To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and the FLU vaccine, co-administered or administered alone.	• Percentage of participants reporting each solicited event with onset within 7 days after vaccine administration (i.e., the day of vaccination and 6 subsequent days). • Percentage of participants reporting unsolicited AEs (pIMD, non-serious AE or serious AE) within 30 days after vaccine administration (i.e., the day of vaccination and 29 subsequent days). • Percentage of participants reporting SAEs after vaccine administration (Day 1) up to study end (6 months after last vaccination). • Percentage of participants reporting pIMDs after vaccine administration (Day 1) up to study end (6 months after last vaccination).
CCI [redacted]	

FLU vaccine refers to FLU aQIV

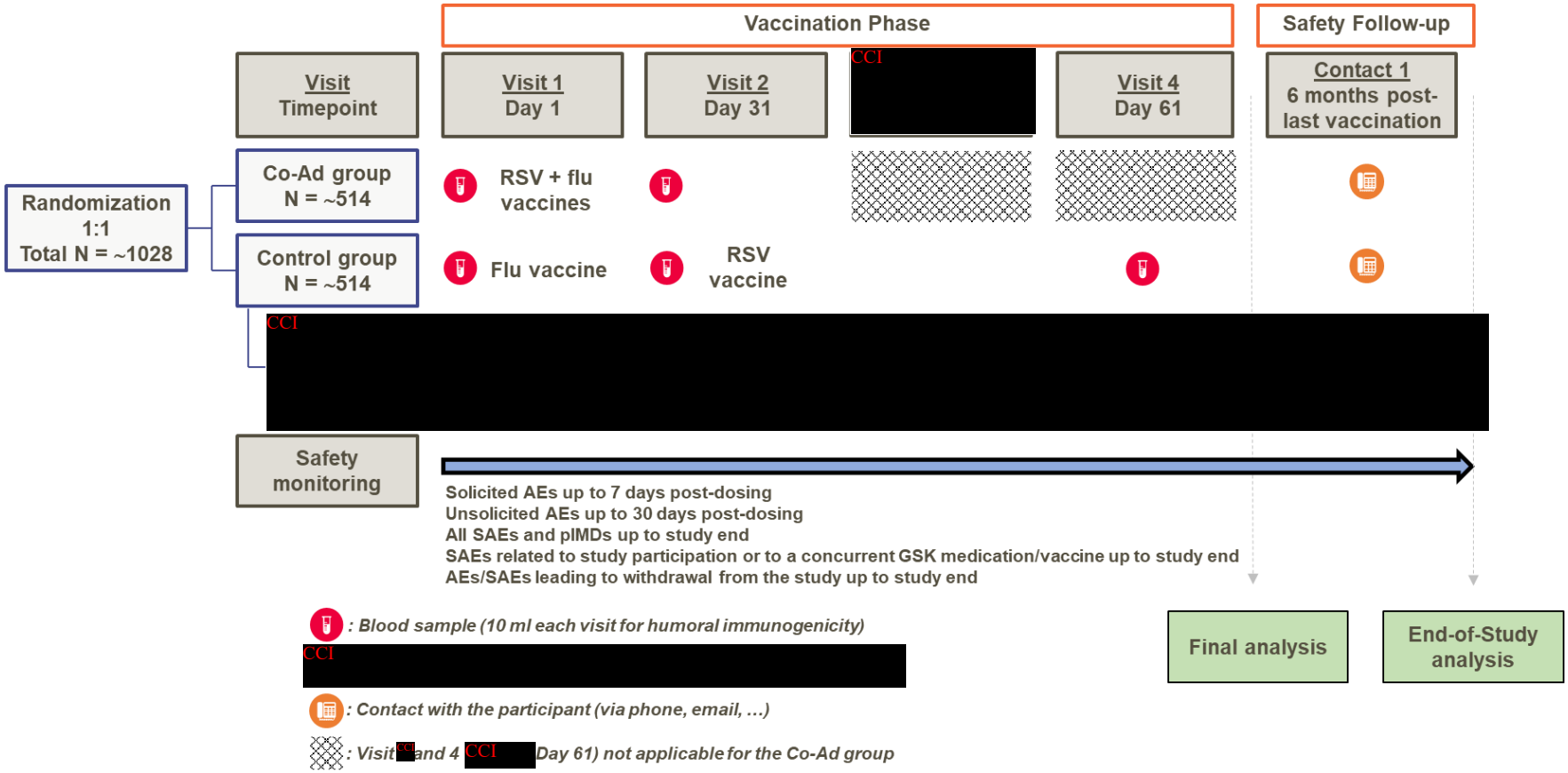
AE = adverse event; CCI [redacted]; **GMT** = geometric mean titer; **HI** = hemagglutination inhibition; **MGI** = mean geometric increase; **RSVPreF3 OA** = respiratory syncytial virus PreFusion protein 3 older adult; **SAE** = serious adverse event; **SCR** = seroconversion rate; **SPR** = seroprotection rate; **pIMD** = potential immune-mediated disease;
SCR = percentage of vaccinees who have either a HI pre-dose titer < 1:10 and a post-dose titer ≥1:40 or a pre-dose titer ≥1:10 and at least a 4-fold increase in post-dose titer.
SPR = percentage of vaccinees with a serum HI titer ≥1:40 that usually is accepted as indicating protection.
MGI = geometric mean of the within-participant ratios of the post-dose titer over the pre-dose titer.

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

4. STUDY DESIGN

4.1. Overall design

Figure 1 Study design overview



AE = adverse event; N = number of participants; pIMD = potential immune-mediated disease; RSV = respiratory syncytial virus; SAE = serious adverse event

- **Type of study**: self-contained.
- **Experimental design:** Phase III, randomized (ratio 1:1), open-label, multi-country study with 2 parallel groups (see Figure 1).
- **Study groups (refer to Figure 1 and Table 6 for an overview of the study groups):**
  - **Co-Ad (co-administration) group**: Participants receiving the RSVPreF3 OA investigational vaccine co-administered with FLU aQIV (referred to as FLU vaccine).
  - **Control group**: Participants receiving the FLU aQIV (referred to as FLU vaccine) and the RSVPreF3 OA investigational vaccine in a sequential manner.
- **Duration of the study**: ~6 months for participants in Co-Ad group; ~7 months for participants in Control group.
- **Primary completion date**: Day 61 (1 month after the RSVPreF3 OA investigational vaccine dose in Control group).
- **Control**: active comparator, i.e., sequential administration of licensed FLU vaccine and RSVPreF3 OA investigational vaccine.
- **Blinding**: open-label. Refer to Section 6.3.5 for details.
- **Data collection**: standardized electronic Case Report Form (eCRF). Solicited events will be collected using an electronic diary card (eDiary). Unsolicited AEs will be collected through questioning at study visits/contacts and reported into the eCRF. See Section 8.3.2 for details.
- **Safety monitoring:** the study will be conducted with oversight by the project Safety Review Team (SRT). Please refer to Section 10.1.5 for the SRT structure.
- **Vaccination schedule:**

Co-Ad group: Participants will be receiving both the RSVPreF3 OA investigational vaccine and FLU vaccine at Visit 1 (Day 1).

Control group: Participants will be receiving the FLU vaccine at Visit 1 (Day 1) and subsequently the RSVPreF3 OA investigational vaccine at Visit 2 (Day 31).

Table 6 Study groups and interventions

Study Groups	Number of Participants	Age (Min-Max)	Study Interventions
Co-Ad	~514	≥ 65 years	RSVPreF3 OA investigational vaccine
			FLU aQIV
Control	~514	≥ 65 years	RSVPreF3 OA investigational vaccine
			FLU aQIV

Co-Ad = co-administration; **RSVPreF3 OA** = respiratory syncytial virus PreFusion protein 3 older adult

4.1.1. Overview of the recruitment plan

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

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

The procedures for participants' identification/recruitment must be approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) together with the material intended for participants' identification/recruitment and participants use. Refer to the Study Procedures Manual (SPM) for additional details.

4.1.2. Enrollment rules

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

- Approximately 25% of participants 65-69 YOA, ~40% of participants 70-79 YOA and ~10% of participants ≥80 YOA. The remaining 25% can be distributed freely across the 3 age categories.
- Approximately 40% of participants from each sex; the remaining 20% can be distributed freely between the 2 sexes.

4.1.3. 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. However, every effort should be done to ensure that only one caregiver enters the data into the eDiary to allow for timely completion.

Caregivers may help the study participants to perform 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, should the caregiver evaluate the participant's health status while completing 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 subsequent study visit(s), the site staff should check again with the participant if he/she wishes to appoint a caregiver or if there were or will be changes in caregiver.

Please refer to the SPM for additional information on the appointment of a caregiver.

4.2. Scientific rationale for study design

The influenza season coincides with the RSV season in temperate countries. Influenza vaccination begins at the start of the flu season, at around the same time when the RSVPreF3 OA investigational vaccine may potentially be recommended for immunization against RSV infection. To date, there is no data available on the safety and immunogenicity of the RSVPreF3 OA investigational vaccine when it is co-administered with an adjuvanted influenza vaccine.

The current study is therefore designed to assess the immunogenicity, safety and reactogenicity of the RSVPreF3 OA investigational vaccine when it is co-administered with a FLU vaccine, compared to administration of the vaccines separately. There are 2 parallel arms:

- **Co-Ad group:** Participants will receive a single dose of RSV investigational vaccine and a single dose of FLU vaccine at Visit 1 (Day 1).
- **Control group**: Participants will receive a single dose of FLU vaccine at Visit 1 (Day 1), followed by a single dose of the RSV investigational vaccine at Visit 2 (Day 31).

The study will enroll older adults ≥ 65 YOA who are primarily responsible for self-care and activities of daily living. Participants may have one or more chronic medical conditions but should be medically stable according to the investigator.

As the RSVPreF3 OA investigational vaccine is adjuvanted, all participants will be followed up for safety for 6 months post-RSV investigational vaccine administration.

The 120 µg RSVPreF3/AS01$_E$ vaccine formulation was selected in a previous study (RSV OA=ADJ-002) where the vaccine was administered intramuscular (IM) according to a 0, 2-month vaccination schedule. Please refer to the IB for details.

4.3. Justification for dose

Based on the results up to 1-month post-Dose 2 from study RSV OA=ADJ-002, a single dose regimen (0.5 mL) and the 120 µg RSVPreF3/AS01$_E$ formulation were selected for further evaluation in the Phase III clinical program. The RSV OA=ADJ-002 study was designed to assess the immunogenicity of a 2-dose AS01-adjuvanted or unadjuvanted vaccine administered according to a 0-, 2-month schedule with the aim to maximize the immune response against RSV and vaccine efficacy over several seasons. Based on the data from clinical development programs for AS01-adjuvanted protein antigen vaccines in OA, such as *Shingrix* and the chronic obstructive pulmonary disease investigational

vaccine, it was expected that immunological responses would reach higher levels 1 month post-Dose 2 compared to 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 response. The humoral response, both in terms of RSV-A neutralizing antibody geometric mean titer (GMTs) and RSVPreF3 IgG geometric mean concentrations, peaked 1 month after the first dose, while the second dose did not increase the level 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 titers over at least one of the 30 µg and 60 µg formulations with the same adjuvant content or unadjuvanted. The data demonstrated an immunological benefit of any $AS01_E$ or $AS01_B$ formulations over unadjuvanted formulations in terms of frequency of RSVPreF3-specific CD4+ T cells expressing at least 2 markers among IL-2, CD40L, TNF-α, IFN-γ in vitro. Importantly, despite lower baseline levels of RSVPreF3-specific CD4+ T cells observed in OA, the AS01-containing formulations induced CD4+ T cells frequencies at a close or similar level than in young adults, which was not observed with the unadjuvanted formulations.

There was no safety concern detected in unadjuvanted groups to be linked to the RSVPreF3 antigen assessed for the first time in OA. The acceptable safety/reactogenicity profile in all 120 µg groups, together with the immunological benefit demonstrated for the 120 µg antigen dose, supports the selection of an 120 µg based formulation. The results also showed that all the AS01-adjuvanted formulations evaluated are considered to have a clinically acceptable safety profile. The AS01-adjuvanted formulation with the lowest reactogenicity profile, i.e., the $AS01_E$-based formulation, was selected. The immunological response observed after 1 vaccine dose of the $AS01_E$-based formulation is considered adequate for a RSVPreF3 OA candidate vaccine.

In the current study, the FLU vaccine will be administered as a single dose (recommended standard of care).

4.4. End of Study definition

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

End of Study (EoS): Last subject last visit (LSLV) (contact at 6 months post-last dose).

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 and 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 electronic diary cards [eDiaries], return for follow-up visits, ability to access and utilize a phone or other electronic communications).

  Note: In case of physical incapacity that would preclude the self-completion of the eDiaries, either site staff can assist the participant (for activities performed during site visits) or the participant may assign a caregiver (refer to Glossary of terms for the definition of 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.*
- A male or female ≥ 65 YOA at the time of the first study intervention administration.
- 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.
- Written or witnessed informed consent obtained from the participant prior to performance of any study-specific procedure.
- Participants who are medically stable in the opinion of the investigator at the time of first study intervention administration. Participants with chronic stable medical conditions with or without specific treatment, such as diabetes, hypertension or cardiac disease, are allowed to participate in this study if considered by the investigator as medically stable.

5.2. Exclusion criteria

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

5.2.1. Medical conditions

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

- Guillain-Barré syndrome (GBS) that occurred within 6 weeks of receipt of prior influenza vaccine.
- Serious or unstable chronic illness.
- Any history of dementia or any medical condition that moderately or severely impairs cognition.

  Note: If deemed necessary for clinical evaluation, the investigator can use tools such as Mini-Mental State Examination (MMSE), Mini-Cog or Montreal Cognitive Assessment (MoCA) to determine cognition levels of the participant.
- Recurrent or uncontrolled neurological disorders or seizures. Participants with medically-controlled 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 eDiaries, attend regular phone calls/study site visits).
- Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival up to study end).
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study interventions during the period beginning 30 days before the first dose of study interventions, or planned use during the study period.
- Administration of an influenza vaccine during the 6 months preceding the study FLU vaccine administration.
- Planned or actual administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first study intervention administration and ending 30 days after the last study intervention administration. In the case of COVID-19 vaccines, this time window can be decreased to 14 days before and after each study intervention administration provided this COVID-19 vaccine use is in line with local governmental recommendations.

  Note: In case an emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organized by the public health authorities outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine, provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly.
- Previous vaccination with an RSV vaccine.
- Administration of long-acting immune-modifying drugs or planned administration at any time during the study period (e.g., infliximab).

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

5.2.3. Prior/Concurrent clinical study experience

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

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

5.2.4. Other exclusions

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

5.3. Lifestyle considerations

This section is not applicable.

5.4. Screening failures

This section is not applicable.

5.5. Criteria for temporarily delaying enrollment/study intervention administration

Enrollment/randomization/study intervention administration may be postponed within the permitted time interval until transient conditions cited below are resolved:

- Acute disease and/or fever at the time of study intervention administration. Refer to Section 1.3 (SoA) 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 dosed at the discretion of the investigator.
- Participants with symptoms suggestive of active Coronavirus Disease 2019 (COVID-19) infection (e.g., fever, cough, etc.). The return of the participant to the site will follow the specific guidance from local public health and other competent authorities (e.g., free of symptoms, COVID-19 negative testing, etc.).
- Participants with known COVID-19 positive contacts may be vaccinated at least 14 days after the exposure, provided that the participant remains symptom-free, and at the discretion of the investigator.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

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

6.1. Study interventions administered

Table 7 Study interventions administered

Study Intervention Name:	**RSVPreF3 OA Investigational Vaccine**		**FLU aQIV (adjuvanted quadrivalent influenza vaccine)****
Formulation:	RSVPreF3 (120 µg)	$AS01_E$: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injections	A/(H1N1) (15 µg HA)***; A/(H3N2) (15 µg HA)***; B/(Victoria Lineage) (15 µg HA)***; B/(Yamagata Lineage) (µg HA)***; adjuvanted with MF59C.1 (Squalene (9.75 mg), Polysorbate 80 (1.175 mg), Sorbitan trioleate (1.175 mg)); Water for injections
Presentation:	Vial; powder for suspension for injection	Vial; suspension for suspension for injection	Syringe: Suspension for injection
Product category:	Biologic		Biologic
Route of administration:	Intramuscular		Intramuscular
Administration site:			
Location	Deltoid		Deltoid
Directionality	Upper		Upper
Laterality	Non-dominant		Co-Ad group: Dominant Control group: Non-dominant
No of Doses:	1		1
Dose Volume⇑:	0.5 mL		0.5 mL
Packaging, labeling & TM:	Refer to the SPM for more details		
Manufacturer:	GSK		Seqirus, Inc.

$AS01_E$ = Adjuvant System 01; **Co-Ad** = co-administration; **HA** = Hemagglutinin; **MPL** = monophosphoryl lipid A; **QS-21** = *Quillaja saponaria* Molina, fraction 21; **RSVPreF3 OA** = respiratory syncytial virus PreFusion protein 3 older adult; **SPM** = Study Procedures Manual

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

**FLU aQIV (adjuvanted quadrivalent influenza vaccine) is marketed by Seqirus as *Fluad Tetra, FLUAD QUADRIVALENT* and *Fluad Quad*

***The vaccine strains recommended by the World Health Organization for the 2022/2023 northern hemisphere influenza season are: an A/Victoria/2570/2019 (H1N1)pdm09-like virus, an A/Darwin/9/2021 (H3N2)-like virus, a B/Austria/1359417/2021 (B/Victoria lineage)-like virus and a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

⇑ Refer to the Study Procedures Manual for the volume after reconstitution.

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

6.2. Preparation, handling, storage, and accountability

The study interventions 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.

Only authorized study personnel should be allowed access to the study interventions. 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 interventions.

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

Approximately 1028 eligible participants will be randomly (1:1) assigned to the 2 study groups using a centralized randomization system on internet (Source data Base for Internet Randomization [SBIR]) at Visit 1 (Day 1).

The randomization of supplies within blocks will be performed at GSK, using MATerial Excellence (MatEx), a program developed for use in Statistical Analysis System (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 thus to 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 randomization algorithm will use a minimization procedure accounting for age (65-69, 70-79 or ≥80 years) and center. Minimization factors will have equal weight in the minimization algorithm. Refer to Section 4.1.2 for 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

first dose. The study intervention numbers to be used for subsequent dosing will be provided by the same automated Internet-based system (SBIR).

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 assay subset

The assay subset included in this study is described in Table 8.

Table 8 Allocation of participants to assay subset

CCI [redacted]
CCI [redacted]; **RSV** = respiratory syncytial virus
CCI [redacted]

6.3.5. Blinding and unblinding (Amended: 13 December 2022)

This is an open-label study because of the difference in dosing schedules between the study groups. Codes will be used to link the participant and study to each sample. ***The laboratory in charge of the serum sample testing will be blinded to the intervention assignment. Codes will be used to link the participant and study (without any link to the intervention attributed to the participant) to each serum sample***. CCI [redacted]

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 each study intervention dose will be recorded in the source documents.

6.5. Dose modification

This section is not applicable.

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

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

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

6.7. Treatment of overdose

This section is not applicable.

6.8. Concomitant therapy

At each study visit/contact, the investigator or his/her delegate 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 medications and vaccinations, except vitamins and dietary supplements, administered during the 30-day period following each dose of study intervention.
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines. Please refer to the Sections 5.2.2 and 9.2.1 for further details.
- All concomitant medication which may explain/cause/be used to treat a serious adverse event (SAE)/pIMD including vaccines/products, as defined in Sections 8.3.1 and 10.3.7. These must also be recorded in the Expedited Adverse Event report.
- Any prophylactic medication (e.g., analgesics, antipyretics) administered on the day of study vaccination (Day 1 in the Co-Ad group, Day 1 and Day 31 in the Control group) in the absence of ANY symptom and in anticipation of a reaction to the vaccination.

Refer to Table 9 (Co-Ad group) and Table 10 (Control group) for an overview of the reporting timeframe for concomitant medication during the study.

The Local Medical Lead (LML) should be contacted if there are any questions regarding concomitant or prior therapy.

Table 9 Reporting timeframe for concomitant medication for the Co-Ad group

	Visit 1		Visit 2	Contact 1
	Day 1	Day 30	Day 31	Month 6
All concomitant medications and vaccinations, except vitamins and dietary supplements				
All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines				
All concomitant medication which may explain/cause/be used to treat a serious adverse event (SAE)/pIMD including vaccines/products				
Any prophylactic medication				

shading indicates applicable timeframe for reporting of concomitant medication

Co-Ad = co-administration

Table 10 Reporting timeframe for concomitant medication for the Control Group

Event	Visit 1		Visit 2	CCI		Visit 4	Contact 1
	Day 1	Day 30	Day 31		Day 60	Day 61	Month 7
All concomitant medications and vaccinations, except vitamins and dietary supplements							
All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines							
All concomitant medication which may explain/cause/be used to treat a serious adverse event (SAE)/pIMD including vaccines/products							
Any prophylactic medication							

shading indicates applicable timeframe for reporting of concomitant medication

CCI [redacted]

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

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

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

- AE requiring expedited reporting to GSK.
- Unsolicited non-serious AE.
- Solicited AE.
- Not willing to be vaccinated.
- Other (specify).

7.1.1. Contraindications to subsequent study intervention(s) administration

The eligibility of participants in the Control group for subsequent study intervention administration must be confirmed before administering the RSV investigational vaccine at Visit 2.

Participants who meet any of the criteria listed below or criteria listed in Sections 5.2.1 and 5.2.2 should not receive additional doses of study intervention. Such participants should be encouraged to continue other study procedures, at the investigator's discretion (Section 10.3.7.2). All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to study intervention (FLU vaccine administered at Visit 1) and that, in the opinion of the investigator, may pose additional risk to the participant if he/she receives the second study intervention (RSV investigational vaccine).
- Participants who develop any new condition that, in the opinion of the investigator, may pose additional risk to the participant if he/she continues to participate in the study.
- Anaphylaxis following the administration of study intervention(s) from Visit 1 onwards.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.

7.2. Participant discontinuation/withdrawal from the study

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

From an analysis perspective, a study 'withdrawal' refers to any participant who 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:

- AE requiring expedited reporting to GSK. Please refer to the section 10.3.9.1 for the details.
- Unsolicited non-serious AE.
- 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 he/she has withdrawn consent and the reason for withdrawal was provided, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.7.2).

7.3. Lost to follow-up

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

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 the participant(s) should discontinue the study intervention.

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

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

If local regulations allow and quality of study procedures is maintained, participants can be offered remote visits (e.g., telemedicine, home visits) for the collection of biological samples and/or safety data/safety assessment(s). These remote visits must be performed by qualified study staff/healthcare professionals (HCPs). Refer to the SoA (Section 1.3) for the timing of these visits. Details of how these visits will be conducted are outlined in the SPM.

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

- Safety follow-up may be performed by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application (or eDiary) as a way of communicating with the participant and monitoring the participant's progress. In addition, qualified study staff/HCPs may also identify AEs and report them to the investigator for evaluation.
- Biological samples may be collected remotely by qualified study staff/HCPs. Biological samples should be collected only if they can be processed in a timely manner and appropriately stored until the intended use. CCI [redacted]
- In exceptional situations (e.g., pandemic), the following approach may be considered:
  - If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Table 3 and Table 4), additional 30 days may be added to the Visit 2 interval (only for RSV investigational vaccine administration in the Control group).

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

For information on the role of a caregiver in study assessments and procedures, please refer to Section 4.1.3.

8.1. Immunogenicity assessments

Biological samples will be used for research planned in the protocol and for purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol.

Findings in this or future studies may make it desirable to use samples acquired in this study for research not planned in this protocol. In this case, all participants in countries where this is allowed will be asked to give consent to allow GSK or a contracted partner to use the samples for further research. The further research will be subject to prior IEC/IRB approval, if required by local legislation.

Information on further research and its rationale can be obtained from GSK.

Sample testing will be done in accordance with the recorded consent of the individual participant.

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 the participant's consent. These additional requirements must be formally communicated to, discussed, and agreed with GSK.

8.1.1. Biological samples

Table 11 Biological samples

Sample type	Quantity	Unit	Timepoint	Group*
Blood for humoral response	~10	mL	Visit 1 (Day 1) Visit 2 (Day 31)	All participants in the Co-Ad group
Blood for humoral response	~10	mL	Visit 1 (Day 1) Visit 2 (Day 31) Visit 4 (Day 61)	All participants in the Control group
CCI [redacted]				
CCI [redacted]				

CCI [redacted]; **Co-Ad** = co-administration; **HI** = hemagglutination inhibition; **RSV** = respiratory syncytial virus

*Refer to Section 6.3.4 for subset description.

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

- Co-Ad group: 2 x ~10 mL = ~20 mL.
- Control group: 3 x ~10 mL = ~30 mL.
- CCI [redacted]

8.1.2. Laboratory assays

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

Table 12 Laboratory assays

Assay type	System	Component	Challenge	Method	Laboratory
Humoral immunity (antibody determination)	Serum	RSV-A antibody		Neutralization	GSK*
		RSV-B antibody		Neutralization	
		H1N1 strain equivalent to vaccine strain (hemagglutinin antibody)		HI	
		H3N2 strain equivalent to vaccine strain (hemagglutinin antibody)			
		B/Yamagata strain equivalent to vaccine strain (hemagglutinin antibody)			
		B/Victoria strain equivalent to vaccine strain (Hemagglutinin antibody)			
CCI [redacted]					

HI = hemagglutination inhibition; **ICS** = intracellular cytokine staining; CCI [redacted]; **RSV** = respiratory syncytial virus

*GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. CLS may delegate testing to a contracted third party.

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

Table 13 Immunological read-outs

Blood sampling timepoint		Subset tested	N of participants	Component
Type of contact and timepoint	Sampling timepoint			
Humoral immunity (on serum samples)				
Co-Ad group				
Visit 1 (Day 1)	Pre-dose 1	All participants	~514	RSV-A neutralizing antibody
		All participants	~514	RSV-B neutralizing antibody
		All participants	~514	H1N1 strain equivalent to vaccine strain (Hemagglutinin antibody)
		All participants	~514	H3N2 strain equivalent to vaccine strain (Hemagglutinin antibody)
		All participants	~514	B/Yamagata strain equivalent to vaccine strain (Hemagglutinin antibody)
		All participants	~514	B/Victoria strain equivalent to vaccine strain (Hemagglutinin antibody)
Visit 2 (Day 31)	Post-dose 1	All participants	~514	RSV-A neutralizing antibody
		All participants	~514	RSV-B neutralizing antibody
		All participants	~514	H1N1 strain equivalent to vaccine strain (Hemagglutinin antibody)
		All participants	~514	H3N2 strain equivalent to vaccine strain (Hemagglutinin antibody)
		All participants	~514	B/Yamagata strain equivalent to vaccine strain (Hemagglutinin antibody)
		All participants	~514	B/Victoria strain equivalent to vaccine strain (Hemagglutinin antibody)
Control group				
Visit 1 (Day 1)	Pre-FLU dose	All participants	~514	H1N1 strain equivalent to vaccine strain (Hemagglutinin antibody)
		All participants	~514	H3N2 strain equivalent to vaccine strain (Hemagglutinin antibody)
		All participants	~514	B/Yamagata strain equivalent to vaccine strain (Hemagglutinin antibody)
		All participants	~514	B/Victoria strain equivalent to vaccine strain (Hemagglutinin antibody)
Visit 2 (Day 31)	Post-FLU dose	All participants	~514	H1N1 strain equivalent to vaccine strain (Hemagglutinin antibody)
		All participants	~514	H3N2 strain equivalent to vaccine strain (Hemagglutinin antibody)
		All participants	~514	B/Yamagata strain equivalent to vaccine strain (Hemagglutinin antibody)
		All participants	~514	B/Victoria strain equivalent to vaccine strain (Hemagglutinin antibody)
	Pre-RSV dose	All participants	~514	RSV-A neutralizing antibody
		All participants	~514	RSV-B neutralizing antibody
CCI [redacted]				
Visit 4 (Day 61)	Post-RSV dose	All participants	~514	RSV-A neutralizing antibody
		All participants	~514	RSV-B neutralizing antibody

Blood sampling timepoint		Subset tested	N of participants	Component
Type of contact and timepoint	Sampling timepoint			
CCI [redacted]				

Co-Ad = co-administration; **N** = number; CCI [redacted]; **RSV** = respiratory syncytial virus; Immunological correlates of protection

8.1.4. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated for the antigens used in the RSVPreF3 OA investigational vaccine or the FLU vaccine.

Although there is no accepted correlate of protection against influenza, either seasonal or pandemic, the protective role of antibodies against hemagglutinin is well established [Rimmelzwaan, 2008; Cox, 2013]. The serum hemagglutination inhibition (HI) assay is commonly used to measure the humoral response to hemagglutinin. HI titers have been shown to correlate with protection from infection in human studies and titers of 1:40 or greater have been accepted as a surrogate marker of potential vaccine efficacy by regulators [Hannoun, 2004; EMEA, 1997; FDA, 2007].

8.2. Safety assessments

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

8.2.1. Pre-intervention administration procedures

8.2.1.1. Collection of demographic data

Record demographic data such as year of birth, sex, race* and ethnicity* in the participant's eCRF.

*Differences in the safety and efficacy of certain medical products, including vaccines [Borchers, 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. Medical/vaccination history

Obtain the participant's medical/vaccination 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 study intervention in the eCRF.

Any vaccine administered up to 1 year before study vaccine administration should be recorded in the eCRF with date of vaccination. Any flu vaccine administered up to 3 years before study intervention should be recorded with the date of vaccination and information about the vaccine formulation (e.g., adjuvanted or non-adjuvanted or high dose).

8.2.1.3. History-directed physical examination/physical examination

- History-directed physical examination will be performed for each participant.
- 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 Section 5.5 for the list of criteria for temporary delay of study intervention administration.
- Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health-care provider.

8.2.1.4. Warnings and precautions to administration of study intervention

Warnings and precautions to administration of study intervention must be checked at each visit with planned administration of study intervention.

8.2.1.5. Pre-vaccination body temperature

The body temperature of each participant needs to be measured prior to any study intervention administration and recorded in the eCRF. The route for measuring temperature can be oral or axillary. If the participant has fever (fever is defined as temperature ≥38.0°C regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (refer to Table 3 and Table 4).

8.2.2. Post-vaccination procedures

8.2.2.1. Safety contact at 6 months post-last vaccination

Six months after the last dose of study intervention (i.e., Month 6 for participants in the Co-Ad group and Month 7 for participants of the Control group), each participant should be contacted to check if he/she has experienced any SAEs or pIMDs since the last study

intervention administration, and to collect information on concomitant medications/vaccinations.

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

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

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

8.3. AEs, SAEs and other safety reporting

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

An overview of the protocol required reporting periods for AE, SAEs and pIMDs is given in Table 14 (Co-Ad group) and Table 15 (Control group).

Table 14 Timeframes for collection and reporting of safety information for the Co-Ad group

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

AE = adverse event; **Co-Ad** = co-administration; **pIMD** = potential immune-mediated disease; **SAE** = serious adverse event; **Vacc.** = vaccination

shading indicates applicable timeframe for reporting of safety information.

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

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

**Six months after study interventions co-administration.

Table 15 Timeframes for collection and reporting of safety information for the Control group

Event	Visit 1	Visit 1			Visit 2		CCI		Visit 4	Contact 1
	Day 1	Day 1	Day 7	Day 30	Day 31	Day 37		Day 60	Day 61	Month 7***
	Pre-Dose*	FLU vacc.			RSV vacc.					Study Conclusion
Administration site and systemic solicited events (eDiary)										
Unsolicited AEs										
All SAEs										
All pIMDs										
SAEs related to study participation or concurrent GSK medication/vaccine										
AEs/SAEs leading to withdrawal from the study										
Intercurrent medical conditions										

Vacc. = vaccination; **AE** = adverse event; **SAE** = serious adverse event; **pIMD** = potential immune-mediated disease

shading indicates applicable timeframe for reporting of safety information.

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

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

CCI [redacted]

***Six months after study interventions co-administration.

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 10.3.9. 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 14. 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 he/she 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 17.

8.3.2. Method of detecting AEs and SAEs and other events

Detection and recording of AE/SAE/pIMD are detailed in Section 10.3.7.

Assessment of AE/SAE intensity, causality and outcome are described in Section 10.3.8.

Open-ended and non-leading verbal questioning of participants is the preferred method of acquiring information related to an AE/SAE/pIMD.

8.3.3. Regulatory reporting requirements for SAEs and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/pIMD, it must be reported to GSK using the required documentation, and within the timeframes mentioned in Table 16. This is essential for meeting GSK legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/pIMDs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.8.2.

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

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, IEC/IRB and investigators.

Please refer to Section 10.3.9 for further details regarding the reporting of SAEs/pIMDs.

Table 16 Timeframes for submitting SAE 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 AE Report	24 hours*	electronic Expedited AE Report
pIMDs	24 hours**, ⌗	electronic Expedited AE Report	24 hours*	electronic Expedited AE Report

SAE = serious adverse event; **pIMD** = potential immune-mediated disease; **AE** = 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.
⌗ The investigator will be required to confirm review of the SAE/pIMD causality within 72 hours of submission of the SAE/pIMD.

8.3.3.1. Contact information for reporting SAEs and pIMDs

Table 17 Contact information for reporting SAEs and pIMDs

Study contact for questions regarding SAEs and pIMDs Refer to the local study contact information document
Back up study contact for reporting SAEs and pIMDs Available 24/24 hours and 7/7 days: **GSK Clinical Safety & Pharmacovigilance** Outside US sites: CCI [redacted] US sites only: CCI [redacted]

8.3.4. Treatment of AE

Any medication administered for the treatment of an SAE/pIMD should be recorded in the Expedited AE Report of the participant's eCRF screen (refer to Section 10.3.9.1).

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 his/her possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/care giver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator or his/her back up.

8.4. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.5. Genetics

Genetics are not evaluated in the current study.

8.6. Biomarkers

Biomarkers are not evaluated in the current study.

8.7. Immunogenicity assessments

Immunogenicity is described in Section 8.1.

8.8. Health outcomes

This section is not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses (Amended 13 December 2022)

Statistical hypotheses are associated with the confirmatory primary NI objectives, which will be tested sequentially to control overall Type I error.

Global type I error is controlled at 2.5% (1-sided).

The non-inferiority margins associated to each objective are provided in Table 18.

Table 18 Study objectives and null hypothesis (Amended: 13 December 2022)

Objectives	Null hypothesis
Primary	
• To demonstrate the non-inferiority of the FLU vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to the FLU vaccine administered alone.	• True Group GMT ratio between the FLU vaccine (Control group) divided by the RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) in HI antibody titers for each of the FLU vaccine strains one month after the FLU vaccine dose is above 1.5.
• To demonstrate the non-inferiority of the RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine compared to the RSVPreF3 OA investigational vaccine administered alone.	• True Group GMT ratio between the RSVPreF3 OA investigational vaccine (Control group) divided by the RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) in RSV-A neutralization antibody titers one month after the RSVPreF3 OA investigational vaccine dose is above 1.5.
• ***To demonstrate the non-inferiority of the RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine compared to the RSVPreF3 OA investigational vaccine administered alone.***	• ***True Group GMT ratio between the RSVPreF3 OA investigational vaccine (Control group) divided by the RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) in RSV-B neutralization antibody titers one month after the RSVPreF3 OA investigational vaccine dose is above 1.5.***

Co-Ad = co-administration; **FLU vaccine** refers to FLU aQIV; **GMT** = geometric mean titer; **HI** = hemagglutination inhibition; **RSVPreF3 OA** = respiratory syncytial virus PreFusion protein 3 older adult

Statistical testing of each endpoint will be organized sequentially to control overall Type I error.

9.2. Analysis sets

Table 19 Analysis sets (Amended: 13 December 2022)

Analysis set	Description
Enrolled	Participants who were randomized or received study intervention or have undergone an invasive procedure.
Exposed	All participants who received a study intervention. Analysis per group is based on the study intervention administered.
Per Protocol	All eligible participants: • who received ***at least one study intervention as per protocol in control group and all study interventions in the Co-Ad group***, • had immunogenicity results pre- and post-dose, • complied with blood draw intervals (refer to Table 3 and Table 4) (contribution of participants to Per Protocol set at specific timepoint will be defined by timepoint), • without intercurrent medical conditions that may interfere with immunogenicity and, • without prohibited concomitant medication/vaccination.

9.2.1. Criteria for elimination from analysis

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

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

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

9.3. Statistical analyses

The Statistical Analysis Plan (SAP) will be developed and finalized before First Subject First Visit (FSFV). This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Supportive analyses, safety and demography summaries will be described in the SAP.

9.3.1. Primary endpoints/estimands analysis (Amended: 13 December 2022)

The primary endpoints/estimands are described in Section 3. The confirmatory analyses of non-inferiority will be based on the PPS.

- Method for non-inferiority of the FLU vaccine in terms of HI GMT ratio for each of the FLU vaccine strains at one month after the FLU vaccine dose (i.e., at Day 31 for both groups):

  The 2-sided 95% confidence interval (CI) for Group GMT ratio between the FLU vaccine administered alone (Control group) over the RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) will be derived from an ANCOVA model* on log_{10} transformed titer.

- Method for non-inferiority of RSV investigational vaccine in terms of RSV-A neutralization antibody GMT ratio at one month after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 for the Co-Ad group and at Day 61 for the Control group):

  The 2-sided 95% CI for Group GMT ratio between the RSVPreF3 OA investigational vaccine administered alone (Control group) over the RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) will be derived from an ANCOVA model* on log_{10} transformed titer.

- ***Method for non-inferiority of RSV investigational vaccine in terms of RSV-B neutralization antibody GMT ratio at 1 month after the RSVPreF3 OA investigational vaccine dose (i.e., at Day 31 for the Co-Ad group and at Day 61 for the Control group).***

  The 2-sided 95% CI for Group GMT ratio between the RSVPreF3 OA investigational vaccine administered alone (Control group) over the RSVPreF3 OA investigational vaccine when co-administered with the FLU vaccine (Co-Ad group) will be derived from an ANCOVA model* on log_{10} transformed titer.

**The model will include the treatment group and age category (age at vaccination: 65-69, 70-79 or ≥80 years) as fixed effects, and the pre-dose log10-transformed titer as covariate. Missing data will not be replaced. Titers below the assay cut-off will be replaced by half the assay cut-off; titers above the upper limit of quantification (ULOQ) will be replaced by the ULOQ.*

Success criteria for non-inferiority ***and testing sequence:***

The following testing sequence will be used:

- ***Sequence 1:***
  - The upper limit (UL) of the 2-sided 95% CI on the Group GMT ratio (Control group divided by Co-Ad group) for each of the FLU vaccine strains are ≤ 1.5.

  AND

  - The UL of the 2-sided 95% CI on the Group GMT ratio (Control group divided by Co-Ad group) for RSV-***A neutralizing antibody*** is ≤ 1.5.
- ***Sequence 2:***
  - ***The UL of the 2-sided 95% CI on the Group GMT ratio (Control group divided by Co-Ad group) for RSV-B neutralizing antibody is ≤ 1.5***

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

9.3.2. Secondary endpoints/estimands analyses

- Method for evaluation of non-inferiority of the FLU vaccine in terms of HI seroconversion rate (SCR) for each of the FLU vaccine strains at one month after the FLU vaccine dose (i.e., at Day 31 for both groups):
  - The 2-sided 95% CI on group difference in SCR (Control group minus Co-Ad group) will be computed based on the method of Miettinen and Nurminen [Miettinen, 1985].
  - Reference criteria for evaluation of non-inferiority:

    The UL of the 2-sided 95% CI on the group difference (Control group minus Co-Ad group) in SCR is ≤10% for anti-HI antibodies.
- The other secondary endpoints are described in Section 3. Descriptive analyses of demography, immunogenicity, and safety will be detailed in the SAP.

Table 20 Definitions of SCR, SPR and MGI

Abbreviation/Term	Definition
HI SCR	The percentage of vaccinees who have either a HI pre-dose titer < 1:10 and a post-dose titer ≥1:40 or a pre-dose titer ≥1:10 and at least a 4-fold increase in post-dose titer.
HI SPR	The percentage of vaccinees with a serum HI titer ≥1:40 that usually is accepted as indicating protection.
MGI	The geometric mean of the within-participant ratios of the post-dose titer over the pre-dose titer.

HI = hemagglutination inhibition; **SCR** = seroconversion rate; **SPR** = seroprotection rate; **MGI** = mean geometric increase

- Additionally, the Center for Biologics Evaluation and Research (CBER) and Committee for Medicinal Products for Human Use (CHMP) criteria for HI SPR and SCR will be assessed as follows:

  CBER's criteria:
  - The lower limit (LL) of the 95% CI for SCR should be ≥30% in participants ≥65 YOA.
  - The LL of the 95% CI for SPR should be ≥60% in participants ≥65 YOA.

  CHMP's criteria:

  At least one of the 3 following criteria should be met:
  - The point estimates of SPR > 60%, SCR > 30%, and MGI > 2.0 for elderly ≥60 YOA for each of the antigen strains.

9.4. Interim analyses

9.4.1. Sequence of analyses

The analyses will be performed stepwise:

A final analysis will be conducted once all immunogenicity data (as clean as possible) are available for the primary and secondary endpoints. This final analysis will include immunogenicity and safety data up to Visit 2/Day 31 (Co-Ad group) or Visit 4/Day 61 (Control group). Participants who undergo Visit 2, Visit 3, or Visit 4 assessments out of the allowed visit interval (see Table 3 and Table 4) may be excluded from the final analysis.

- An EoS analysis with all data (including data obtained until 6 months post-last dose) will be performed.

9.4.2. Statistical considerations for interim analysis

This section is not applicable.

9.5. Sample size determination

The **target enrollment** will be **1028 participants** (514 in the group receiving the RSVPreF3 OA investigational vaccine co-administered with FLU aQIV [Co-Ad group] and 514 in the Control group where RSVPreF3 OA investigational vaccine and FLU aQIV are administered in a sequential manner). This allows to obtain at least 924 **evaluable participants** (462 in the Co-Ad group and 462 in the Control group) for the evaluation of the primary objectives, assuming that 10% of the enrolled participants will not be evaluable.

Participants who withdraw from the study will not be replaced.

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

Table 21 Overall power to demonstrate primary objectives: non-inferiority of the immunogenicity of the RSVPreF3 OA investigational vaccine when co-administered with FLU aQIV compared to when administered alone – assuming approximately 462 participants are available in each group (Amended: 13 December 2022)

Endpoint	Standard deviation of log_{10} concentration	Reference ratio	Non inferiority margin	Type II error	Power
FLU non-inferiority* (1-sided test with alpha=2.5%)					
GMTs HI H1N1 strain	0.6	1.05	1.5	2.5%	97.5%
GMTs HI H3N2 strain	0.6	1.05	1.5	2.5%	97.5%
GMTs HI B/Yamagata	0.6	1.05	1.5	2.5%	97.5%
GMTs HI B/Victoria strain	0.6	1.05	1.5	2.5%	97.5%
RSV-*A* non-inferiority* (1-sided test with alpha = 2.5%)					
GMTs RSV-A neutralization antibody	*0.45*	*1.05*	*1.5*	*0.1%*	*99.9%*
RSV-B Non-inferiority* (1-sided test with alpha = 2.5%)					
GMTs RSV-B neutralization antibody	*0.45*	*1.05*	*1.5*	*0.1%*	*99.9%*
Global Type II error to show non-inferiority				~10.0%	
Global power					~90.0%

GMT = geometric mean titer; **HI** = hemagglutination inhibition; **RSV** = respiratory syncytial virus
*Pass 2019 alpha = 2.5%, Two-Sample T-Tests for Non-Inferiority Assuming Equal Variance and Equal mean
For RSV: non-inferiority limit = 0.176 (=log_{10}[1.5]).
For each Flu vaccine strain: non-inferiority limit = 0.176 (=log10[1.5]).
Reference Ratio= 0.0212 (=log_{10}[1.05])

Considering a potential slight interference of 1.05 in true GMTs in both groups with a common population standard error of 0.45 for the RSV-A ***and RSV-B neutralization antibodies*** and 0.6 for each of the FLU strains in log_{10} transformed concentration, the study has at least 90.0% power to meet the primary objectives.

Nominal powers to evaluate the secondary objective

The nominal power to evaluate the non-inferiority on SCR for each of the FLU strains is above 86%, depending on the plausible rates.

Table 22 Evaluation of non-inferiority in terms of HI antibody SCR when FLU aQIV is co-administered with the RSVPreF3 OA investigational vaccine compared to FLU aQIV when administered alone assuming approximately 462 participants are available in each group for a range of plausible SCRs (Amended: 13 December 2022)

N evaluable participants per group	Threshold	Plausible rates in Control group**	Type II error	Nominal Power
		FLU vaccine: Non-inferiority* in terms of SCR		
462	10%	70%	***8.7%***	***91.3%***
462	10%	50%	***13.9%***	***86.1%***
462	10%	35%	***11.0%***	***89.0%***
462	10%	25%	***6.1%***	***93.9%***

SCR = Seroconversion Rate.
*Pass 2019 alpha = 2.5%, for SCR – Non-inferiority: Proportions – Two independent Proportions – Non-Inferiority Tests for the Difference Between Two Proportions.
** SCR observed in the Control group in Zoster-004 study range from 35.3% to 60.9%.

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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable International Council on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IEC/IRB 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 IEC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB.
- Notifying the IEC/IRB of SAE(s) or other significant safety findings as required by IEC/IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IEC/IRB, 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 or his/her representative 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 and participant informed assent, as appropriate, prior to participation in the study.

The content of the informed consent form (ICF) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IEC/IRB 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 sponsor. 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:

- His/her personal study-related data will be used by the sponsor in accordance with local data protection law.
- His/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC/IRB 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 initiating the study in that country. This includes IECs/IRBs for review and approval of the protocol and subsequent amendments, ICF and any other documentation.

Safety oversight will be provided by an 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 document). 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, IEC/IRB 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.

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

from the QTLs and remedial actions taken will be summarized in the Clinical Study Report (CSR).

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

First act of recruitment

The start of study is defined as FSFV at a country-level.

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 IEC/IRB 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 International Committee of Medical Journal Editors (ICMJE).

10.2. Appendix 2: Clinical laboratory tests

RSV-A and RSV-B neutralization assays

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

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

Viral plaques are counted using an automated microscope coupled to an image analyzer (Scanlab system with a Reading software or equivalent). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at each serum dilution and the number of plaques in the virus control wells (no serum added). The serum neutralizing antibody titer is expressed in Estimated Dilution 60 (ED60) and corresponds to the inverse of the interpolated serum dilution that yields a 60% reduction in the number of plaques compared to the virus control wells, as described by others [Barbas, 1992; Bates, 2014]. For the testing of Phase III studies, secondary standards calibrated against the international reference [NIBSC 16/284; McDonald, 2018;

McDonald, 2020] will be included in every run to allow conversion into international units.

Hemagglutination inhibition assay

HI antibody titers are determined using the method derived from the WHO Manual on Animal Influenza Diagnosis and Surveillance, WHO/CDS/CSR/NCS/2002.5.

Measurements are conducted on thawed frozen serum samples with a standardized and comprehensively validated micro method using 4 hemagglutinating units (4 HAU) of the appropriate antigens and a 0.45% fowl erythrocyte suspension. Non-specific serum inhibitors are removed by heat treatment and receptor-destroying enzymes.

Starting with an initial dilution of 1:10, a dilution series (by a factor of 2) is prepared up to an end dilution of 1:10 240. The titration endpoint is taken as the highest dilution step that shows complete inhibition of hemagglutination. All assays are performed in triplicate, and the final titer corresponds to the GMT of the 3 values. The usual cut-off value is = 10 1/DIL.

CCI

CCI

[redacted]

10.3. Appendix 3: Adverse events – 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 (Amended: 13 December 2022)

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. 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 one 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

a. Solicited administration site events

The following administration site events will be solicited:

Table 23 Solicited administration site events

Pain
Erythema/Redness
Swelling

b. Solicited systemic events

The following systemic events will be solicited:

Table 24 Solicited systemic events

Fever
Headache
Fatigue
Myalgia
Arthralgia

Note: participants will be instructed to measure and record the oral or axillary 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 electronic diary.

10.3.4. Unsolicited adverse events

An unsolicited adverse event is an adverse event that was not included in a list of solicited events using a Participant Diary. Unsolicited events must have been spontaneously communicated by a participant who has signed the informed consent. Unsolicited AEs 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)

pIMDs are the only AESIs collected during this study.

10.3.5.1. Potential immune-mediated diseases

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 Table 25. Please refer to the Section 10.3.7.1 for reporting details.

The investigator must exercise his/her medical/scientific judgment to determine whether other diseases have an autoimmune origin (i.e., pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

Table 25 List of potential immune-mediated diseases (pIMDs)

Medical concept	Additional notes
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	• Frequently used related terms include: "autoimmune thrombocytopenic purpura", "idiopathic thrombocytopenic purpura (ITP)", "idiopathic immune thrombocytopenia", "primary immune thrombocytopenia".
Evans syndrome	
Pernicious anemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	• Also known as "Moschcowitz-syndrome" or "microangiopathic hemolytic anemia"
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/Pericarditis	Including but not limited to: • Autoimmune / Immune-mediated myocarditis • Autoimmune / Immune-mediated pericarditis • Giant cell myocarditis

Medical concept	Additional notes
Idiopathic pulmonary fibrosis	Including but not limited to: • Idiopathic interstitial pneumonia (frequently used related terms include "Interstitial lung disease", "Pulmonary fibrosis", "Immune-mediated pneumonitis") • Pleuroparenchymal fibroelastosis (PPFE)
Pulmonary alveolar proteinosis (PAP)	• Frequently used related terms include: "pulmonary alveolar lipoproteinosis", "phospholipidosis"
Endocrine disorders	
Addison's disease	
Autoimmune / Immune-mediated thyroiditis	Including but not limited to: • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) • Atrophic thyroiditis • Silent thyroiditis • Thyrotoxicosis
Autoimmune diseases of the testis and ovary	• Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow's disease	• Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis • Vogt-Koyanagi-Harada disease
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	Including but not limited to: • Crohn's disease • Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis

Medical concept	Additional notes
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 other inflammatory demyelinating variants	Includes the following: • Acute necrotizing myelitis • Bickerstaff's brainstem encephalitis • Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) • Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis
Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
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)

Medical concept	Additional notes
	• 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 • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
Lichen planus	• Includes liquen planopilaris
Localized Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	

Medical concept	Additional notes
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) • 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	

10.3.6. 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 Sections 10.3.1 and 10.3.2).

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

10.3.7. Recording and follow-up of AEs, SAEs, and pIMDs

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 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 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 instead of individual signs/symptoms.

An eDiary will be used in this study to capture solicited administration site or systemic events:

The participant should be trained on how and when to complete the eDiary. Anyone who measures administration site or systemic events and who will record the event in the eDiary should be trained on using the eDiary. This training must be documented in the participant's source record. If any individual other than the participant is making entries into the eDiary, their identity should be documented in the participant's source records.

Data on solicited events reported in the eDiary will be electronically transferred to the eDiary vendor, where it can be monitored by appropriately qualified site staff and sponsor staff through a web-based portal. Appropriately qualified site staff should monitor eDiary data online at frequent intervals for subject compliance and reported events that were of concern to the subject.

Completion of the eDiary should be verified during discussions with the participant at Visit 2 (all participants) and Visit 4 (only participants in the Control group).

Refer to the SPM for more information regarding the use of eDiary.

10.3.7.1. Time period for collecting and recording AEs, SAEs and pIMDs

All solicited events that occur during the 7 days following administration of each dose of study intervention (Day of study intervention administration and the 6 following days) must be recorded in the eDiary, irrespective of intensity. For solicited events that are still ongoing between Day 8 and Day 30, participants will also be instructed to record these in the eDiary, irrespective of intensity.

All unsolicited AEs that occur during the 30 days following administration of the study interventions (Day of study intervention administration and 29 following days) must be recorded into the appropriate section of the eCRF, irrespective of their intensity.

The time period for collecting and recording SAEs and pIMDs will begin at the first receipt of study interventions and will end 6 months after the last administration of the study interventions.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study intervention until the participant is discharged from the study. 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.

10.3.7.2. Follow-up of AEs, SAEs and pIMDs

After the initial AE/SAE and pIMDs or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and pIMDs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

10.3.7.2.1. Follow-up during the study

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

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

10.3.7.2.2. 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 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.

10.3.7.3. Updating of SAE and pIMD information after removal of write access to the participant's eCRF

When additional SAE or pIMD information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study contact for reporting SAEs (refer to Section 8.3.3.1 or to GSK VCSP department within the defined reporting timeframes specified in the Table 16).

10.3.8. Assessment of intensity and toxicity

10.3.8.1. Assessment of intensity

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

Table 26 Intensity scales for solicited events (Amended: 13 December 2022)

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
Headache	0	None
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	***None***
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia	0	None
	1	Mild: Myalgia present but does not interfere with activity
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia	0	None
	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 Section 1.3 (SoA) for the definition of fever and the preferred location for temperature measurement.

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

	Erythema/swelling	Fever
0:	≤ 20 mm	< 38.0°C
1:	> 20 - ≤ 50 mm	≥ 38.0°C - ≤ 38.5°C
2:	> 50 - ≤ 100 mm	> 38.5°C - ≤ 39.0°C
3:	> 100 mm	> 39.0°C

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 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.

10.3.8.2. Assessment of causality

The investigator must assess the relationship between study intervention and the occurrence of each unsolicited AE/SAE using clinical judgment. Where several different interventions were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific intervention. When a causal relationship to a specific study intervention cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all interventions.

Alternative possible causes, such as the natural history of underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study intervention will be considered and investigated. The investigator will also consult the IB and/or SmPC and/or Prescribing Information for marketed products to assist in making his/her assessment.

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

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

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

If an event meets the criteria to be determined '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 one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.8.3. Medically attended visits

For each solicited and unsolicited AE the participant experiences, the participant will be asked if he/she/the participant received medical attention (defined as hospitalization, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the eDiary/eCRF, as applicable.

10.3.8.4. Assessment of outcomes

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

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

10.3.9. Reporting of SAEs and pIMDs

10.3.9.1. Events requiring expedited reporting to GSK

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 16 for the details on timeframes for reporting of SAEs/pIMDs.

The investigator will be required to confirm the review of SAE causality in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

Refer to Section 10.3.9.2 for information on back-up systems in case the electronic reporting system does not work.

10.3.9.2. 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

This section is not applicable.

10.5. Appendix 5: Genetics

This section is not applicable.

10.6. Appendix 6: Country-specific requirements

Following information will only be applicable in case France will be selected as participating country.

10.6.1. France

This appendix includes all applicable requirements of French Public Health Code/specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

10.6.1.1. Concerning the «selection of study population and withdrawal criteria»

The following vulnerable subject populations will be excluded: minors, protected subjects, adult subjects not in condition to express their consent, subjects deprived of liberty, subjects receiving psychiatric cares, subjects hospitalized in a Health and Social Establishment for other purpose than the participation to the study.

A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code law L.1121-8-1) (except for a participant to a non-interventional study or to a participant to an interventional study if authorized by the Ethics Committee).

It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject:

- is either affiliated to or beneficiary of a social security category;
- has got an authorization by the Ethics Committee.
- Subjects will be compensated for the inconvenience of participating in the study. The amount of compensation is stated in the ICF. Subjects not completing the study for whatever reason could be compensated generally on a pro rata basis.
- According to French Public Health Code law (L.1121-16 and R.1121-16), the following people must be registered in National File ("Fichier National"):
  - Healthy volunteer.
  - Subjects if the aim of the study is not linked to their disease.
  - Subjects on request of the Ethics Committee regarding study risks and constraints.

The following details will be described:

- Reference of the study
- Surname and first name
- Date and place of birth
- Gender

- Dates of beginning and termination of the study
- Exclusion period during which the subject cannot participate to another study (French Public Health Code law L.1121-12)
- The total amount of compensation, if any.

The subjects' registration in National File ("Fichier National") should be documented in the source document - subject notes and monitored by the CRA.

10.6.1.2. Concerning the "study governance considerations"

- **In section "Regulatory and Ethical Considerations, including the Informed Consent Process" of study protocol**
  - Concerning **the process for informing the subject** and/or his/her legally authorized representative, the following text is added:
  - French Patient ICF is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent. It also contains a reference to the authorization of ANSM and the approval from the French Ethics Committee.
  - Concerning **the process for obtaining** subject informed consent:
  - **Concerning the management of the Patient Informed Consent Forms**, the following text is added:

  French Patient ICF is in duplicate (triplicate for minor subject).

  The first page of the Patient ICF is given to the investigator. The copy is kept by the patient or legally authorized representative.

- **NOTIFICATION TO THE HOSPITAL DIRECTOR**

In accordance with Article L1123-13 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-69).

- **INFORMATION TO THE HOSPITAL PHARMACIST**

In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g., included in the IB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

- **Ethnic origin**

In accordance with the data privacy regulation, the ethnic origin, as any personal data, can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **TESTING OF BIOLOGICAL SAMPLES**

In accordance with the French Public Health Code law – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

10.6.1.3. Concerning the "data management" the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the data privacy regulation, each of these people aforesaid has a right of access, correction, and opposition on their own data through GSK (Clinical Operations Department).

10.6.1.4. Concerning data privacy

In accordance with the applicable data privacy regulation, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction, or damage, using appropriate technical or organizational measures. The processing is whether deemed to be compliant with one of the methodology of reference **(MR-001)** or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GSK in accordance with the legal provisions.

10.7. Appendix 7: Abbreviations and glossary of terms

10.7.1. List of abbreviations

AAION	Arteritic Anterior Ischemic Optic Neuropathy
ACTM	Acute Complete Transverse Myelitis
ADE:	Adverse Device Effect
ADE	Antibody-Dependent Enhancement
ADEM	Acute Disseminated Encephalomyelitis
AE:	Adverse Event
AESIs	Adverse events of special interest
AHEI	Acute Hemorrhagic Edema of Infancy
ALPS	Autoimmune lymphoproliferative syndrome
AMSAN	Acute Motor and Sensory Axonal Neuropathy
ANCA	Anti-Neutrophil Cytoplasmic Antibody
APTM	Acute Partial Transverse Myelitis
ARI	Acute Respiratory Infection
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CIAP	Chronic Idiopathic Axonal Polyneuropathy
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
CIS	Clinically Isolated Syndrome
CIOMS	Council for International Organizations of Medical Sciences
CLS:	Clinical Laboratory Sciences
CCI	[redacted]

CoP:	Correlate of Protection
COVID-19:	Coronavirus Disease 2019
CREST	Calcinosis, Raynaud's Phenomenon, Esophageal Dysmotility, Sclerodactyly, and Telangiectasia
CSR:	Clinical Study Report
DRE:	Disease-related event
EBA	Epidermolysis Bullosa Acquisita
eCRF:	electronic Case Report Form
ED60	Estimated Dilution 60
eDiary	Electronic Diary
EEC	European Economic Community
EMA:	European Medicines Agency
EoS:	End of Study
ERD	Enhanced Respiratory Disease
ES:	Exposed Set
FDA:	Food and Drug Administration, United States of America
FSFV	First Subject First Visit
GBS:	Guillain-Barré Syndrome
GCP:	Good Clinical Practice
GMT:	Geometric Mean Titer
GSK:	GlaxoSmithKline
HAU	Hemagglutinating Units
HCPs	Healthcare Professionals
HI:	Hemagglutination inhibition
HIPAA	Health Insurance Portability and Accountability Act
HRP	horse-radish peroxidase

IAF:	Informed Assent Form
IB:	Investigator's Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC:	Independent Ethics Committee
IM:	Intramuscular/Intramuscularly
IND:	Investigational New Drug
IRB:	Institutional Review Board
iSRC:	Internal Safety Review Committee
ITP	Idiopathic Thrombocytopenic Purpura
IWRS:	Interactive Web Response System
LABD	Linear IgA-Mediated Bullous Dermatosis
LL	Lower Limit
LML:	Local Medical lead
LRTI	Lower Respiratory Tract Infection
LSLV:	Last Subject Last Visit
LTCF	Long-Term Care Facility
MatEx	MATerial Excellence
MedDRA:	Medical Dictionary for Regulatory Activities
MGI:	Mean Geometric Increase
MIS-A	Multisystem Inflammatory Syndrome in Adults
MIS-C	Multisystem Inflammatory Syndrome in Children
MMN	Multifocal Motor Neuropathy
MMSE	Mini-Mental State Examination

MoCA	Mini-Cog or Montreal Cognitive Assessment
MS	Multiple Sclerosis
NAb	Neutralizing Antibody
OA:	Older Adult
PAP	Pulmonary alveolar proteinosis
pIMD:	Potential Immune-Mediated Disease
PMR	Polymyalgia Rheumatica
PPFE	Pleuroparenchymal fibroelastosis
PPS:	Per Protocol Set
PRE:	Population-Related event
PreF3	PreFusion Protein 3
PsA	Psoriatic Arthritis
PRO:	Patient-Related Outcomes
QTL:	Quality Tolerance Limit
RIS	Radiologically Isolated Syndrome
RNA	Ribonucleic Acid
RS	Reynolds Syndrome
RSV:	Respiratory Syncytial Virus
RSVPreF3 OA:	Respiratory Syncytial Virus PreFusion Protein 3 Older Adult investigational vaccine
SADE:	Serious Adverse Device Effect
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SAS	Statistical Analysis System
SBIR:	Source data Base for Internet Randomization
SCLS	Systemic Capillary Leak Syndrome

SCR:	Seroconversion Rate
SDV:	Source Document Verification
SJS	Stevens-Johnson Syndrome
SLS	Shrinking Lung Syndrome
SmPC:	Summary of Product Characteristics
SoA:	Schedule of Activities
SPM:	Study Procedures Manual
SPR:	Seroprotection Rate
SRT:	Safety Review Team
SUSAR	Suspected Unexpected Serious Adverse Reactions
TED	Thyroid Eye Disease
TEN	Toxic Epidermal Necrolysis
TTS	Thrombosis With Thrombocytopenia Syndrome
UL	Upper Limit
ULOQ	Upper Limit of Quantification
US	United States
USADE:	Unanticipated Serious Adverse Device Effect
VAED	Vaccine Associated Enhanced Disease
VMED	Vaccine-Mediated Enhanced Disease
YOA:	Year Of Age

10.7.2. Glossary of terms

Adverse event: Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Blinding: A procedure in which 1 or more parties to the 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 open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.

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 his/her 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 this study, a caregiver can be appointed by the participant to oversee and support the participant’s compliance with protocol-specific procedures (such as transcribing responses to eDiaries, receiving phone calls, planning study visits, etc.). However, at no time, the caregiver should evaluate the participant’s health status while completing eDiaries 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.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrollment:	The process of registering a participant into a clinical study by assigning participant identification number after signing the ICF.
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.
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.
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 amendment:	The International Council on Harmonization (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.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.
Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Remote visit:	This term refers to the visit conducted in the place other than the study site.
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.
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.

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