CLINICAL STUDY PROTOCOL

Primary Study Intervention	GlaxoSmithKline Biologicals S.A. (GSK)'s investigational respiratory syncytial virus (RSV) vaccine BIO RSV OA=ADJ (GSK3844766A)
Other Study Intervention	Comirnaty Omicron XBB.1.5 COVID-19 mRNA vaccine
Study Identifier	217848 (RSV OA=ADJ-013)
EU CT Number	2023-510196-59-00
Approval Date	09 Jan 2024
Title	A Phase 3, open-label, randomized, controlled study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with a COVID-19 mRNA vaccine (Omicron XBB.1.5) in adults aged 50 years and above.
Brief Title	A study on the immune response and safety of a vaccine against respiratory syncytial virus (RSV) when given alone and together with a vaccine against SARS-CoV-2 in adults aged 50 years and above.
Sponsor	GlaxoSmithKline Biologicals S.A. Rue De L'Institut 89 1330 Rixensart Belgium
Sponsor signatory	Nadia Meyer, MD Clinical Project Lead RSV Older Adults

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

Protocol Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained on-site or elsewhere without the approval of GSK and the express physical 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 and data management processes of the study with respect to data entry and 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 study intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

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

Study identifier	217848 (RSV OA=ADJ-013)
EU CT Number	2023-510196-59-00
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Investigator name	_____
Signature	_____
Date of signature (DD Month YYYY)	_____

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

Abbreviation	Definition
AAION	Arteritic anterior ischemic optic neuropathy
Ab	Antibody
ADEM	Acute disseminated encephalomyelitis
AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial fibrillation
ANCA	Anti-neutrophil cytoplasmic antibody
ANCOVA	Analysis of Covariance
Anti-S	Anti-Spike
APTM	Acute partial transverse myelitis
ARI	Acute Respiratory Infection
$AS01_E$	Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
CIOMS	Council for International Organizations of Medical Sciences
CIS	Clinically isolated syndrome
CLS	Clinical Laboratory Sciences
CONSORT	Consolidated Standards of Reporting Trials
CoP	Correlates of protection
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
DNA	Deoxyribonucleic Acid
EBA	Epidermolysis Bullosa Acquisita
ECL	Electrochemiluminescence
eCRF	electronic Case Report Form
EMA	European Medicines Agency

Abbreviation	Definition
EoS	End of study
ES	Exposed Set
FDA	Food and Drug Administration
FSFV	First subject first visit
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline Biologicals SA
HCP	Healthcare Professional
HIPAA	Health Insurance Portability and Accountability Act
HRP	Horseradish peroxidase
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IMP	Investigational medicinal product
IRB	Institutional Review Board
LABD	Linear IgA-mediated bullous dermatosis
LLOQ	Lower Limit of Quantification
LNP	Lipid Nanoparticle
LRTD	Lower Respiratory Tract Disease
LSLV	Last subject last visit
MGI	Mean Geometric Increase
MMSE	Mini-Mental State Examination

Abbreviation	Definition
MoCA	Mini-Cog or Montreal Cognitive Assessment
MPL	Monophosphoryl Lipid A
mRNA	Messenger Ribonucleic Acid
MS	Multiple sclerosis
MSD	Meso Scale Discovery (Rockville, US)
NAAT	Nucleic acid amplification test
Nab	Neutralizing Antibody
NI	Non-inferiority
OA	Older Adults
Omi	Omicron
pIMD	Potential Immune-Mediated Disease
PPS	Per Protocol Set
PT	Preferred terms
QTL	Quality Tolerance Limit
RLU	Relative light units
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Infection
RTSM	Registration and Medication Ordering System
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SAS	Statistical Analysis System
SCLS	Systemic capillary leak syndrome
SD	Standard Deviation
SoA	Schedule of activities
SRR	Seroresponse Rate
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse reaction
TED	Thyroid eye disease
TM	Transverse myelitis
TPA	Tripropylamine

Abbreviation	Definition
ULOQ	Upper Limit Of Quantification
US	United States
VAED	Vaccine associated enhanced disease
VAERD	Vaccine associated enhanced respiratory disease
VSV	Vesicular Stomatitis Virus
WOCBP	Woman of childbearing potential
YOA	Years of Age

Definition of terms

Term	Definition
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 adverse event (AE) can therefore be any unfavourable 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 SAE. 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 their daily health care (e.g., a relative of the participant, a nurse who helps with

	daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol-specified procedures.
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.
Co-administered (concomitant) products	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Comparator	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled participant	'Enrolled' means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to the Section 9.2 for the definition of 'enrolled set' applicable to the study.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Evaluable	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis.
Immunological correlate of protection	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.

Intercurrent medical condition	A condition that has the capability of altering the immune response to the study vaccine or is confirmed to have an alteration of the participant's initial immune status.
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Invasive medical device	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'.
Investigational product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.
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 on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.

Protocol amendment	The International Council on Harmonisation (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.
Serious Adverse Reaction	All noxious and unintended responses to an IMP related to any dose administered that result in death, are life-threatening, require patient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, or are a congenital anomaly or birth defect.
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	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. Note: “Study intervention” and “study treatment” are used interchangeably unless otherwise specified.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Suspected Unexpected Serious Adverse Reaction	A Suspected Unexpected Serious Adverse Reaction is a Serious Adverse Reaction whose nature, severity or outcome is not consistent with the reference safety information.
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.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 3, open-label, randomized, controlled study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with a COVID-19 mRNA vaccine (Omicron XBB.1.5) in adults aged 50 years and above.

Brief Title:

A study on the immune response and safety of a vaccine against respiratory syncytial virus (RSV) when given alone and together with a vaccine against SARS-CoV-2 in adults aged 50 years and above.

Rationale: Refer to Section 2.1.

Objectives, Endpoints, and Estimands: Refer to Section 3.

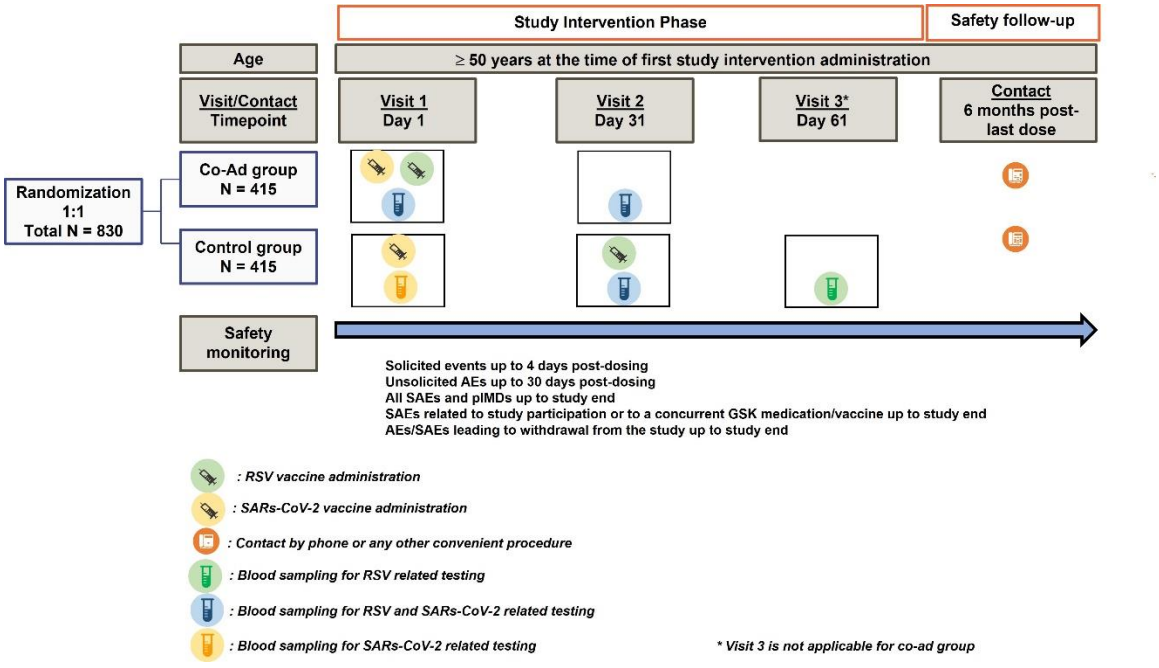
Overall Design: Refer to Section 1.2 and Section 4.1.

Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Schema

Figure 1 Study design overview



1.3. Schedule of activities (SoA)

Table 1 SoA for Co-Ad group

Type of contact	Visit 1	Visit 2**	Contact	Notes
Timepoints	Day 1	Day 31	Month 6[1]	
Baseline and demography assessments				
Informed consent	●[2]			See Section 10.1.3
Distribution of participant card	○			See Section 8.4.8
Inclusion and exclusion criteria	●			See Section 5.1 and Section 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 8 for details
Demography	●			See Section 8.1.1
Medical and vaccination history	●			See Sections 8.1.2
History directed physical examination	○			See Section 8.3.1
Screening conclusion	●			See Section 5.4
Laboratory assessment				
Urine pregnancy test (only for women of childbearing potential)	●[3]			See Section 8.3.3
Blood sampling from all participants for humoral response assessment (~15 mL)	●[4]	●[5]		See Section 8.2.2
Study Intervention administration				
Check contraindications, warnings and precautions to vaccination	○			See Sections 7.1.1
Check criteria for temporary delay for enrollment and/or study intervention administration*	○			See Section 5.5
Randomization, study group and intervention number allocation	○			See Section 6.3.2 and Section 6.3.3
Body temperature before study interventions administration	●			The preferred location for measuring temperature will be oral cavity/axilla (see Section 8.1.3). Fever is defined as temperature ≥38.0°C/100.4°F, regardless of the location of measurement.
Study interventions administration (COVID-19 mRNA vaccine + RSVPreF3 OA investigational vaccine on separate arms) (including 30-minute post-vaccination observation)	●			See Section 6.1
Recording of administered study interventions numbers	●			See Section 6.3.3
Safety assessment				
Distribution of diary cards for solicited events and unsolicited AEs	○			See Section 10.3.5
Record concomitant medications/vaccinations	●	●	●	See Section 6.9
Recording of intercurrent medical conditions	●	●	●	See Section 9.2.1 and Table 9
Recording of solicited events (Days 1–4 after study intervention administration)	●			See Section 10.3.5
Recording of unsolicited AEs (Days 1-30 after study intervention administration)[6]	●	●		See Sections 10.3.5
Recording of all SAEs and pIMDs[6]	●	●	●	See Section 10.3.5.

Type of contact Timepoints	Visit 1 Day 1	Visit 2** Day 31	Contact Month 6[1]	Notes
Recording of pregnancy	●	●	●	See Section 10.3.5
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[7]	●	●	●	See Section 10.3.5
Return of diary cards		○		See Section 10.3.5.1
Diary card review and transcription by investigator/delegate		●		See Section 10.3.5.1
Recording of AEs/SAEs leading to withdrawal from the study	●	●	●	See Section 10.3.5
Phone contact for safety follow-up			●	See Sections 10.3.5.5
Study Conclusion			●	See Section 4.4

Note: The double-line borders following Day 31 and Month 6 indicates analyses which will be performed on all data obtained up to these time points.

AE = adverse event; AESI = Adverse event of special interest, AF = Atrial fibrillation, pIMDs = potential immune-mediated diseases; SAE = Serious Adverse Event; eCRF = electronic case report form.

● 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.

* Visit 1 procedures should preferably be done on the same day. If not, all the visit procedures must be repeated prior to the study interventions administration and recorded in the eCRF when required, excluding the informed consent, the collection of demographic data. All efforts should be made to collect the blood sample on the day of study intervention administration, however if the blood sampling was previously taken for this visit, the blood sample does not need to be retaken.

** Visit 2 should preferably be done on site but if local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g., home visits) conducted by an authorized staff. Any further information from the participant, not collected during the home visit, can be obtained by means of a phone call conducted by the site staff.

1. Month 6 = 6 months after last study intervention administration. For this contact, multiple formats can be proposed by the study site (refer to Section 8.3.5.1 for details).
2. Freely given and written informed consent must be obtained from each study participant at Visit 1.
3. The urine sample for pregnancy test (only for women of childbearing potential) should be taken prior to study intervention administration. If the study intervention administration is delayed by any reason, the sample will need to be collected again on the day of study intervention administration.
4. Sample collected at Day 1 will be used as baseline for both COVID-19 mRNA and RSVPreF3 OA investigational vaccine-related testing.
5. Sample collected at Day 31 will be used for the post-vaccination testing related to both COVID-19 mRNA and RSVPreF3 OA investigational vaccine-related testing.
6. AF will be considered as AESI in this study and will be additionally reported in the AF follow-up questionnaire (electronic or paper) in eCRF. The collection of AF will be performed following the AE/SAE reporting periods. The reporting of non-serious AF will be performed according to the unsolicited AE reporting period. The reporting of AF meeting the SAE definition (serious AF) will be performed according to the SAE reporting period.
7. 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 SoA for Control group

Type of contact Timepoints	Visit 1 Day 1	Visit 2 Day 31	Visit 3** Day 61	Contact Month 7[1]	Notes
Baseline and demography assessments					
Informed consent	●[2]				See Section 10.1.3
Distribution of participant card	○				See Section 8.4.8
Inclusion and exclusion criteria	●				See Sections 5.1 and Section 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 8 for details

Type of contact Timepoints	Visit 1 Day 1	Visit 2 Day 31	Visit 3** Day 61	Contact Month 7[1]	Notes
Demography	●				See Section 8.1.1
Medical and vaccination history	●				See Section 8.1.2
History directed physical examination	○				See Section 8.3.1
Screening conclusion	●				See Section 5.4
Laboratory assessment					
Urine pregnancy test (only for women of childbearing potential)	●[3]	●[3]			See Section 8.3.3
Blood sampling from all participants for humoral response assessment (~15 mL)	●[4]	●[5]	●[6]		See Section 8.2.2
Study Intervention Administration					
Check contraindications, warnings and precautions to study intervention administration	○	○			See Sections 7.1.1
Check criteria for temporary delay of study intervention administration*	○	○			See Section 5.5
Randomization, study group and intervention number allocation	○				See Section 6.3.2 and Section 6.3.3
Body temperature before study intervention administration	●	●			The preferred location for measuring temperature will be oral cavity/axilla (see Section 8.1.3). Fever is defined as temperature ≥38.0°C/100.4°F, regardless of the location of measurement.
Study intervention administration: COVID-19 mRNA vaccine (including 30-minute post-vaccination observation)	●				See Section 6.1
Study intervention administration: RSVPreF3 OA investigational vaccine (including 30-minute post-vaccination observation)		●			See Section 6.1
Recording of administered study intervention number	●	●			See Section 6.3.3
Safety assessment					
Distribution of diary cards for solicited events and unsolicited AEs	○	○			See Section 10.3.5
Record concomitant medications/vaccinations	●	●	●	●	See Section 6.9
Recording of intercurrent medical conditions	●	●	●	●	See Section 9.2.1 and Table 9
Recording of solicited events (Days 1–4 after study intervention administration)	●	●			See Section 10.3.5
Recording of unsolicited events (Days 1-30 after study intervention administration)[7]	●	●	●		See Sections 10.3.5
Recording of SAEs and pIMDs[7]	●	●	●	●	See Section 10.3.5
Recording of pregnancy	●	●	●	●	See Section 10.3.5
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[8]	●	●	●	●	See Section 10.3.5
Return of diary cards		○	○		See Section 10.3.5.1
Diary card review and transcription by investigator/delegate		●	●		See Section 10.3.5.1
Recording of Aes/SAEs leading to withdrawal from the study	●	●	●	●	See Section 10.3.5

Type of contact	Visit 1	Visit 2	Visit 3**	Contact	Notes
Timepoints	Day 1	Day 31	Day 61	Month 7[1]	
Phone contact for safety follow-up				●	See Sections 10.3.5.5
Study Conclusion				●	See Section 4.4

Note: The double-line borders following Day 61 indicate analyses which will be performed on all data obtained up to these time points.

AE = adverse event; AESI = Adverse event of special interest; AF = Atrial fibrillation, pIMDs = potential immune-mediated diseases; SAE = Serious Adverse Event; eCRF = electronic case report form.

● 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

* Visit 1 procedures should preferably be done on the same day. If not, all the visit procedures must be repeated prior to the study intervention administration and recorded in the eCRF when required, excluding the informed consent, the collection of demographic data. All efforts should be made to collect the blood sample on the day of study intervention administration, however if the blood sampling was previously taken for this visit, the blood sample does not need to be retaken.

If during Visit 2 the study intervention administration is postponed, all the visit procedures must be repeated prior to the study intervention administration and recorded in the eCRF when required, excluding blood sampling if previously taken for this visit.

** Visit 3 should preferably be done on site but if local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g. home visits) conducted by authorized staff. Any further information from the participant, not collected during the home visit, can be obtained by means of a phone call conducted by the site staff.

1. Month 7 = 6 months after last administration of RSVPreF3 OA investigational vaccine. For this contact, multiple formats can be proposed by the study site (refer to Section 8.3.5.1 for details).
2. Freely given and written informed consent must be obtained from each study participant at Visit 1.
3. The urine samples for pregnancy test (only for women of childbearing potential) should be taken on the same day, prior to study intervention administration of any dose. If the study intervention administration is delayed by any reason, the samples will need to be collected again on the day of study intervention administration.
4. Sample collected at Day 1 will be used as baseline for the COVID-19 mRNA vaccine-related testing.
5. Sample collected at Day 31 will be used as baseline for the RSVPreF3 OA investigational and for the post-vaccination COVID-19 mRNA vaccine-related testing.
6. Sample collected at Day 61 will be used for the post-vaccination RSVPreF3 OA investigational vaccine-related testing.
7. AF will be considered as AESI in this study and will be additionally reported in the AF follow-up questionnaire (electronic or paper) in eCRF. The collection of AF will be performed following the AE/SAE reporting periods. The reporting of non-serious AF will be performed according to the unsolicited AE reporting period. The reporting of AF meeting the SAE definition (serious AF) will be performed according to the SAE reporting period.
8. 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 → Visit 2	30 days	30-42 days
Visit 1 → Contact	180 days	180-210 days

Table 4 Intervals between study visits (Control group)

Interval	Planned visit interval	Allowed interval range
Visit 1 → Visit 2	30 days	30-42 days
Visit 2 → Visit 3	30 days	30-42 days
Visit 2 → Contact	180 days	180-210 days

2. INTRODUCTION

2.1. Study rationale

GSK has developed a new RSVPreF3 OA vaccine against RSV-associated (subtypes A and B) disease in adults ≥ 60 YOA at an increased risk of RSV-LRTD. The RSVPreF3 OA vaccine was approved for protection against LRTD caused by RSV in adults ≥ 60 YOA in the US on 3 May 2023, under the trade name *Arexvy.* To date the vaccine is also approved in the EU and in other countries.

GSK is aiming to expand the label indication to include a population of 50 to 59 years of age with comorbidities that place them at increased risk for RSV-LRTD. A study to evaluate immune response and safety of RSVPreF3 OA investigational vaccine in adults 50 to 59 YOA, versus adults ≥60 YOA is ongoing.

The current study will assess the immunogenicity, safety and reactogenicity of the RSVPreF3 OA investigational vaccine when co-administered with a COVID-19 mRNA vaccine (Omicron XBB.1.5) in adults ≥ 50 YOA.

Note: In some sections of this protocol, for readability, the COVID-19 mRNA vaccine (Omicron XBB.1.5) is referred as "COVID-19 mRNA vaccine".

2.2. Background

RSV is an RNA virus of which 2 antigenically distinct subtypes exist, referred to as RSV A and RSV B [Borchers, 2013]. RSV causes RTI in people of all ages. RSV can cause severe lower respiratory tract infection in OA and adults with chronic medical conditions including cardiopulmonary and immunocompromising conditions.

Based on epidemiological data collected prospectively in 2008-2010 in 14 countries worldwide (including North America, Europe, and East Asia), the average percentage of documented RSV infections in OA with influenza-like illness is 7.4%, with values between 0% and 17.1% across countries [Falsey, 2014]. In 2015, an estimated 1.5 million episodes of RSV related acute respiratory illness occurred in OA in industrialized countries; approximately 14.5% of these episodes involved a hospital admission [Nam, 2019].

Currently, there are two vaccines available for prevention of RSV infections in adults ≥ 60 YOA; *Arexvy* (manufactured by GSK) and *Abrysvo* (manufactured by Pfizer Inc).

Recent in-house results from a Phase 3 clinical trial in OA (RSV OA=ADJ-004) demonstrated that one dose of the RSV OA investigational vaccine-induced strong humoral and cell-mediated immune responses, which remained above pre-vaccination levels up to at least the 13 months post-vaccination readout timepoint. In another large Phase 3 vaccine clinical trial (RSV OA=ADJ-006) in adults aged 60 years and above, the vaccine candidate demonstrated an overall vaccine efficacy of 82.6% (96.95% CI,

57.9-94.1) against RSV-LRTD up to 6 months post-vaccination. The vaccine was well tolerated with a favorable safety profile [Papi, 2023].

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

The COVID-19 mRNA vaccine which will be used in this study contains 30 micrograms of raxtozinameran embedded in lipid nanoparticles. Raxtozinameran is a single-stranded, 5'-capped mRNA produced using a cell-free *in vitro* transcription from the corresponding DNA templates encoding the viral spike (S) protein of SARS-CoV-2 (Omicron XBB.1.5).

The US FDA and the EMA have authorized the Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion as a single dose injection as active immunisation to prevent COVID-19 caused by the SARS-CoV-2, in individuals 12 years of age and older [Comirnaty product information package insert, EMA, 2023; US FDA, 2023].

Although a consistent and anticipated pattern of COVID-19 seasonality is yet to be determined, the analysis of severe COVID-19 outcomes (such as hospitalizations, ICU admissions, and COVID-19 deaths) since the start of the pandemic revealed that the disease has had a more significant impact during the time frame that aligns with the conventional influenza and RSV seasons [Stockholm, 2023].

Since both vaccines will be indicated for use in individuals within similar age groups, evaluation of the co-administration of the RSVPreF3 OA vaccine and COVID-19 mRNA vaccine is of interest.

2.3. Benefit/risk assessment

2.3.1. Risk assessment

Detailed information about the known and expected benefits, potential risks and reasonably expected AEs of the RSVPreF3 OA investigational vaccine can be found in the IB and/or package insert.

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
RSV investigational vaccine		
pIMDs	pIMDs are considered a theoretical risk, as for all vaccines containing an adjuvant system.	Refer to Section 8.4.4.1 for details.
Hypersensitivity reactions (including anaphylaxis)	Previous exposure to components of the vaccine might have induced an immune response that results in an exaggerated or inappropriate reaction.	Participants with a history of hypersensitivity or severe allergic reaction to any component of the vaccine are excluded from study enrollment. All participants will remain under observation at the clinical center for at least 30 minutes after study intervention administration or longer if deemed necessary by site personnel. Appropriate medical care must be readily available during this period.
Syncope (fainting)	Syncope (fainting) can occur following or even before study intervention administration as a psychogenic response to the needle insertion.	Participants who mention experiencing previous episodes of fainting or dizziness before, during or after vaccination, will be asked to lie down during the intervention and remain under observation at the clinical center for at least 30 minutes after study intervention administration or longer if deemed necessary by site personnel. Appropriate medical care must be readily available during this period.
Study procedures		
Local reactions at the injection site	Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, erythema/redness, and swelling.	As a mitigation strategy, physicians can implement the measures that they consider necessary.
Local reactions at site of blood draw	Pain, redness, irritation, and bruising may occur at the site where blood is drawn.	Physicians can implement the measures that they consider necessary.
Syncope (fainting)	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 be asked to lie down during the intervention and remain under observation at the clinical center for at least 30 minutes after blood draw or longer if deemed necessary by site personnel. Appropriate medical care must be readily available during this period.

For expected adverse reactions associated with the COVID-19 mRNA vaccine, please refer to the Prescribing Information.

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

In parallel with the RSVPreF3 OA clinical development program, another RSV vaccine development program was initiated by GSK. GSK developed an investigational RSV vaccine for administration to pregnant women, with the aim of preventing medically assessed, RSV-associated LRTIs in their infants up to 6 months of age, by transfer of maternal antibodies.

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

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

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

The safety concern is specific to women who received the RSV maternal vaccine candidate during the late second or third trimester of pregnancy. To date, analyses of the available safety data have not established what caused the observed imbalance in preterm births. The overall incidence of preterm birth in the study was low in both treatment groups and remained below the preterm birth background rates for the majority of the participating countries. The imbalance in preterm births was observed more in low and middle-income countries (relative risk 1.57 [95% CI: 1.17 - 2.10) than high-income countries (relative risk 1.04 [95% CI: 0.68 - 1.58]).

The vaccine candidate for older adults (RSV PreF3 OA vaccine) contains the same RSV antigen as the RSV maternal vaccine candidate but the RSVPreF3 OA vaccine is combined with GSK's established AS01E adjuvant to boost the immune response in the OA population.

For women in the 50-59 YoA age group, the incidence of spontaneous pregnancy is about 4 in 100000 women [Salihu, 2003]. As a precautionary measure, no pregnant women will be included and all WOCBP will be required to use adequate contraception and have a

negative pregnancy test prior to each vaccination in this study. Study participants will be adequately informed of the risks associated with pregnancy as the informed consent contains specific information regarding the RSV Maternal study.

The RSVPreF3 OA vaccine clinical trials are closely monitored for safety with all available safety data reviewed by the sponsor. In addition, the Phase 3 RSV OA=ADJ-006 clinical study is monitored by an IDMC on an ongoing basis. The IDMC has not raised any concern for safety in the OA population. The RSVPreF3 OA vaccine has not been studied in pregnant women to date.

2.3.2. Benefit assessment

In a pre-specified efficacy interim analysis of an ongoing Phase 3 trial (RSV OA=ADJ-006) in participants >60 YoA, for those receiving a single dose of the RSVPreF3 OA investigational vaccine, the primary endpoint was met with a high vaccine efficacy during the first RSV season and no safety concerns were observed (refer to IB).

By receiving the RSVPreF3 OA vaccine the participant may have the benefit of being protected against RSV-associated disease. All participants will receive a COVID-19 mRNA vaccine as part of the study. By receiving this vaccine as part of standard medical care, the participant may have the benefit of continued protection against COVID-19.

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

2.3.3. Overall benefit-risk conclusion

Considering the measures taken to minimize the risk to participants participating in this study, the potential or recognized risks identified in association with the study vaccines (RSVPreF3 OA investigational vaccine and COVID-19 mRNA vaccine) and study procedures are justified by the potential benefits that may be afforded to the participants receiving these vaccines and by the value of information to be gained.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

3.1. Objectives and endpoints

Table 4 Study objectives, endpoints and estimands

Objectives	Endpoints and Estimands
Primary	
• To demonstrate non-inferiority* of humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with a COVID-19 mRNA vaccine compared to RSVPreF3 OA investigational vaccine administered alone.	• RSV-A neutralization titers expressed as group GMT ratio 1 month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralization titers expressed as group GMT ratio 1 month after the RSVPreF3 OA investigational vaccine dose.
• To demonstrate non-inferiority* of humoral immune response to a COVID-19 mRNA vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to COVID-19 mRNA vaccine administered alone.	• SARS-CoV-2 Omicron XBB.1.5 neutralization titers against pseudovirus bearing S protein expressed as group GMT ratio 1 month after the COVID-19 mRNA vaccine.
Secondary	
• To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with a COVID-19 mRNA vaccine or administered alone.	• RSV-A neutralization titers expressed as GMT, MGI and SRR at 1 month after the RSVPreF3 OA investigational vaccine dose. • Percentage of participants having RSV-A neutralizing titers ≥ assay cut-off (i.e., LLOQ) at pre-vaccination and 1 month after the RSVPreF3 OA investigational vaccine dose. • RSV-B neutralization titers expressed as GMT, MGI and SRR at 1 month after the RSVPreF3 OA investigational vaccine dose. • Percentage of participants having RSV-B neutralizing titers ≥ assay cut-off (i.e., LLOQ) at pre-vaccination and 1 month after the RSVPreF3 OA investigational vaccine dose.
• To evaluate the humoral immune response to a COVID-19 mRNA vaccine when co-administered with the RSVPreF3 OA investigational vaccine or administered alone.	• SARS-CoV-2 Omicron XBB.1.5 neutralization titers against pseudovirus bearing S protein expressed as GMT and MGI at 1 month after the COVID-19 mRNA vaccine. • Percentage of participants having SARS-CoV-2 Omicron XBB.1.5 neutralization titers ≥ assay cut-off (i.e., LLOQ) at pre-vaccination and 1 month after the COVID-19 mRNA vaccine dose.

Objectives	Endpoints and Estimands
• To evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and a COVID-19 mRNA vaccine, co-administered or administered alone.	• Percentage of participants reporting each solicited administration site event and systemic event within 4 days post study intervention administration (i.e., the day of vaccination and 3 subsequent days). • Percentage of participants reporting unsolicited AEs within 30 days post study intervention administration (i.e., the day of vaccination and 29 subsequent days). • Percentage of participants reporting SAEs after study intervention administration (Day 1) up to study end (6 months after last study intervention administration). • Percentage of participants reporting pIMDs after study intervention administration (Day 1) up to study end (6 months after last study intervention administration).

AE: adverse event; GMC: Geometric Mean Concentration; GMT: Geometric Mean Titer; MGI: Mean Geometric Increase; pIMD: potential immune mediated disease; SAE: serious adverse event, SRR: Seroreponse rate. MGI and SRR are defined in Section 9.3.2.

* Non-inferiority criteria are defined in Section 9.3.1.

3.2. Estimands

3.2.1. Immunogenicity Objectives

Primary objective:

The primary question of interest is to demonstrate the non-inferiority of the humoral immune response after RSVPreF3 OA investigational vaccine is co-administered with a dose of COVID-19 mRNA vaccine when compared to RSVPreF3 OA investigational vaccine administered alone and COVID-19 mRNA vaccine administered alone, in adults aged 50 years vaccinated as per protocol.

The secondary objectives are the following:

- To evaluate the humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with a dose of COVID-19 mRNA vaccine or when administered alone.

To evaluate the humoral immune response to a dose of COVID-19 mRNA vaccine when co-administered with the RSVPreF3 OA investigational vaccine or when administered alone.

Attributes						Summary measure
Objectives	**Treatment**	**Population**	**Endpoint (Variable)**	**Intercurrent events (ICEs)**		
				Description	**Handling strategy**	
Primary	Co-ad group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 1 Control group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 31	Adults ≥ 50 years at the time of first vaccination	• RSV-A and RSV-B neutralizing titers measured at 1 month (at Day 61 for Control group, at Day 31 for Co-ad group) after RSVPreF3 OA investigational vaccine administration). • SARS-CoV-2 Omicron XBB.1.5 neutralization titers measured at 1 month (at Day 31 for both groups) after COVID-19 mRNA vaccine administration.	1. Study vaccination not administered as per protocol. 2. Prohibited medication, vaccination or intercurrent medical condition prior to the blood sample.	Data collected after ICEs will be excluded from the analysis. (Hypothetical strategy) Rationale: To evaluate the immunogenicity parameters in the absence of ICE	• Ratio of GMTs with 95% CI for RSV-A and RSV-B neutralizing titers 1 month after RSVPreF3 OA investigational vaccine administration between the Control group versus Co-ad group. • Ratio of GMTs with 95% CI for SARS-CoV-2 Omicron XBB.1.5 titers 1 month after COVID-19 mRNA vaccine administration between the Control group versus Co-ad group.

Attributes						Summary measure
Objectives	**Treatment**	**Population**	**Endpoint (Variable)**	**Intercurrent events (ICEs)**		
				Description	**Handling strategy**	
Secondary	Co-ad group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 1 Control group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 31	Adults ≥ 50 years at the time of first vaccination	• RSV-A and RSV-B neutralizing titers measured at pre-vaccination (at Day 1 for Co-ad group and at Day 31 for Control group) and at 1 month (at Day 31 for Co-ad group and at Day 61 for Control group) after RSVPreF3 OA investigational vaccine administration. • Fold increase in RSV-A and RSV-B neutralizing titers from pre-vaccination to 1-Month post RSVPreF3-OA investigational vaccine administration. • RSV-A and RSV-B neutralizing titers ≥ assay cut-off at pre-vaccination and 1 month after the RSVPreF3 OA investigational vaccine dose administration. • Seroresponse in RSV-A and RSV-B, defined as a fold increase in neutralizing titers from pre-vaccination to 1-Month post RSVPreF3-OA investigational vaccine administration ≥4.	1. Study vaccination not administered as per protocol. 2. Prohibited medication, vaccination or intercurrent medical condition prior to the blood sample.	Data collected after ICEs will be excluded from the analysis. (Hypothetical strategy) Rationale: To evaluate the immunogenicity parameters in the absence of ICE	• GMTs with 95% CI for RSV-A and RSV-B neutralizing titers at pre-vaccination and at 1 month after RSVPreF3 OA investigational vaccine dose administration. • MGI with 95% CI for RSV-A and RSV-B neutralizing titers at 1 month after RSVPreF3 OA investigational vaccine dose administration • Percentage of participants having RSV-A and RSV-B neutralizing titers ≥ cut-off and 95% CI at pre-vaccination and 1 month after the RSVPreF3 OA investigational vaccine dose administration. • Seroresponse rate (SRR) with 95% CIs for RSV-A and RSV-B, defined as the proportion of participants having a fold increase in neutralizing titers from pre-vaccination to 1-Month post RSVPreF3-OA investigational vaccine administration ≥4.

Attributes						Summary measure
Objectives	**Treatment**	**Population**	**Endpoint (Variable)**	**Intercurrent events (ICEs)**		
				Description	**Handling strategy**	
Secondary	Co-ad group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 1 Control group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 31	Adults ≥ 50 years at the time of first vaccination	• SARS-CoV-2 Omicron XBB.1.5 neutralization titers measured at pre-vaccination (at Day 1) and at 1 month (at Day 31) after COVID-19 mRNA vaccine administration. • Fold increase in SARS-CoV-2 Omicron XBB.1.5 neutralization titers from pre-vaccination to 1-Month post COVID-19 mRNA vaccine administration. • SARS-CoV-2 Omicron XBB.1.5 neutralizing titers ≥ assay cut-off at pre-vaccination and 1 month after the COVID-19 mRNA vaccine vaccine dose administration.	1. Study vaccination not administered as per protocol. 2. Prohibited medication, vaccination or intercurrent medical condition prior to the blood sample.	Data collected after ICEs will be excluded from the analysis. (Hypothetical strategy) Rationale: To evaluate the immunogenicity parameters in the absence of ICE	• GMTs with 95% CI for SARS-CoV-2 Omicron XBB.1.5 neutralizing titers at pre-vaccination and at 1 month after COVID-19 mRNA vaccine dose administration. • MGI with 95% CI for SARS-CoV-2 Omicron XBB.1.5 neutralizing titers at 1 month after COVID-19 mRNA vaccine dose administration. • Percentage of participants having SARS-CoV-2 Omicron XBB.1.5 neutralizing titers ≥ cut-off and 95% CI at pre-vaccination and 1 month after the COVID-19 mRNA vaccine dose administration.

3.2.2. Safety Objectives

The secondary question of interest is to evaluate the safety and reactogenicity following administration of the RSVPreF3 OA investigational vaccine and a dose of COVID-19 mRNA vaccine, co-administered or administered alone.

Attributes					Summary measure
Treatment	Population	Endpoint (Variable)	Intercurrent events (ICEs)		
			Description	Handling strategy	
Co-ad group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 1 Control group: COVID-19 mRNA vaccine at Day 1 and RSVPreF3 OA investigational vaccine at Day 31	Adults ≥50 years at the time of first vaccination	• Occurrence of each solicited administration site event with onset within 4 days after study intervention administration. • Occurrence of each solicited systemic event with onset within 4 days after study intervention administration. • Occurrence of unsolicited AEs within 30 days after study intervention administration. • Occurrence of SAEs after study intervention administration (Day 1) up to study end (6 months after last study intervention administration). • Occurrence of pIMDs after study intervention administration (Day 1) up to study end (6 months after last study intervention administration).	1. Study vaccination not administered as per protocol. 2. Prohibited medication, vaccination or intercurrent medical condition prior to the blood sample.	All the data collected for the variable of interest are used regardless of whether the intercurrent event occurs (treatment policy).	The percentage of participants by group who report each of the endpoint.

4. STUDY DESIGN

4.1. Overall design

The study design overview is presented in Figure 1.

- **Type of study**: Self-contained.
- **Experimental design:** Phase 3, randomized, open-label study with 2 parallel groups (see Figure 1).
- **Study groups and randomization:** Approximately 830 eligible participants will be randomly assigned (1:1) to the following 2 groups: Co-Ad group and Control group at Visit 1 (Day 1). Each group will include approximately include 415 participants.
- **Vaccination schedule:**
  - **Co-Ad group:** Participants will receive a single dose of COVID-19 mRNA vaccine and a single dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1).
  - **Control group**: Participants will receive a single dose of COVID-19 mRNA vaccine at Visit 1 (Day 1), followed by a single dose of the RSVPreF3 OA investigational vaccine at Visit 2 (Day 31).
- **Primary completion date:** Day 61 (1 month after the RSVPreF3 OA investigational vaccine dose in Control group).
- **Duration of the study:** ~ 6 months for participants in Co-Ad group; ~ 7 months for participants in Control group.
- **Control:** Active comparator, i.e., staggered administration of licensed COVID-19 mRNA vaccine and RSVPreF3 OA investigational vaccine.
- **Blinding:** Open-label. Refer to Section 6.4 for details.
- **Data collection:** Standardized eCRF. Solicited events and unsolicited AEs will be collected using a participant Diary card (paper Diary card).
- **Safety monitoring:** The study will be conducted with oversight by the project SRT. Please refer to Section 10.1.6 for the SRT structure.
- **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 30% of participants 50-59 YOA, approximately 30% of participants 60-69 YOA and approximately 25% of participants ≥ 70 YOA. The remaining 15% can be distributed freely across the 3 age categories. The enrollment of participants as per the age categories, and percentage of participants in each age category, if any, will be guided by the feasibility assessment.

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

4.2. Scientific rationale for study design

Vaccination programs with SARS-CoV-2 mRNA vaccines have been implemented in many countries worldwide. SARS-CoV-2 mRNA vaccines are administered throughout the year and may thus be administered 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 a SARS-CoV-2 mRNA vaccine.

RSV is associated with serious illness in OA and high-risk adults, including those with chronic lung and heart disease or other co-morbidities that may lead to increased risk of RSV-LRTD. A large US prospective, population-based study reported the overall annual estimated incidence of RSV infection during 3 seasons among different age groups, in two different settings (New York City and Rochester). The specific estimated incidence ranged from 7.7–11.9/100 000 population, 33.5–57.5/100 000, and 136.9–255.6/100 000 in patients 18–49, 50–64, and ≥65 YOA, respectively. Moreover, the incidence of RSV infection in hospitalized adults of 50–64 and ≥65 YOA was approximately 5 and 15 times higher, respectively, than incidence among patients 18–49 YOA [Branche, 2022]. In another prospective study it was determined that the hospitalization rates for RSV were similar to those associated with influenza in adults aged ≥50 YOA [Widmer, 2012].

The US FDA and the EMA have authorized the Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion as a single dose for injection for active immunisation to prevent COVID-19 caused by the SARS-CoV-2, in individuals 12 years of age and older [Comirnaty product information package insert, EMA, 2023; US FDA, 2023].

Both RSVPreF3 OA investigational vaccine and SARS-CoV-2 vaccines will be available for individuals within similar age groups. These data are expected to help public health authorities provide more evidence-based guidance and health care providers to make decisions on such vaccine co-administrations.

The current study is therefore designed to assess the safety, reactogenicity and immunogenicity of the RSVPreF3 OA investigational vaccine when it is co-administered with a COVID-19 mRNA vaccine, compared to administration of the vaccines separately in adults aged 50 years and above.

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

4.2.1. Participant input into design

Not applicable.

4.3. Justification for dose

A single dose (0.5 mL) of the licensed formulation (120 µg RSVPreF3/AS01E) will be used in this study.

In the current study, the authorized Comirnaty Omicron XBB.1.5 30 micrograms/dose dispersion for injection will be administered.

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled contact as described in the protocol.

EoS: LSLV (contact at 6 months post-last dose) or Date of the last testing/reading released of the Human Biological Samples, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV.

5. STUDY POPULATION

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

5.1. Inclusion criteria

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

- Participants, who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits). **INC#1**

  Note: In case of physical incapacity that would preclude the self-completion of the diary cards, either site staff can assist the participant (for activities performed during site visits) or the participant may assign a caregiver to assist him/her with this activity (for activities performed at home). However, at no time will the site staff or caregiver evaluate the participant's health status while answering diaries or make decisions on behalf of the participant.
- Written or witnessed informed consent obtained from the participant (participant must be able to understand the informed consent) prior to performance of any study-specific procedure. **INC#2**
- A male/female of ≥50 YOA at the time of the first study intervention administration. **INC#3**
- Participants who are medically stable in the opinion of the investigator at the time of first vaccination. 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. **INC#4**

A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment.

- 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. **INC#5**
- Participants who have received previously a SARS-CoV-2 vaccine, being administered at least 3 months prior to study vaccination. **INC#6**
- Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and post-menopause. **INC#7**
- Female participants of childbearing potential may be enrolled in the study if the participant. **INC#8**
  - has practiced adequate contraception from 1 month prior to study intervention administration and agreed to continue adequate contraception for at least 1 month after the last vaccination.
  - has a negative pregnancy test on the day of and prior to study intervention administration.

Refer to Section 10.4.1 for definitions of women of childbearing potential, non-childbearing potential, menarche and menopause and section 10.4.2 on adequate contraception.

5.2. Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

5.2.1. Medical Conditions

- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study interventions, including a known history of severe allergic reaction (e.g., anaphylaxis) (For details on components of study interventions administered, refer to Table 5, [*Arexvy* Prescribing Information package insert, 2023] [*Arexvy* Summary of Product Characteristics, 2023] and *Comirnaty* Omicron XBB.1.5 COVID-19 mRNA vaccine SmPC/Prescribing information). **EXC#1**
- 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). **EXC#2**
- Any history of myocarditis or pericarditis. **EXC#3**

- Recurrent history 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 diary cards, attend regular phone calls/study site visits). **EXC#4**
- Serious or unstable chronic illness. **EXC#5**
- Any history of dementia or any medical condition that moderately or severely impairs cognition. **EXC#6**

  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.
- 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). **EXC#7**
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe. **EXC#8**
- Any SAE attributed to a previous dose of the SARS-CoV-2 mRNA vaccine. **EXC#9**
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the participant due to participation in the study. **EXC#10**
- Recent SARS-CoV-2 infection within 3 months prior to the COVID-19 vaccine dose administration. Timelines to be determined from symptoms onset or positive COVID-19 test (if infection was asymptomatic). **EXC#11**

5.2.2. Prior/Concomitant Therapy

- Use of any investigational or non-registered product (drug, vaccine or invasive medical device) other than the study interventions during the period beginning 30 days before the first dose of study interventions and ending 30 days after the last vaccine administration, or their planned use during the study period. **EXC#12**

  Note: 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'.
- Planned administration of a vaccine in the period starting 30 days before the first dose and ending 30 days after the last dose of study intervention(s) administration*, with the exception of inactivated and subunit influenza vaccines which can be administered up to 14 days before or from 14 days after the study vaccination. **EXC#13**

  *If emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organized by public health authorities outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine, provided it is used according to the local governmental recommendations and Sponsor is notified.

- Chronic administration of immune-modifying drugs (defined as more than 14 consecutive days in total) and/or planned use of long-acting immune-modifying treatments at any time up to the last blood sampling visit. **EXC#14**
  - Up to 3 months prior to the study intervention administration:
    - For corticosteroids, this will mean prednisone equivalent ≥ 20 mg/day. Inhaled and topical steroids are allowed.
    - Administration of immunoglobulins and/or any blood products or plasma derivatives.
  - Up to 6 months prior to study intervention administration: long-acting immune-modifying drugs including among others immunotherapy (e.g., TNF-inhibitors), monoclonal antibodies and antitumoral medication.
- Administration of any SARS-CoV-2 vaccine during the 3 months preceding the study COVID-19 mRNA vaccine administration. **EXC#15**
- Previous vaccination with licensed or investigational RSV vaccine. **EXC#16**

5.2.3. Prior/Concurrent Clinical Study Experience

- Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational intervention (drug/invasive medical device). **EXC#17**

5.2.4. Other Exclusion Criteria

- Pregnant or lactating female participant. **EXC#18**
- Female participant planning to become pregnant or planning to discontinue contraceptive precautions. **EXC#19**
- 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. **EXC#20**
- Participation of any study personnel or their immediate dependents, family, or household members. **EXC#21**
- Planned move during the study conduct that prohibits participation until study end. **EXC#22**
- Bedridden participants. **EXC#23**

5.3. Lifestyle considerations

Not applicable for this study.

5.4. Screen failures

A screen failure occurs when a participant who consents to participate in this study but is not entered in the study/randomized to a study intervention.

For screen-failed participants, limited data for screen failures (including demography, medical and vaccination history, eligibility criteria, concomitant medication, reason for screen failure and any SAEs that occurred at the visit) will be collected and reported in the eCRF to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities.

5.5. Criteria for temporarily delaying enrollment/ administration of study intervention

Study intervention administration may be postponed within the permitted time interval as deemed appropriate by the investigator until transient conditions cited below are resolved. Participants meeting these criteria at Visit 1 will be considered screen failures if enrollment has closed once the condition(s) has/have resolved:

- Acute disease and/or fever at the time of study intervention administration. Refer to the SoA (Section 1.3) for definition of fever and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- Participants with symptoms suggestive of active COVID-19 infection (e.g., fever, cough, etc.). The return of the participant to the site will follow the specific guidance from local public health and other competent authorities (e.g. free of symptoms, COVID-19 negative testing, etc.). Please refer to Exclusion criteria Section 5.2.1 for time interval for study COVID-19 vaccination after a recent COVID-19 infection.
- In case of administration of inactivated, subunit or split influenza vaccines (fully licensed): postponement of study intervention administration within given protocol timelines and prior to the end of the study enrollment period, to allow respect of at least 14 days interval between above mentioned influenza vaccination and study intervention administration.
- Other issues (e.g., technical or administrative) preventing dose administration on day of visit.

All efforts should be made so that blood sample is taken on the same date as vaccination. For Visit 1, if the planned study intervention administration is delayed, blood sampling does not need to be repeated if it was obtained during enrollment visit. The following procedures must be repeated prior to the delayed study intervention administration:

- Urine pregnancy test
- Body temperature
- Re-check contraindications, warnings, and precautions to study intervention

- Re-check inclusion/exclusion criteria

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

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

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

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of Definition of terms.

6.1. Study interventions administered

Refer Section 4 for the study intervention administration schedule.

Table 5 Study Intervention(s) Administered

Study intervention name:	**RSVPreF3 OA investigational vaccine**		**Comirnaty Omicron XBB.1.5 COVID-19 mRNA vaccine**
Study intervention formulation:	RSVPreF3 (120 µg)	AS01$_E$: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injections	Raxtozinameran (30 µg) embedded in LNP; Water for injections
Presentation:	Powder for suspension for injection; in vial	Suspension for suspension for injection; in vial	Dispersion for injection; in vial
Type:	Investigational		Comparator
Product category:	Biological		Biological
Route of administration:	IM injection		IM injection
Administration site:			
• **Location**	Deltoid		Deltoid
• **Directionality**	Upper		Upper
• **Laterality** **	Co-ad group: Dominant Control group: Non-dominant		Co-ad group: Non-dominant Control group: Non-dominant
Number of doses to be administered:	1		1
Volume to be administered by dose ***	0.5 mL		0.3 mL
Packaging and labelling:	Refer to the pharmacy manual for more details		Refer to the pharmacy manual for more details
Manufacturer:	GSK Biologicals SA		Pfizer-BioNTech

IM: Intramuscular; LNP: Lipid nanoparticle; MPL: Monophosphoryl lipid A.

* QS-21: *Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation).
** The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the study intervention in the non-dominant arm, an injection in the dominant arm may be performed.
*** Refer to the pharmacy manual for the volume after re-constitution.

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, syncope.

6.1.1. Medical devices

- There are no GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study. Other medical devices (not manufactured by or for GSK) provided for use in this study are thermometer for body temperature measurement, ruler for skin reaction measurement, materials for study intervention administration, syringes, blood collection kits, pregnancy kits and cup for urine collection.
- All medical devices are CE marked and will be used for their intended use. Instructions for medical device use are provided in Laboratory Manual and Pharmacy Manual.

6.2. Preparation, handling, storage, and accountability

- The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

6.3. Assignment to study intervention

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 830 eligible participants ≥50 YOA will be randomly assigned (1:1) to the study groups (Co-Ad or Control).

Participants will be assigned to study treatment in accordance with the randomization schedule. The randomization schedule, including stratification, will be generated using the GSK validated randomization software RANDALL NG. The randomization schedule is comprised of a series of blocks, with 1:1 treatment allocation within each block, which are shared across centers via central randomization.

6.3.3. Intervention allocation to the participant

An automated Internet-based system RTSM will be used for randomization and for identification of intervention material. The randomization algorithm will use a permutated block procedure, including age (50-59, 60-69 or ≥ 70 years) as stratification factor.

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 number(s) to be used for subsequent dosing will be provided by the same automated Internet-based system (RTSM).

When RTSM is not available, please refer to the RTSM user guide or pharmacy manual for specific instructions.

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

6.4. Blinding

This is an open-label study because of the difference in dosing schedules between the study groups. However, the specific study intervention to be taken by a participant will be assigned using randomization system on internet (RTSM). Study site personnel will be required to register participants using RTSM for assignment of a unique identifier (designating the participant's randomization code and treatment sequence assignment) for each participant participating in the study

The site will record the study intervention assignment on the applicable eCRF. Potential bias will be reduced by the following steps: [central randomization, adjudications].

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

6.5. 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 and time of administration of each study intervention dose will be recorded in the source documents.

6.6. Dose modification

Not applicable.

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

Not applicable.

6.8. Treatment of overdose

Not applicable.

6.9. Prior and 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 prior vaccines within 1 year before the first study vaccination administration, and all prior COVID-19 vaccines.
- All concomitant medication leading to discontinuation of the study intervention or elimination from the analysis, including products/vaccines. Please refer to Section 5.2.2 and Section 9.2.1 for further details.
- All concomitant medication which may explain/cause/be used to treat an SAE/pIMD including vaccines/products, as defined in Sections 8.4 and Section 10.3.5.7. These must also be recorded in the Expedited Adverse Event report.
- For all AF AESIs (including serious and non-serious), concomitant drugs which could be associated with development or worsening of AF must be reported in the AF follow-up questionnaire.
- Any prophylactic medication (e.g., analgesics, antipyretics) administered on the day of study 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 study intervention administration.

- All concomitant medication, including vaccines/products, except vitamins and dietary supplements, that the participant is receiving at the time of enrollment or up to 30-day post-last study intervention.
  - Reason for use
  - Dates of administration including start and end dates
  - Dosage information including dose and frequency

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

Any antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination need to be recorded on the eCRF.

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. In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if possible, 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 based on the list below:

Reasons	Additional items/Sub-reasons
AE	Unsolicited AE Solicited AE SAE/pIMDs
Lost to follow-up	
Withdrawal by Participant	Burden of Procedure Participant Relocated COVID-19 Other, specify
Investigator decision	Specify
Protocol Deviation	Specify
Site Terminated by Sponsor	
Study Terminated by Sponsor	
Pregnancy	
Death	
Other	Specify

AE= Adverse event; COVID-19= Coronavirus disease; pIMD= Potential immune-mediated disease; SAE= Serious adverse event.

7.1.1. Contraindications to subsequent study intervention(s) administration

The eligibility for participants in the control group for subsequent study intervention administration must be confirmed before administering the RSVPreF3 OA investigational vaccine at Visit 2.

Participants who meet any of the criteria listed below or criteria listed in Section 5.2.1 and Section 5.2.2 should not receive the RSVPreF3 OA investigational vaccine at Visit 2. Such participants should be encouraged to continue other study procedures, at the investigator's discretion. All relevant criteria for discontinuation of study intervention administration must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to the first study intervention (COVID-19 mRNA vaccine administered at Visit 1) or non-study concomitant vaccine/product, including hypersensitivity reactions and that, in the opinion of the investigator, may pose additional risk to the participant if he/she receives the second study intervention (RSVPreF3 OA investigational vaccine).
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participants if they continue to participate in the study.
- Anaphylaxis following the administration of study intervention(s).
- Condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Pregnant and lactating female participant (Refer Section 8.4.6) and lactation.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the participant to unacceptable risk from subsequent vaccination. In such cases, the investigator should use their clinical judgment prior to administering the next dose of the study intervention(s). Refer to Section 8.4.4.1 for the definition of pIMD.
- Occurrence of a new Adverse Event of Special Interest (AESI) or the exacerbation of an existing AESI that, in the opinion of the investigator, exposes the participant to unacceptable risk from subsequent doses of study intervention. Refer to Section 8.4.4 for the definition of AESI.

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

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. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. Local regulations may also require that any samples taken and not yet tested at the time a participant withdraws from the study are destroyed.

A participant can also request for the destruction of their samples any time during the study. The investigator must document the request in the site study records.

The primary reason for participant discontinuation/ withdrawal from the study will be documented in the eCRF based on the list below:

Reasons	Additional items/Sub-reasons
AE	Unsolicited AE Solicited AE SAEs/pIMDs
Lost to follow-up	
Withdrawal by Participant	Burden of Procedure Participant Relocated COVID-19 Other, specify
Investigator decision	Specify
Protocol Deviation	Specify
Site Terminated by Sponsor	
Study Terminated by Sponsor	
Pregnancy	
Death	
Other	Specify

AE= Adverse event; COVID-19= Coronavirus disease; pIMD= Potential immune-mediated disease; SAE= Serious adverse event.

Participants who are withdrawn from the study because of AEs/SAEs/AESIs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE/AESI until the event is resolved (see Section 10.3.5.5).

7.3. Lost to follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Subjects who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- Study participants may decide to assign a caregiver to help them fulfilling the study procedures. Please refer to the Definition of terms for the definition of a caregiver.
  - A caregiver can be appointed by the participant at any time during the study, when the participant feels it is necessary. Each caregiver should receive the caregiver information letter before providing support to the study participant.

Ideally, a single caregiver should be appointed by the participant but, in some situations, it may happen that several caregivers will support a study participant throughout the conduct of the study. This should be recorded in the source documents.

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

- If allowed by country regulation/ethics, study assessments may be conducted remotely by a HHS professional and/or virtually (TM, secure video conferences, phone calls, or a web portal and/or mobile application); however, on-site visits are required as per the SoA (Section 1.3).
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 30 mL Co-Ad group and 45 mL for Control group. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative and baseline procedures

8.1.1. Collection of demographic data

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

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

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

Year of birth is collected to stratify the population and determine the impact of the study intervention by age.

8.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history by interviewing the participant and/or review of the participant's medical/vaccination records. Record any relevant pre-existing conditions, signs and/or symptoms present prior to the study interveniton in the eCRF. History of previous SARS-CoV-2 infection(s) should also be recorded.

History of following vaccine administration should be recorded in the eCRF.

- Any vaccine administered up to 1 year before study vaccine administration (if possible, with date of vaccination).
- COVID-19 vaccine administration (if possible, with the date of vaccination; this information should be collected even if administration was >1 year).

8.1.3. 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/100.4°F regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit, refer to Table 4 for the Control group.

8.2. Immunogenicity assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA (see Section 1.3).

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

8.2.1. Biological samples

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

- Co-Ad group: 2 x ~15 mL = ~30 mL
- Control group: 3 x ~15 mL = ~45 mL

Refer to Table 6 and SoA (Section 1.3) for information on volumes collected for different assessments.

Table 6 Biological samples

Sample type	Quantity	Unit	Timepoint	Group
Blood for humoral response	~15	mL	Visit 1 (Day 1) Visit 2 (Day 31)	All participants in the Co-Ad group
Blood for humoral response	~15	mL	Visit 1 (Day 1) Visit 2 (Day 31) Visit 3 (Day 61)	All participants in the Control group

8.2.2. Laboratory assays

Table 7 Laboratory assays

Test Classification	System	Component	Method	Laboratory*
RSV Humoral Immunity (functional capacity)	Serum	RSV A neutralization titer	Neutralization	GSK**
		RSV B neutralization titer	Neutralization	
SARS-CoV-2 Humoral immunity (functional capacity)	Serum	SARS-CoV-2 Omicron XBB 1.5 variant Neutralization titer	Neutralization assay against pseudoviruses	Nexelis

* Refer to the list of clinical laboratories for details.
** GSK laboratory refers to the Vaccines Clinical Laboratory and Assay Portfolio (Vx CL&AP) in Rixensart, Belgium; Wavre, Belgium. Vx CL&AP may delegate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Siena, Italy or to a contracted CRO.
† Other serological assays or methods may be used to characterize the antibody responses.

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.

8.2.3. Immunological read-outs

Table 8 Immunological read-outs

Blood sampling timepoint		Subset name	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Co-Ad group				
Visit 1 (Day 1)	Pre-dose 1	All participants	415	RSV A neutralization titer
				RSV B neutralization titer
				SARS-CoV-2 Omicron XBB 1.5 variant neutralization titer
Visit 2 (Day 31)	Post-dose 1	All participants	415	RSV A neutralization titer
				RSV B neutralization titer
				SARS-CoV-2 Omicron XBB 1.5 variant neutralization titer
Control group				
Visit 1 (Day 1)	Pre-SARS-CoV-2 dose	All participants	415	SARS-CoV-2 Omicron XBB 1.5 variant neutralization titer
Visit 2 (Day 31)	Post-SARS-CoV-2 dose	All participants	415	SARS-CoV-2 Omicron XBB 1.5 variant neutralization titer
	Pre-RSV dose	All participants	415	RSV A neutralization titer
				RSV B neutralization titer
Visit 3 (Day 61)	Post-RSV dose	All participants	415	RSV A neutralization titer
				RSV B neutralization titer

8.2.4. Cytology

Not applicable.

8.2.5. Immunological correlates of protection

No generally accepted immunological CoP has been demonstrated so far for the antigen used in the RSVPreF3 OA investigational vaccine or in the COVID-19 mRNA vaccine.

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. History directed physical examination

- History directed physical examination will be performed for each participant. At each subsequent visit, a targeted physical examination will be performed, as needed.
- If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to the Section 5.5 for the list of criteria for temporary delay of study intervention administration. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

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

8.3.2. Clinical safety laboratory tests

No clinical safety laboratory tests are scheduled for this study.

8.3.3. Pregnancy testing

- Female participants of childbearing potential must perform a urine pregnancy test before the administration of any dose of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- Refer to Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

8.3.4. Safety monitoring AND Committee

- Participant safety will be continuously monitored by the Medical Monitor, designated Safety Lead (or delegate) and Safety Review Team (SRT), throughout the study. Pertinent findings and conclusions are shared with the product's SRT for review of the overall benefit-risk profile of the product.

8.3.5. Post-vaccination procedures

8.3.5.1. 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 any AESIs since last study intervention administration, and to collect information on concomitant medications/ vaccinations.

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

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

8.4. Adverse Events (AEs), serious adverse events (SAEs), and other safety reporting

For definitions relating to safety information see Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information and remain responsible for following up all AEs or AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

All AEs and SAEs will be collected at the timepoints specified in the SoA (Section 1.3).

AF reporting will follow the same reporting periods as for AEs and SAEs. Non-serious AF with an onset during the 30-day period following each study vaccine administration will be collected. The reporting of AF meeting the SAE definition (serious AF) will be performed according to the SAE reporting period.

SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product (non-IMP) will be recorded from the time a participant consents to participate in the study.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

Table 9 Timeframes for collecting and reporting of safety information

Co-Ad group								
Event	**Pre-dose***	**Vacc Co-Ad**						**6 months post-last dose** Study conclusion**
		D1	**D4**	**D31**				
Solicited administration site and systemic events								
Unsolicited AEs***								
Control group								
Event	**Pre-dose***	**Vacc SARS-CoV-2**			**Vacc RSV**			**6 months post-last dose** Study conclusion**
		D1	**D4**	**D31**	**D31**	**D34**	**D61**	
Solicited administration site and systemic events								
Unsolicited AEs***								
All participants								
All SAEs***								
All pIMDs								
Pregnancy								
SAEs related to study participation or concurrent GSK medication/vaccine								
AEs/SAEs leading to withdrawal from the study								
Intercurrent medical conditions								

D: day; AE: adverse event; AESI = Adverse event of special interest; AF = Atrial fibrillation; SAE: serious adverse event; pIMD: potential immune-mediated disease.

* i.e., consent obtained on Day 1 (prior to vaccination).

** Post-last dose= 6 months after Co-Ad study intervention administration (Co-Ad group) or 6 months after RSV study intervention administration (Control group).

*** AF will be considered as AESI in this study and will be additionally reported in the AF follow-up questionnaire in eCRF. The reporting of non-serious AF will be performed according to the unsolicited AE reporting period. The reporting of AF meeting the SAE definition (serious AF) will be performed according to the SAE reporting period. Fatal AF and Serious AF judged as related to study vaccination will be reported according to the fatal SAE and related SAE reporting period, respectively.

Note: COVID-19 cases will be collected during the same timeframes as those used for collecting and reporting the other safety information (unsolicited AEs/SAEs, etc.)

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. 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 period defined in Section 8.4.1 and Table 9.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 8.4.4) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For AF cases, the investigator will provide any new or updated relevant information on previously reported AF during the study to GSK using a paper/electronic Expedited AEs Report and the AF follow-up questionnaire as applicable. Further information on follow-up procedures is provided in Section 10.3.5.5.

8.4.4. Adverse events of special interest

pIMDs and Atrial Fibrillation are the AESIs collected during the study.

8.4.4.1. Potential immune-mediated diseases

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 the Table 10.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators at study start.

The investigator(s) must exercise their medical/scientific judgment to determine whether other diseases have an autoimmune origin (i.e., pathophysiology involving systemic or

organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD. In addition, the investigator should categorize each pIMD either as a new onset condition (if it started following vaccination) or as an exacerbation of a pre-existing chronic condition (if it exacerbated following vaccination) in the eCRF.

Table 10 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
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)

Medical Concept	Additional Notes
	• 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	
Graves' 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	

Medical Concept	Additional Notes
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis • Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease • Felty's syndrome
Sjögren's syndrome	
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blenorrhagica • Psoriatic spondylitis • Reactive Arthritis • 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 Raynaud's syndrome, 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 necrotising 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)

Medical Concept	Additional Notes
	• Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis
Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	Including but not limited to: • Cranial nerve neuritis (e.g. Optic neuritis) • Idiopathic nerve palsies/paresis (e.g. Bell's palsy) • Melkersson-Rosenthal syndrome • Multiple cranial nerve palsies/paresis
Multiple Sclerosis (MS)	Includes the following: • Clinically isolated syndrome (CIS) • Malignant MS (the Marburg type of MS) • Primary-progressive MS (PPMS) • Radiologically isolated syndrome (RIS) • Relapsing-remitting MS (RRMS) • Secondary-progressive MS (SPMS) • Uhthoff's phenomenon
Myasthenia gravis	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy
Peripheral inflammatory demyelinating neuropathies and plexopathies	Including but not limited to: • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) • Antibody-mediated demyelinating neuropathy • Chronic idiopathic axonal polyneuropathy (CIAP) • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) • Multifocal motor neuropathy (MMN)
Transverse myelitis (TM)	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis

Medical Concept	Additional Notes
	• 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
Localised Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Takayasu's arteritis
Medium sized and/or small vessels vasculitis	Including but not limited to: • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Behcet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis)

Medical Concept	Additional Notes
	• Erythema induratum (also known as nodular vasculitis) • Henoch-Schonlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis • Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Granulomatosis with polyangiitis
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	

8.4.4.2. Atrial fibrillation (AF)

AEs of AF are considered as AESI in this study.

In the efficacy study (RSV OA=ADJ-006), at the time of safety analysis (data lock point [DLP]) of 30 April 2022, a numerical imbalance in events of AF was observed within 30 days post-vaccination, with 10 events of AF (among which 7 [0.1%] were serious) in the RSVPreF3 group versus 4 (among which 1 [<0.1%] was serious) in the placebo group. No imbalance was observed for serious events of AF reported within 6 months

post-vaccination. To further characterize events of AF, AF will be considered as an AESI.

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

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

8.4.5. Regulatory reporting requirements for SAEs/AESIs /pregnancies

- Prompt notification by the investigator to the sponsor of an SAE/AESI /pregnancies is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- For SAEs /AESIs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.5.3.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Table 11 Timeframes for submitting SAEs, pregnancies and pIMDs to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*	electronic Adverse Events Report	24 hours*	electronic Adverse Events Report
pIMDs	24 hours**	electronic Adverse Events Report	24 hours*	electronic Adverse Events Report
Serious AF***	24 hours**	electronic AEs Report + AF follow-up questionnaire	24 hours*	electronic AEs Report + AF follow-up questionnaire
Pregnancies	24 hours*	electronic pregnancy report	24 hours*	electronic pregnancy report

* 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 an AESI.
*** Only AF meeting SAE definition will be reported in electronic AEs Report and in the specific AF follow-up questionnaire. Non-serious AF will be reported in the non-serious adverse event eCRF screen and in the AF follow-up questionnaire.

8.4.6. Pregnancy

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

- Details of all pregnancies in female participants will be collected after the start of study intervention and until end of study (refer Section 5.1).
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. See Table 11 for reporting timeframes.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.4.7. Contact information for reporting SAEs, AESIs, and pregnancies

Table 12 Contact information for reporting SAEs, AESIs, and pregnancies

Study contact for questions regarding SAEs, AESIs and pregnancies Contact GSK's local and/or medical contacts
Contacts for reporting SAEs, AESIs and pregnancies Available 24/24 hours and 7/7 days ogm28723@gsk.com

8.4.8. Participant card

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

8.5. Pharmacokinetics

PK is not evaluated in this study.

8.6. Pharmacodynamics

PD is not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity assessments

Immunogenicity is described in Section 8.2.

8.10. Health economics or medical resource utilization and health economics

Not applicable for this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

Statistical hypotheses are associated to the confirmatory primary non-inferiority (NI) objectives, which will be tested to control overall Type I error. Global Type I error is controlled at 2.5% (1-sided). The study includes three confirmatory primary objectives. The NI margins associated to each objective are provided in Table 13.

Table 13 Study Objectives and Null Hypothesis

Objectives	Null hypothesis	Success criteria
Primary		
To demonstrate non-inferiority of humoral immune response to RSVPreF3 OA investigational vaccine when co-administered with a COVID-19 mRNA vaccine compared to RSVPreF3 OA investigational vaccine administered alone.	• True Group GMT ratio between Control group (at Day 61) divided by Co-ad group (at Day 31) for RSV-A neutralization titers 1-month after the RSVPreF3 OA investigational vaccine dose is above 1.5. • True Group GMT ratio between Control group (at Day 61) divided by Co-ad group (at Day 31) in RSV-B neutralization titers 1-month after the RSVPreF3 OA investigational vaccine dose is above 1.5.	• The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for RSV-A neutralization titer 1-month after the RSVPreF3 OA investigational vaccine dose is ≤1.5. • The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for RSV-B neutralization titer 1-month after the RSVPreF3 OA investigational vaccine dose is ≤1.5.
To demonstrate non-inferiority of humoral immune response to a COVID-19 mRNA vaccine when co-administered with the RSVPreF3 OA investigational vaccine compared to a COVID-19 mRNA vaccine administered alone.	• True Group GMT ratio between Control group (at Day 31) divided by Co-ad group (at Day 31) for SARS-CoV-2 neutralization titers 1-month after the COVID-19 mRNA vaccine dose is above 1.5.	• The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 31) versus Co-ad group (at Day 31) for SARS-CoV-2 neutralization titers 1-month after the COVID-19 mRNA vaccine dose is ≤1.5.

Abbreviations: Co-ad=co-administration group; CI=confidence interval, GMT=geometric mean titer, RSV-A=respiratory syncytial virus subtype A; RSV-B=respiratory syncytial virus subtype B; RSVPreF3-OA=respiratory syncytial virus prefusion protein 3 older adult investigational vaccine.

Co-ad group: RSVPreF3 OA investigational vaccine when co-administered with the COVID-19 mRNA vaccine.

Control group: Administration of COVID-19 mRNA vaccine, followed by RSVPreF3 OA investigational vaccine with one month difference.

9.2. Analysis sets

Analysis sets are presented in Table 14.

Table 14 Analysis sets

Analysis set	Description
Screened Set	All participants who were screened for eligibility.
Enrolled Set [1]	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure).
Exposed Set	All participants who received the study intervention. Analysis per group is based on the administered intervention.
RSV PPS [2]	All eligible participants: • Who received RSV vaccine as per-protocol in the control group and received all the study interventions in the Co-ad group • Who had immunogenicity results pre and post-dose for RSV neutralization titers • Who comply with the blood draw intervals for RSV samples • Without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination up to blood sample post RSV vaccination • Who do not meet any of the criteria for elimination up to blood sample post RSV vaccination
COVID-19 mRNA PPS [2]	All eligible participants: • Who received a COVID-19 mRNA vaccine as per-protocol in the control group and received all the study interventions in the Co-ad group • Who had immunogenicity results pre and post-dose for SARS-CoV-2 neutralization titers • Who comply with the blood draw intervals for SARS-CoV-2 samples • Without intercurrent medical conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination up to blood sample post COVID-19 mRNA vaccination • Who do not meet any of the criteria for elimination up to blood sample post COVID-19 mRNA vaccination

[1] Screen failures (who never passed screening) and participants screened but never enrolled into the study (met eligibility but not needed to reach the target enrollment) are excluded from the Enrolled Set as they did not enter the study.
[2] Contribution of participants to PPS will be defined by timepoint.

9.2.1. Criteria for elimination from analysis

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

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

The co-primary endpoints are described in Table 4. The confirmatory analyses of non-inferiority will be based on the PPS.

If in any study group the percentage of vaccinated participants with serological results excluded from the PPS is more than 5%, a second analysis based on the ES will be performed to complement the PPS analysis.

- Method for non-inferiority of RSV-A specific neutralization titer 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 RSVPreF3 OA investigational vaccine administered alone (Control group) over RSVPreF3 OA investigational vaccine when co-administered with the COVID-19 mRNA vaccine (Co-Ad group) and derived from an analysis of covariance (ANCOVA) model on $\log_{10}$ transformed titer. The model will include the treatment group, the age category (age at vaccination: 50-59, 60-69 or ≥70 years) as fixed effects, and the pre-dose $\log_{10}$-transformed titer as covariate. Missing data will not be replaced. Titers below the assay lower limit of quantification (LLOQ) will be replaced by half the assay cut-off, titers above the upper limit of quantification (ULOQ) will be replaced by the ULOQ.

- Method for non-inferiority of RSV-B specific neutralization titer 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 RSVPreF3 OA investigational vaccine administered alone (Control group) over RSVPreF3 OA investigational vaccine when co-administered with the COVID-19 mRNA vaccine (Co-Ad group) and derived from an analysis of covariance (ANCOVA) model on $\log_{10}$ transformed titer. The model will include the treatment group, the age category (age at vaccination: 50-59, 60-69 or ≥70 years) as fixed effects, and the pre-dose $\log_{10}$-transformed titer as covariate. Missing data will not be replaced. Titers below the assay LLOQ will be replaced by half the assay cut-off, titers above the ULOQ will be replaced by the ULOQ.

- Method for non-inferiority of SARS-CoV-2 neutralization titers GMT ratio at 1 month after the COVID-19 mRNA vaccine (i.e., at Day 31 for both groups):

  The 2-sided 95% CI for group GMT ratio between COVID-19 mRNA vaccine administered alone (Control group) over RSVPreF3 OA investigational vaccine when co-administered with the COVID-19 mRNA vaccine (Co-Ad group) and derived from an ANCOVA model on $\log_{10}$ transformed titer. The model will include

the treatment group and the age category (age at vaccination: 50-59, 60-69 or ≥70 years) as fixed effects, and the pre-dose log_{10}-transformed concentration as covariate. Missing data will not be replaced. Titers below the assay LLOQ will be replaced by half the assay cut-off, titers above ULOQ will be replaced by the ULOQ.

Success criteria for non-inferiority:

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

AND

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

AND

The upper limit of the 2 sided 95% CI of the GMT ratio between the Control group (at Day 61) versus Co-ad group (at Day 31) for SARS-CoV-2 neutralization titer 1-month after the COVID-19 mRNA vaccine dose is ≤1.5.

9.3.2. Secondary endpoints/estimands analyses

The secondary endpoints are described in Table 4. Descriptive analyses of demography, immunogenicity and safety will be detailed in the SAP.

Mean geometric increase (MGI) is defined as the geometric mean of the within subject ratios of the post-dose titer over the pre-dose titer.

The SRR is defined as the proportion of participants having a fold increase in neutralization titers (1 month post-study intervention administration over pre-study intervention administration) ≥4.

9.4. Interim analyses

No interim analysis will be performed.

9.4.1. Sequence of analyses

The analyses will be performed stepwise:

- A first analysis will be performed on all immunogenicity, reactogenicity and safety data available and as clean as possible, when data are available for primary and secondary endpoints up to and including Visit 3 (Day 61) are available for all participants. This analysis will be considered as final for those endpoints.
- An end of study (EoS) analysis will be performed when all data up to the contact 6 months post-last dose will be available for all participants.

9.4.2. Statistical Considerations for Interim Analyses

This section is not applicable.

9.5. Pre-dose sample size determination

Table 15 shows that the probability (global power) to reach the non-inferiority criterion with 722 evaluable participants (361 in Co-Ad and 361 in Control group) is at least 90.1%, with a 1-sided alpha = 0.025.

Table 15 Power to demonstrate non-inferiority of the Co-Ad group compared to the Control group in terms of GMT with 361 evaluable participants per group.

Endpoint	Standard deviation of log10 concentration	Reference ratio	Non inferiority margin	Type II error	Power
RSVPreF3 OA investigational vaccine Non-inferiority* (1-sided test with alpha = 2.5%)					
GMT RSV-A neutralization titers	0.45	1.05	1.5	0.4%	99.6%
GMT RSV-B neutralization titers	0.45	1.05	1.5	0.4%	99.6%
COVID-19 mRNA vaccine Non-inferiority* (1-sided test with alpha=2.5%)					
GMT SARS-CoV-2 neutralization titer	0.63	1.05	1.5	9.1%	90.9%
Global Power and Global Type II error				9.9%	90.1%

GMT: geometric mean titer
Non-inferiority limit = 0.176 (=$\log_{10}$[1.5]).
Reference Ratio = 0.0212 (=$\log_{10}$[1.05])
Pass 2022 (Non-Inferiority test of 2 independent means). Power = 100-the Type II error (Beta). The Type II error (Beta) has been adjusted using Bonferroni's method (overall Type II error = sum of the individual Type II errors).

The primary objective analysis will be performed on the PPS. Assuming about 13% non-evaluable rate among enrolled participants up to 2-month post-vaccination (participants dropped-out or excluded from the PPS), a total of 830 participants (415 per group) will have to be vaccinated in order to reach 361 participants evaluable for the primary objective.

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 the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that physical informed consent was obtained before the participant was enrolled in the study and the date the physical consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical copy of the ICF(s) must be provided to the participant.
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.
- In case of unexpected pregnancy, participant must be informed that Personal Information such as date of birth, sex of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Recruitment strategy

No screening visit is planned for this study. 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.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, that their data will be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

10.1.6. Committees structure

A SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

10.1.7. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical 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, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-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.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs 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 CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the Quality Plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/ equivalent summary unless local regulations or institutional policies require a

different 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.

- When copies of source documents are shared externally for review by a central reader mechanism (e.g., endpoint adjudication committee; expert reader), documents are stored by the external body for 25 years.

10.1.9. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Definition of terms.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Copies of documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g. endpoint adjudication committee; expert reader). The non-exhaustive list of documents shared to inform the central reader may include discharge summaries, imaging reports, ECG reports etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the investigator sites prior to transfer. Details of the list of documents and the redaction procedure are provided in the site manual or equivalent. These documents will be used by the third party solely for the purpose indicated within this protocol.

10.1.10. Study and site start and closure

Start of study and first act of recruitment

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

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily 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 temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication policy

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

10.2. Appendix 2: Clinical laboratory tests

RSV A/B neutralization assay

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

Virus neutralization is performed by incubating a fixed amount of RSV A strain (Long, ATCC No. VR-26) or RSV B strain (18537, ATCC No. VR-1580) with serial dilutions of the test serum. The serum-virus mixture is then transferred onto a layer of Vero cells (African Green Monkey, kidney, *Cercopitheus aethiops*, ATCC CCL 81) and incubated for 2 days to allow infection of the Vero cells by non-neutralized virus and the formation of plaques in the cell layer. Following a fixation step, RSV-infected cells are detected using a primary antibody directed against RSV (Polyclonal anti-RSV A/B IgG) and a secondary antibody conjugated to horseradish 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). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at each serum dilution and the number of plaques in the virus control wells (no serum added). The serum neutralization titer is expressed in ED60 (Estimated Dilution 60) and corresponds to the inverse of the interpolated serum dilution that yields a 60% reduction in the number of plaques compared to the virus control wells, as described by others [Barbas, 1992; Bates, 2014]. Titers will also be expressed in International Units per milliliter (IU/mL). Secondary standard calibrated against the international reference (NIBSC 16/284 [McDonald, 2018; McDonald, 2020]) will be included in the runs.

Pseudotyped Virus Neutralization Assay (PNA)

The SARS-CoV-2 PNA evaluates the level of SARS-CoV-2 neutralization titers present in the human serum samples. Pseudotyped virus particles are made from a modified Vesicular Stomatitis Virus (VSVΔG) backbone and bear the spike glycoprotein of the SARS-CoV-2 variant of interest. In addition, the pseudoparticles contain a luciferase reporter gene to allow detection and quantification of VSVΔG internalized by the target cells. The intensity of luminescence is quantified in relative luminescence units (RLU) and is inversely proportional to the neutralization titer. The neutralizing titer of a serum sample is calculated as the reciprocal serum dilution corresponding to the 50% signal reduction (NT50) for that sample.

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

10.3.1. Definition of AE

AE definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. NOTE: 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 study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (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 diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- Results in death
- Is life threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect in the offspring of a study participant
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)
- Is a suspected transmission of any infectious agent via an authorized medicinal product

- **Other situations:**
  - Possible Hy's Law case: ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (>35% direct bilirubin) or INR >1.5 must be reported as SAE
  - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Solicited events

Solicited events are predefined events administration site events and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Table 16 Solicited administration site events

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

Table 17 Solicited systemic events

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

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

10.3.4. Unsolicited AE

• **Definition of unsolicited AE**
An unsolicited AE is an AE that was either not included in the list of solicited events or could be included in the list of solicited events but with an onset outside the specified period of follow-up for solicited events. Unsolicited AEs must have been communicated by participants who has signed the informed consent. Unsolicited AEs include both serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The 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 nor 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. Recording, assessment and follow-up of AEs, SAEs AESIs and pregnancies

10.3.5.1. AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the eCRF/required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- A diary card 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 diary card.
- Anyone who measures administration site or systemic events and who will record the event in the diary card should be trained on using the diary card. This training must be documented in the participant's source record.

- For each solicited and unsolicited AE the participant experiences, the participant will be asked if they received medical attention (defined as unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the participant's diary (for solicited AEs) and in the participant's eCRF as part of normal AE reporting (for unsolicited AEs). Medical attention received for SAEs/AESIs will have to be reported using the normal AE reporting process in the eCRF.
- If any individual other than the participant is making entries in the paper Diary, their identity must be documented in the participant's source record.
- Collect and verify completed diary card during discussions with the participant on Visit 2 (from all participants) and Visit 3 (only from participants in the Control group).
- Any unreturned diary card will be sought from the participant through telephone call(s) or any other convenient procedure.
- The investigator or delegate will transcribe the required information into the eCRF in English.

10.3.5.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE, AESIs, SAE and pegnancies reported during the study and assign it to one of the following categories:

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

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

Table 18 Intensity scales for solicited events in participants ≥50 YOA

Event	Intensity grade	Parameter
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Redness at administration site	See Table 16	Greatest surface diameter in mm
Swelling at administration site	See Table 16	Greatest surface diameter in mm
Temperature*	See Table 17	Temperature in °C/°F
Headache	0	None/Normal**
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	None/Normal**
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia	0	None/Normal**
	1	Mild: Myalgia present but does not interfere with activity
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia	0	None/Normal**
	1	Mild: Arthralgia present but does not interfere with activity
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

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

**For participants already experiencing some of the solicited systemic events, 'Normal' corresponds to 'similar to baseline' and only discomfort above baseline is to be reported as ≥1.

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

Table 19 Intensity scales of administration site erythema/swelling, and fever

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

The 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 judgement.

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.

10.3.5.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.5.4. Assessment of outcomes

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

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

10.3.5.5. Follow-up of AEs, SAEs, AESIs, and pregnancies

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.
- After the initial AE/SAE/AESI /pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.
- Other non-serious AEs must be followed until end of the study or until the participant is lost to follow-up.

Follow-up during the study

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

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

Follow-up of pregnancies

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

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

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.5.7.

10.3.5.6. Updating of SAE, AESI and pregancy information after removal of write access to the participant's eCRF

When additional SAE, AESI or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.3).

10.3.5.7. Reporting of SAEs, AESIs and pregnacies

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section).
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

Contacts for SAE reporting can be found in Section 8.4.7.

SAE Reporting to GSK via Paper Data Collection Tool

- Email/fax transmission of the SAE paper data collection tool is the preferred method to transmit this information.
- In rare circumstances and in the absence of email/fax equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.

Contacts for SAE reporting can be found in Section 8.4.7.

10.4. Appendix 4: Guidance on Contraception, Women not considered as WOCBP and collection of pregnancy information

This section covers wording on the definition of what we consider to be a woman of childbearing potential as well as guidance on what is considered as adequate contraception.

10.4.1. Definitions

10.4.1.1. Woman of childbearing potential (WOCBP)

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal unless permanently sterile (see below).

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.4.1.2. Woman of Nonchildbearing potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female permanently sterile due to one of the following procedures:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For permanently sterile individuals due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry. If reproductive status is questionable, additional evaluation should be considered.

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

- Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

  - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception guidance

10.4.2.1. Woman of childbearing potential (WOCBP)

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods (Table 20).

Table 20 Highly effective contraceptive methods

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

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

[b] For WOCBP taking hormonal contraception, an additional barrier contraception method is recommended if they are concomitantly taking drugs that interact and reduce effectiveness of hormonal contraception. The investigator should check the list of drugs that could reduce hormonal contraceptive effectiveness (Potent drug enzyme inducers).

10.5. Appendix 5: Country-specific requirements

Not applicable.

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