CLINICAL STUDY PROTOCOL

Primary Study Intervention	GSK's investigational respiratory syncytial virus (RSV) vaccine BIO RSV OA=ADJ (GSK3844766A)
Study Identifier	222253 (RSV OA=ADJ-025)
EU CT Number	2023-510190-34-00
Approval Date	03 May 2024
Title	A Phase 3b, open-label study to evaluate the non-inferiority of the immune response and to evaluate the safety of the RSVPreF3 OA investigational vaccine in adults 18-49 years of age at increased risk for respiratory syncytial virus disease, compared to older adults ≥60 years of age.
Brief Title	A study on the immune response and safety of vaccine against respiratory syncytial virus given to adults 18 to 49 years of age at increased risk for respiratory syncytial virus disease, compared to older adults 60 years of age and above.
Sponsor	GlaxoSmithKline Biologicals S.A. Rue De L'Institut 89 1330 Rixensart Belgium
Sponsor signatory	Veronica Hulstrøm, MD, PhD Clinical Project Lead RSV Older Adults

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

Protocol Amendment 1 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 and/or the participant's LAR.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of GSK in the monitoring 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	222253 (RSV OA=ADJ-025)
EU CT number	2023-510190-34-00
Approval date	03 May 2024
Title	A Phase 3b, open-label study to evaluate the non-inferiority of the immune response and to evaluate the safety of the RSVPreF3 OA investigational vaccine in adults 18-49 years of age at increased risk for respiratory syncytial virus disease, compared to older adults ≥60 years of age.
Investigator name	
Signature	
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	03 May 2024
Original Protocol	18 December 2023

Amendment 1 (03 May 2024)

Overall rationale for the current Amendment:

The purpose of this amendment is to implement a new Cohort 3 as a Part B of this study to collect safety information in an extended sample size to better characterize the safety profile of the RSVPreF3 OA investigational vaccine in a population of individuals at increased risk for RSV disease 18-49 years of age. It is planned to include an extra ~600 adults 18-49 years of age at increased risk for RSV disease, who will be monitored for reactogenicity and safety for a period of 6 months following the administration of one dose of RSVPreF3 OA investigational vaccine at Visit 1. The same inclusion and exclusion criteria as well as enrolment rules as for participants of Cohort 1 will apply for Cohort 3.

Minor editorial changes for consistency and clarity have also been made and typographical errors have been corrected.

Other updates made to the protocol are described in the table below.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
1.2 Schema	Included the study design overview for Part B	The study population has been extended to include a cohort of AIR participants 18-49 YOA to better characterize the safety profile of the RSVPreF3 OA investigational vaccine in this population.
1.3 Schedule of activities	A separate table for Part B schedule of activities and intervals between study visits has been added.	
3 Objectives, endpoints and estimands	Differentiated the objectives, endpoints and estimands that are specific to Part A and Part B	
4.1 Overall design	Study design details for Part B (Cohort 3) have been included.	
5.1 Inclusion criteria	Numbering has been added for each inclusion criterion.	This change has been made to align with latest protocol template
5.2 Exclusion criteria	Numbering has been added for each exclusion criterion.	This change has been made to align with latest protocol template
6.3.3 Intervention allocation to the participant	Participants enrolment in Part B has been included	The study population has been extended to include a cohort of AIR participants 18-49 YOA to better characterize the safety profile of the RSVPreF3 OA investigational vaccine in this population.
9 Statistical considerations	Additional details for Cohort 3 has been provided where applicable.	
10.5. Appendix 5: Country-specific requirements	Added South Africa specific requirements for HIV participants	This change has been made to align with local requirements.
10.6 Appendix 6: Grading scaled for chronic diseases in scope of the AIR population	Added Appendix 6: Grading scales for chronic diseases in scope of the AIR population	This was added to clarify the grading of medical conditions mentioned in Section 5.1.1.
Throughout protocol	Administrative and editorial changes were made to align table numbers, formatting, and cross references.	To maintain consistency with template guidance.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AAION	Arteritic Anterior Ischemic Optic Neuropathy
ACTM	Acute Complete Transverse Myelitis
ADE	Adverse device effect
AE	Adverse event
AESI	Adverse event of special interest
AF	Atrial fibrillation
AHEI	Acute Hemorrhagic Edema of Infancy
AIR	At Increased Risk
AMSAN	Acute Motor and Sensory Axonal Neuropathy
ANCA	Anti-Neutrophil Cytoplasmic Antibody
APTM	Acute Partial Transverse Myelitis
AS01	Adjuvant System 01
ATCC	American Type Culture Collection
BYOD	Bring Your Own e-Device
CA	Competent authority
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CIAP	Chronic Idiopathic Axonal Polyneuropathy
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
CIOMS	Council for International Organizations of Medical Sciences
CIS	Clinically Isolated Syndrome
CCI	[redacted]

Abbreviation	Definition
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CREST	Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia
CRO	Clinical Research Organization
CSR	Clinical study report
DLP	Data lock point
DRE	Disease-related event
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic Diary
EOS	End-of-study
ERD	Enhanced Respiratory Disease
ES	Exposed Set
EU	European Union
EUA	Emergency use authorization
FSFV	First subject first visit
FSH	Follicle Stimulating Hormone
GCP	Good clinical practices
GMT	Geometric Mean Titer
GOLD	Global Initiative for Chronic Disease Obstructive Lung Disease
GSK	GlaxoSmithKline Biologicals SA
HHS	Home healthcare services

Abbreviation	Definition
HIPAA	Health Insurance Portability and Accountability Act
HLT	High Level Term
HRT	Hormonal Replacement Therapy
IAF	Informed assent form
IB	Investigator Brochure
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICSR	Individual case safety reports
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IgG	Immunoglobulin
IM	Intramuscular
IMP	Investigational medicinal product
IRB	Institutional review board
ITP	Idiopathic thrombocytopenic purpura
LABD	Linear IgA-mediated Bullous Dermatosis
LAR	Legally acceptable representative
LRTD	Lower Respiratory Tract Disease
LSLV	Last Subject Last Visit
MART	Maintenance and Reliever Therapy
MGI	Mean Geometric Increase
MIS-A	Multisystem Inflammatory Syndrome in Adults

Abbreviation	Definition
MIS-C	Multisystem Inflammatory Syndrome in Children
MMN	Multifocal Motor Neuropathy
MS	Multiple Sclerosis
NI	Non-inferiority
OA	Older Adults
PI	Principal Investigator
pIMD	Potential immune-mediated disease
PPFE	Pleuroparenchymal fibroelastosis
PPS	Per-Protocol Set
QS-21	*Quillaja saponaria* Molina, fraction 21
QTL	Quality tolerance limit
RS	Reynolds Syndrome
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Infections
RTSM	Randomization and Trial Supply Management
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SJS	Stevens-Johnson Syndrome
SLS	Shrinking Lung Syndrome
SmPC	Summary of product characteristics
SoA	Schedule of activities
SOC	System Organ Class

Abbreviation	Definition
SRR	Seroresponse rate
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse reaction
TED	Thyroid Eye Disease
TEN	Toxic Epidermal Necrolysis
TNF	Tumor Necrosis Factor
TTS	Thrombosis with thrombocytopenia syndrome
UK	United Kingdom
US/USA	United States of America
USADE	Unanticipated serious adverse device effect
VAED	Vaccine Associated Enhanced Disease
VAERD	Vaccine Associated Enhanced Respiratory Disease
VMED	Vaccine-Mediated Enhanced Disease
Vx CL&AP	Vaccines Clinical Laboratory and Assay Portfolio
WOCBP	Woman of childbearing potential
WONCBP	Woman of nonchildbearing 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 AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For

Term	Definition
	marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Adverse event of special interest	An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a 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.

Term	Definition
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.
Current smoker	A person who is currently smoking or who has stopped smoking within 6 months before study start.
eDiary	Electronically registered patient data and automated data entries on, for example, a handheld mobile device, tablet or computer.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled participant	All participants who entered the study (who received study intervention administration or underwent a post-screening study procedure). Note: screening failures (who never passed screening) and participants screened (met eligibility) but never enrolled into the study are excluded from the Enrolled analysis set as they did not enter the study. Refer to the Section 9.2 for the definition of 'Enrolled Set' applicable to the study.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Evaluable	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per-protocol analysis.
Former smoker	A person who stopped smoking for at least 6 months at the time of study start.
Home Healthcare Services	Deployment of mobile health care professional(s) (nurses or phlebotomists) to perform study activities remotely.
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.

Term	Definition
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
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.
Legally acceptable representative	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
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.

Term	Definition
	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.
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.
Screened participant	All participants who were screened for eligibility.
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 adverse 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).

Term	Definition
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 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 monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
SUSAR	Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting.
Unsolicited adverse event	Any AE reported in addition to those solicited during the clinical study. Also, any ‘solicited’ symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
Virtual visit	This term refers to study visits conducted using multimedia or technological platforms.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3b, open-label study to evaluate the non-inferiority of the immune response and to evaluate the safety of the RSVPreF3 OA investigational vaccine in adults 18-49 years of age at increased risk for respiratory syncytial virus disease, compared to older adults ≥60 years of age.

Brief Title: A study on the immune response and safety of vaccine against respiratory syncytial virus given to adults 18 to 49 years of age at increased risk for respiratory syncytial virus disease, compared to older adults 60 years of age and above.

Rationale: Refer to Section 2.1.

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

Overall Design: Refer to Section 4.1.

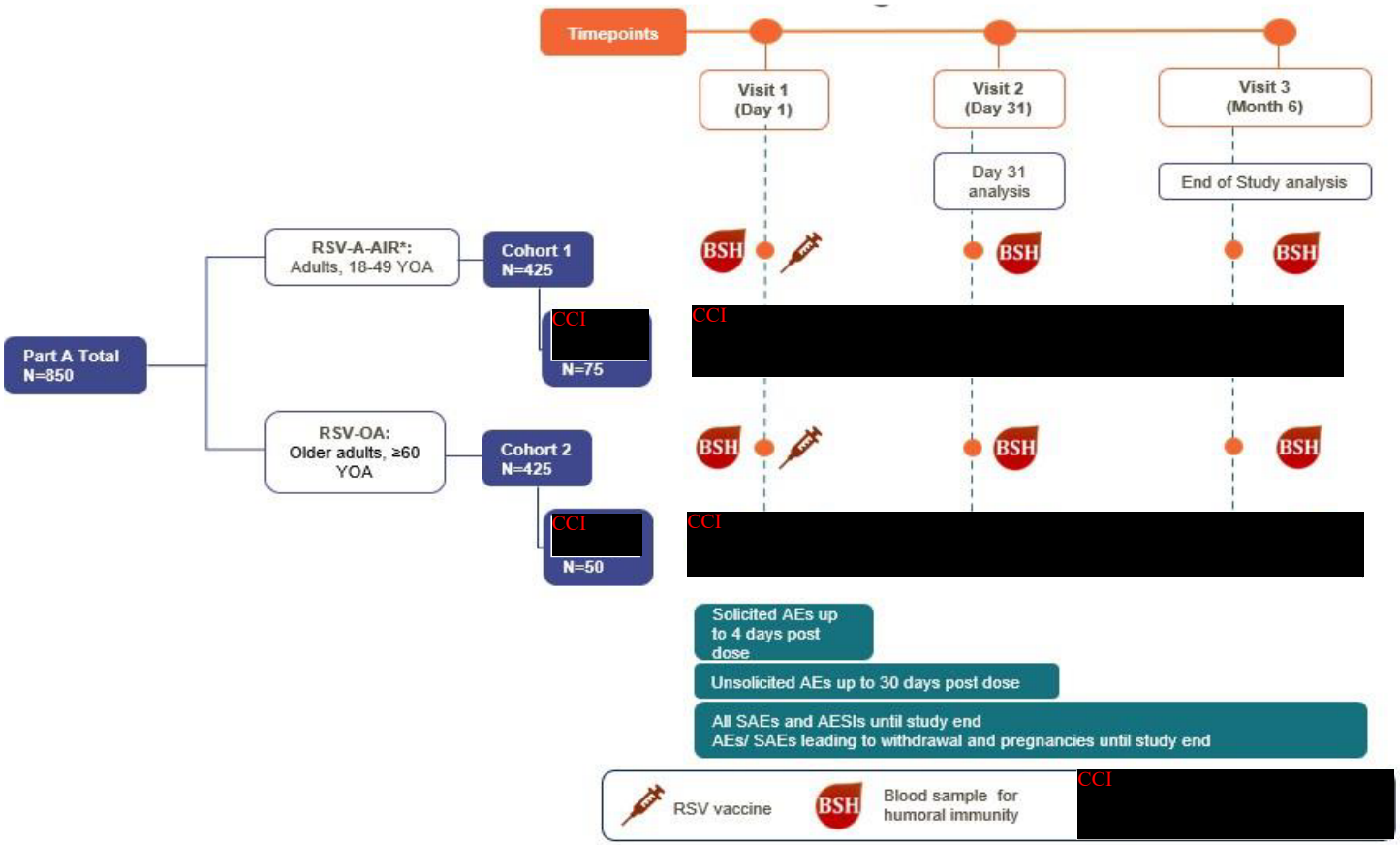
Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Schema

The study design overview for Part A and Part B is presented in Figure 1 and Figure 2, respectively.

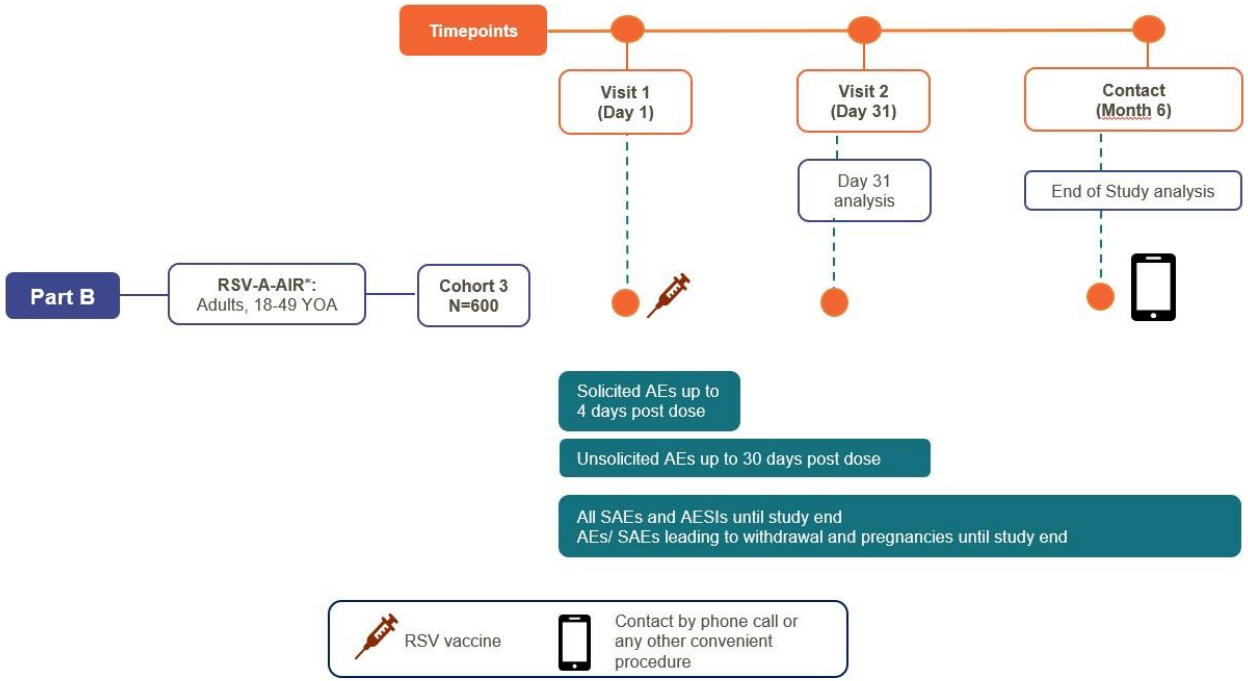
Figure 1 Study design overview (Part A)



A= Adults; AE=Adverse event; AESI=Adverse events of special interest; AIR=At increased risk; CCI ; N=Number of participants; OA=Older adults; pIMD=Potential immune-mediated disease; RSV=Respiratory syncytial virus; SAE=Serious adverse event; YOA=Years of age.

*Participants with underlying medical conditions such as chronic pulmonary and cardiovascular diseases, diabetes mellitus types 1 and 2, chronic liver and renal diseases, and neurologic or neuromuscular conditions.

Figure 2 Study design overview (Part B)



A= Adults; AE=Adverse event; AESI=Adverse events of special interest; AIR=At increased risk; CCI [redacted]; N=Number of participants; pIMD=Potential immune-mediated disease; RSV=Respiratory syncytial virus; SAE=Serious adverse event; YOA=Years of age.

*Participants with underlying medical conditions such as chronic pulmonary and cardiovascular diseases, diabetes mellitus types 1 and 2, chronic liver and renal diseases, and neurologic or neuromuscular conditions.

1.3. Schedule of activities (SoA)

Table 1 Schedule of Activities (Part A)

Type of contact	Visit 1	Visit 2	Visit 3	Notes
Timepoints	**Day 1**	**Day 31**	**Month 6**	
Informed consent/Informed assent	●			See Section 10.1.3 for details
Inclusion and exclusion criteria	●			See Sections 5.1 and 5.2 for details
Distribution of 'participant card'	○			See Section 8.4.8 for more details
Check with participants if he/she will appoint a caregiver, and distribute information letter to caregiver, when applicable	○	○	○	
Baseline and demography assessments				
Collect demographic data	●			See Section 8.1.1 for more information
Measure height and weight	●			See Section 8.1.3 for more information
Record medical and vaccination history	●			See Section 8.1.2 for more details
Physical examination/vital signs	●	○ [1]	○ [1]	See Section 8.3.1.2 for more information.
Record smoking status and smoking exposure history (including electronic smoking devices)	●			See Section 8.1.4 for more details
Screening conclusion	●			
Clinical specimen for laboratory assessment				
Blood sampling for humoral immune response assessment (~15 mL)	● [2,a]	● [a]	● [a]	See Section 8.2.1 for more information
CCI				
Urine pregnancy test (only for women of childbearing potential in Cohort 1)[3]	●			See Section 8.3.1.3 for more details

Type of contact	Visit 1	Visit 2	Visit 3	Notes
Timepoints	**Day 1**	**Day 31**	**Month 6**	
Study intervention				
Check contraindications, warnings and precautions to vaccination	○			See Section 8.3.3 for details
Check criteria for temporary delay for enrolment and/or study intervention administration	○			See Section 5.5 for more information
Record body temperature before study intervention administration	●			The route for measuring temperature can be oral or axillary. Fever is defined as temperature ≥ 38.0°C/100.4°F, regardless of the location of measurement
Study intervention number allocation	●			
Study intervention administration (including 30-minutes post-study intervention administration observation)	●			
Record administered study intervention number	●			
Safety assessments				
Set-up of eDiary and/or distribute eDiary device	○			See Section 10.3.5.1 for more details
Training on use of eDiary	○			See Section 10.3.5.1 for more details
Record solicited administration site and systemic events (Days 1–4 post-dose)	○ [a]			See Section 8.4.1 for more information
Review eDiary		○ [4]		
Collect eDiary or assist participant to delete application		○		
Record unsolicited AEs (Days 1-30 post-study intervention administration)	●	●		See Section 10.3.5 for more details
Record concomitant medications/vaccinations	●	●	●	See Section 6.9 for more information
Record any intercurrent medical conditions	●	●	●	
Record all SAEs, AESI (including pIMDs and AF[5]) and pregnancy	●	●	●	See Section 10.3.5 for more details

Type of contact	Visit 1	Visit 2	Visit 3	Notes
Timepoints	Day 1	Day 31	Month 6	
Record AE/SAEs leading to withdrawal from the study	●	●	●	See Section 10.3.5.1 for more details
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine[6]	●	●	●	See Section 10.3.5 for more details
Study conclusion			●	See Section 4.4 for more details

Note: The double-line border indicates the analyses which will be performed on all data (i.e., data that are as clean as possible) obtained up to these timepoints. See Section 9.4.1 for more details.

AE=Adverse event; AESI=Adverse event of specific interest; AF=Atrial fibrillation; eCRF=electronic case report form; pIMD=Potential immune-mediated diseases; SAE=Serious adverse event.

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

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

○[a] Is used to indicate a study procedure recorded in eDiary by participants.

●[a] Is used to indicate a study procedure that requires documentation in Site2Test app

[1] If deemed necessary by the investigator.

[2] Blood sampling at Visit 1 should be performed prior to study intervention administration. If the study intervention administration is delayed by any reason, blood sampling needs to be repeated on the day of study intervention administration.

[3] The urine sample for pregnancy test must be taken on the same day, prior to study intervention administration. If the study intervention administration is delayed by any reason, urine pregnancy test needs to be repeated on the day of study intervention administration.

[4] Designated site staff must review the responses in the eDiary frequently in the portal during the active event collection period to assess participant compliance and monitor reported events to ensure correct data is provided.

[5] 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. AF reporting will follow the same reporting periods as for AEs and SAEs. 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.

[6] 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.

Return of the eDiary device is not applicable if the participant has a “Bring Your Own” e-device.

Visit 3 should preferably be done on-site but in case of exceptional circumstances where the participant cannot come to the site, this study visit can be replaced by a home visit conducted by authorized staff. Any information from the participant required according to study procedures and not collected during the home visit can be obtained by multiple formats (e.g., email, text, message, fax or phone call) conducted by the site staff. CCI [redacted]

Table 2 Schedule of Activities (Part B)

Type of contact	Visit 1	Visit 2	Contact	Notes
Timepoints	**Day 1**	**Day 31**	**Month 6**	
Informed consent/Informed assent	●			See Section 10.1.3 for details
Inclusion and exclusion criteria	●			See Sections 5.1 and 5.2 for details
Distribution of 'participant card'	○			See Section 8.4.8 for more details
Check with participants if he/she will appoint a caregiver, and distribute information letter to caregiver, when applicable	○	○	○	
Baseline and demography assessments				
Collect demographic data	●			See Section 8.1.1 for more information
Measure height and weight	●			See Section 8.1.3 for more information
Record medical and vaccination history	●			See Section 8.1.2 for more details
Physical examination/vital signs	●	○ [1]		See Section 8.3.1.2 for more information.
Record smoking status and smoking exposure history (including electronic smoking devices)	●			See Section 8.1.4 for more details
Screening conclusion	●			
Clinical specimen for laboratory assessment				
Urine pregnancy test (only for women of childbearing potential)[2]	●			See Section 8.3.1.3 for more details
Study intervention				
Check contraindications, warnings and precautions to vaccination	○			See Section 8.3.3 for details
Check criteria for temporary delay for enrolment and/or study intervention administration	○			See Section 5.5 for more information
Record body temperature before study intervention administration	●			The route for measuring temperature can be oral or axillary. Fever is defined as temperature ≥ 38.0°C/100.4°F, regardless of the location of measurement
Study intervention number allocation	●			

Type of contact	Visit 1	Visit 2	Contact	Notes
Timepoints	**Day 1**	**Day 31**	**Month 6**	
Study intervention administration (including 30-minutes post-study intervention administration observation)	●			
Record administered study intervention number	●			
Safety assessments				
Set-up of eDiary and/or distribute eDiary device	○			See Section 10.3.5.1 for more details
Training on use of eDiary	○			See Section 10.3.5.1 for more details
Record solicited administration site and systemic events (Days 1–4 post-dose)	○ [a]			See Section 8.4.1 for more information
Review eDiary		○ [3]		
Collect eDiary or assist participant to delete application		○		
Record unsolicited AEs (Days 1-30 post-study intervention administration)	●	●		See Section 10.3.5 for more details
Record concomitant medications/vaccinations	●	●	●	See Section 6.9 for more information
Record any intercurrent medical conditions	●	●	●	
Record all SAEs, AESI (including pIMDs and AF[4]) and pregnancy	●	●	●	See Section 10.3.5 for more details
Record AE/SAEs leading to withdrawal from the study	●	●	●	See Section 10.3.5.1 for more details
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine[5]	●	●	●	See Section 10.3.5 for more details
Study conclusion			●	See Section 4.4 for more details

Note: The double-line border indicates the analyses which will be performed on all data (i.e., data that are as clean as possible) obtained up to these timepoints. See Section 9.4.1 for more details

AE=Adverse event; AESI=Adverse event of specific interest; AF=Atrial fibrillation; eCRF=electronic case report form; pIMD=Potential immune-mediated diseases; SAE=Serious adverse event.

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

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

○ [a] Is used to indicate a study procedure recorded in eDiary by participants.

[1] If deemed necessary by the investigator.

[2] The urine sample for pregnancy test must be taken on the same day, prior to study intervention administration. If the study intervention administration is delayed by any reason, urine pregnancy test needs to be repeated on the day of study intervention administration.

[3] Designated site staff must review the response in the eDiary in the portal frequently during the active event collection period to assess participant compliance and monitor reported events to ensure correct data is provided.

[4] 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. AF reporting will follow the same reporting periods as for AEs and SAEs. 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.

[5] 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.

Return of the eDiary device is not applicable if the participant has a “Bring Your Own” e-device.

Visit 2 should preferably be done on-site but in case of exceptional circumstances where the participant cannot come to the site, this study visit can be replaced by a home visit conducted by authorized staff. Any information from the participant required according to study procedures and not collected during the home visit can be obtained by multiple formats (e.g., email, text, message, fax or phone call) conducted by the site staff.

Table 3 Intervals between study visits (Part A)

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

If the study intervention date is different from the ICF signature date, the study intervention date needs to be taken as a reference for calculating intervals relative to subsequent visits.
Interval is computed as the difference between 2 dates.

Table 4 Intervals between study visits (Part B)

Interval	Planned visit interval	Allowed interval range
Visit 1→Visit 2	30 days	30-42 days
Visit 1→ Contact (Month 6)	180 days	180-210 days

If the study intervention date is different from the ICF signature date, the study intervention date needs to be taken as a reference for calculating intervals relative to subsequent visits.
Interval is computed as the difference between 2 dates.

2. INTRODUCTION

2.1. Study rationale

GSK has developed an RSV PreFusion protein F3 Older Adult (referred to as RSVPreF3 OA vaccine throughout this document) which consists of 120 µg of the RSVPreF3 recombinant antigen and the AS01E adjuvant system administered as a single dose, to address the unmet medical need for prevention of RSV-LRTD in older adults. The vaccine was approved for use in adults ≥60 YOA in the US on 03 May 2023, under the tradename *Arexvy*. To date, the vaccine is also approved in the EU, UK, Canada, Japan Hongkong, Australia and other countries. However, some younger patient groups also have an increased risk for RSV disease. The aim of this open-label study is to demonstrate the NI of the immune response and to evaluate safety of the RSVPreF3 OA investigational vaccine in adults 18-49 YOA, who are AIR for RSV disease, versus adults ≥60 YOA, where vaccine efficacy against RSV disease has been assessed in another clinical study (RSV OA=ADJ-006).

2.2. Background

RSV is a ribonucleic acid virus of which 2 antigenically distinct subtypes exist, referred to as RSV-A and RSV-B [Borchers, 2013]. RSV causes respiratory tract infections (RTI) in people of all ages. RSV can cause severe disease in infants, OA and adults AIR due to presence of chronic diseases. Currently, there are 2 vaccines available for prevention of RSV infection in adults ≥60 YOA; *Arexvy* (manufactured by GSK) and *Abrysvo* (manufactured by Pfizer Inc).

RSV is recognized as an important cause of hospitalization for severe respiratory illness in OA and those with underlying medical conditions [Branche, 2022a; Jain, 2015]. RSV

infections are increasingly recognized as a cause of serious illness in high-risk, non-immunocompromised adults, including those with chronic lung and heart disease, diabetes mellitus, chronic renal and liver disease, and neurologic disease [Melgar, 2023]. In a prospective cohort study over 4 RSV seasons in healthy elderly patients (≥65 YOA) and high-risk adults (≥21 YOA) with chronic heart or lung disease, RSV infection developed annually in 3% to 7% of healthy elderly patients and in 4% to 10% of high-risk adults [Falsey, 2005; Shi, 2021].

In patient populations with chronic diseases, both the prevalence and incidence of RSV infections is increased, leading to an increased need for medical care and hospitalization in high income countries. In a major study in the United States (US), the incidence among chronic pulmonary disease patients ranged between 1.47 to 4.68 per 10 000 patients aged 18-49 years. Among patients with diabetes, the incidence of RSV-hospitalizations ranged between 6.54 to 8.34 per 10 000 patients aged 18-49 years. For patients with congestive heart failure (CHF), the incidence ranged between 11.5 to 29.52 per 10 000 patients aged 20-39 years and 23.16 to 48.59 per 10 000 patients aged 40-59 years [Branche, 2022b].

The RSVPreF3 OA vaccine induces humoral and cellular immune responses to both RSV-A and RSV-B at 1-month post-vaccination in adults 50-59 YOA, including adults AIR for RSV disease. The results observed in adults 50-59 YOA are consistent with the robust immunogenicity data observed in the pivotal Phase 3 study RSV OA=ADJ-004 and study RSV OA=ADJ-006, where overall vaccine efficacy of 82.6% (96.95% CI, 57.9-94.1) against RSV-LRTD up to 6 months post-vaccination was demonstrated. Based on these results, licensure of the RSV OA vaccine was received in different countries [Papi, 2023; Leroux-Roels, 2023]. Currently, studies in participants < 60 YOA who are more vulnerable to severe disease as result of RSV infection are ongoing, among which is the RSV OA=ADJ-018-NI study in patients with chronic diseases AIR for RSV-LRTD in 50-59 YOA and RSV OA=ADJ-023- evaluating the immune response and safety of the vaccine in renal and lung SOT patients ≥ 18 YOA.

The aim of this study is to demonstrate the NI of the immune response and evaluate safety of RSVPreF3 OA investigational vaccine in non-immunocompromised adults 18-49 YOA, who are AIR for RSV disease, versus adults ≥60 YOA, where vaccine efficacy against RSV disease has been demonstrated.

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

2.3. Benefit/risk assessment

2.3.1. Risk assessment

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

Table 5 Risk Assessment

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
RSVPreF3 OA investigational vaccine		
pIMDs	pIMDs are considered a theoretical risk, as for all vaccines containing an adjuvant system.	Refer to Section 8.4.4 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.	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. Participants with a history of hypersensitivity or severe allergic reaction to any component of the vaccine are excluded from study enrollment.
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.	Physician can implement the measures that they consider necessary. Solicited local AE will be collected and reviewed up to Day 4 following vaccination.
Local reactions at site of blood draw	Pain, redness/erythema, irritation, and bruising may occur at the site where blood is drawn.	Physician 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.

pIMD: Potential immune-mediated disease; AE-Adverse event

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

In parallel with the RSVPreF3 OA clinical development program, another RSV vaccine development program was initiated by GSK. 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 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 the Day 43 post-birth interim analysis (DLP 04 October 2022) of the 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 [Dieussaert, 2024]. 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 OA (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.

After further consideration of the preterm birth safety signal observed in the RSV Maternal study and recommendations by external experts, GSK has assessed that WOCBP can be included in this study. 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 (see Section 5.1.1). 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

The participants may or may not benefit directly from participating in this study. By receiving the RSVPreF3 OA vaccine, the participant may have the benefit of being protected against RSV-LRTD. 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 82.6% vaccine efficacy (96.95% CI, 57.9-94.1) [Papi, 2023] during the first RSV season and no unexpected safety concerns observed (refer to IB). A study in adults 50-59 YOA, in which half of the population was AIR for RSV disease, showed that the immune response was not lower in adults 50-59 YOA-AIR for RSV compared to older adults ≥ 60 YOA.

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

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

2.3.3. Overall benefit-risk conclusion

The RSVPreF3 OA vaccine's marketing authorization has been initially granted for use in adults ≥ 60 YOA. The clinical development of the RSVPreF3 PA investigational vaccine in other populations is ongoing. Considering the measures taken to minimize the risk to participants in this study, the potential risks are justified by the potential benefits linked to the development of this vaccine.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 6 Objectives and Endpoints

Objective	Endpoint
Primary* (Part A)	
• To demonstrate the NI** of the humoral immune response in participants 18-49 YOA at increased risk for RSV disease compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• RSV-A neutralizing titers expressed as GMT ratio (RSV-OA over RSV-A-AIR) at 1 month (Day 31) after study intervention administration***. • Seroresponse in RSV-A neutralizing titers from Day 1 to Day 31***.
• To demonstrate the NI** of the humoral immune response in participants 18-49 YOA at increased risk for RSV disease compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• RSV-B neutralizing titers expressed as GMT ratio (RSV-OA over RSV-A-AID) at 1 month (Day 31) after study intervention administration***. • Seroresponse in RSV-B neutralizing titers from Day 1 to Day 31***.
Secondary Safety (Part A and Part B)	
• To evaluate the safety and reactogenicity after the RSVPreF3 OA investigational vaccine administration.	• Occurrence of each solicited administration site event with onset within 4 days after dosing (i.e., the day of study intervention administration and 3 subsequent days).

Objective	Endpoint
	• Occurrence of each solicited systemic event with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days). • Occurrence of unsolicited AEs within 30 days after study intervention administration (i.e., the day of study intervention administration and 29 subsequent days). • Occurrence of all SAEs (including fatal and related SAEs) and AESIs after study intervention administration (Day 1) up to study end (Month 6).
Secondary Immunogenicity (Part A)	
• To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine until 6 months after study vaccination for both populations.	• RSV-A and RSV-B neutralizing titers, at pre-study intervention administration and 1 month and 6 months after study intervention administration.
Tertiary Immunogenicity (Part A)	
CCI [redacted]	

AE=Adverse event; AESI=Adverse event of special interest; AIR=At increased risk; CCI [redacted]; CCI [redacted]; GMT=Geometric mean titer; NI=Non-inferiority; OA=Older adults; RSV=Respiratory syncytial virus; SAE=Serious adverse event; YOA=Years of age.

* Refer to Section 9.3.1 for the testing sequence of primary objectives.

** NI criteria are defined in Section 9.3.1.1.

*** Co-primary endpoints. Refer to Section 9.1 for statistical hypotheses.

Primary estimands (for Part A)

The primary question of interest is to evaluate the NI of the humoral immune response after RSVPreF3 OA investigational study intervention in RSV-A-AIR group (18-49 YOA), vaccinated as per protocol when compared to RSV-OA (≥60 YOA) group.

Table 7 Primary estimands (Part A)

Attributes					Summary measure
Treatment	Population	Endpoint (variable)	Intercurrent events (ICEs)		
			Description	Handling strategy	
RSVPreF3 OA investigational vaccine at Day 1.	Non-immunocompromised adults at increased risk for RSV disease with 18-49 YOA. OA with ≥60 YOA.	• RSV-A neutralizing titers (expressed in ED60) measured at 1 month (Day 31) after study intervention administration. • Seroresponse in RSV-A neutralizing titers (expressed in ED60) from Day 1 to Day 31. • RSV-B neutralizing titers (expressed in ED60) measured at 1 month (Day 31) after study intervention administration. • Seroresponse in RSV-B neutralizing titers (expressed in ED60) from Day 1 to Day 31.	Taking prohibited medication /vaccine or intercurrent medical condition prior to Day 31.	Data collected after ICEs will be excluded from the analysis at Day 31 (Hypothetical strategy) Rationale: To evaluate the immunogenicity parameters in the absence of ICE	Ratio of GMTs with 95% CI and difference in seroresponse rate (SRR) with 95% CI for RSV-A and RSV-B neutralizing titers (ED60) at Day 31 between the RSV-OA group (≥60 YOA) and the RSV-A-AIR group (18-49 YOA)

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

AIR=At increased risk; CI=Confidence interval; ED60= Estimated dilution 60; GMT=Geometric mean titer; OA=Older adults; YOA=Years of age

Rationale for estimand:

The primary estimands address the objective of demonstrating the NI of the humoral immune response in non-immunocompromised adults aged 18-49 YOA AIR for RSV disease, when compared to older adults aged ≥ 60 YOA after administration of a single dose of RSVPreF3 OA investigational vaccine. This is done by estimating the true effect of the vaccine without any confounding of other medications/vaccinations/medical condition(s) on the target population since the impact of developing medical condition(s) forbidden by protocol and use of forbidden medications and vaccinations is anticipated to modify the vaccine effect.

Table 8 Secondary estimands for safety (Part A and Part B)

Attributes					Summary measure
Treatment	Population	Endpoint (Variable)	Intercurrent events (ICEs)		
			Description	Handling strategy	
RSVPreF3 OA investigational vaccine at Day 1.	Non-immunocompromised adults at increased risk for RSV disease with 18-49 YOA. OA with ≥60 YOA.	• 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 (including fatal and related SAEs) and AESIs after study intervention administration (Day 1) up to study end (Month 6).	Taking prohibited medication /vaccine or intercurrent medical condition during respective duration.	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 endpoints.

AE=Adverse event; AESI=Adverse event of special interest; RSV=Respiratory syncytial virus; SAE=Serious adverse event; YOA=Years of age.

4. STUDY DESIGN

4.1. Overall design

- **Type of study:** Self-contained.
- **Experimental design:** Phase 3b, open-label, uncontrolled (as there is no comparative intervention), non-randomized study. The study will be conducted in 2 Parts - Part A and Part B. Part A will include 2 parallel cohorts (Cohort 1 and Cohort 2) (See Figure 1) and Part B will include 1 Cohort (Cohort 3) (see Figure 2)
  - Enrollment rules will be applied to ensure adequate representation by sex category within Part A (Cohort 1 and 2) and Part B (Cohort 3):
    - Approximately 35% of male participants per cohort.
    - Approximately 35% of female participants per cohort.
    - The remaining 30% can be distributed freely across the 2 categories.

Part A:

- Cohort 1: approximately 425 adults (A)18-49 YOA AIR for RSV disease (RSV-A-AIR Group) will receive 1 dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1).
- Enrollment rules for disease categories within Cohort 1:
  - At least ~25% of participants with cardiopulmonary conditions.
  - At least ~25% of participants with diabetes mellitus.
  - The remaining ~50% can be distributed freely across the above 2 disease categories as well as include participants with chronic renal or liver disease or neurological or neuromuscular disease.
- Cohort 2: approximately 425 adults ≥60 YOA (RSV-OA Group) will receive 1 dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1).
- Enrollment rules will be applied to ensure adequate representation by age category within Cohort 2:
  - Approximately 40% of participants 60-69 YOA.
  - Approximately 30% of participants 70 YOA or above.
  - The remaining 30% can be distributed freely across the 2 age categories.

Part B:

- Cohort 3: Approximately 600 adults (A)18-49 YOA AIR for RSV disease (RSV-A-AIR Group) will receive 1 dose of RSVPreF3 OA investigational vaccine at Visit 1 (Day 1).
- Enrollment rules for disease categories within Cohort 3:
  - At least ~25% of participants with cardiopulmonary conditions.

  - At least ~25% of participants with diabetes mellitus.
  - The remaining ~50% can be distributed freely across the above 2 disease categories as well as include participants with chronic renal or liver disease or neurological or neuromuscular disease.

- **Duration of the study**: Approximately 6 months for all participants.
- **Sampling schedule**: Three blood samples (approximately 15 mL each) will be collected from all participants in Part A (Cohort 1 and Cohort 2) to evaluate humoral immune response to the investigational RSVPreF3 OA vaccine on Visit 1 (pre-intervention), Visit 2 (Day 31, post-study intervention) and Visit 3 (Month 6, post-study intervention). CCI [redacted]. No blood samples will be collected from participants in Part B (Cohort 3).
- **Primary completion date**: Completion of last Visit 2 at Day 31 after the study intervention for participants in Part A.
- **Blinding**: Open-label, all participants will receive the RSVPreF3 OA investigational vaccine.
- **Data collection**: A standardized electronic case report form (eCRF) will be used. Solicited events will be collected by the participant using an eDiary. Unsolicited AEs and new concomitant medications/vaccinations will be collected in source documents by the PI or delegated study team member prior to entering them in the eCRF and this until study end.
- **Safety monitoring**: The study will be conducted with oversight by the project SRT.
- **Dosing schedule**: Participants will receive a single dose of the investigational study intervention (RSVPreF3 OA) at Visit 1 (Day 1).

Refer to the SoA in Section 1.3 for additional details.

4.2. Scientific rationale for study design

RSV is a respiratory infection which may lead to an increased risk for RSV disease in OA and adults AIR for RSV disease. The efficacy of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV disease in OA ≥60 YOA has been established in the Phase 3 clinical study RSV OA=ADJ-006 (refer to IB).

The immune response of AIR patients has been shown to be non-inferior in patients aged 50-59 compared to the OA population as of 60 YOA. Part A of this study aims to continue exploring the immune response of patients considered AIR between the ages of 18-49. By including a cohort of OA with the same inclusion and exclusion criteria as in the pivotal RSV OA=ADJ-006 efficacy study in this study, vaccine efficacy can potentially be inferred based on NI of the immune response.

CCI [redacted]

Lastly, safety of the RSVPreF3 OA investigational vaccine will be evaluated in Part A and Part B of the study. By including Part B, safety will be evaluated in a larger sample size of adults AIR aged between 18-49, which will allow better characterization of the safety profile of the RSVPreF3 OA investigational vaccine in this population.

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.

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed visits of the study including the last visit or the last scheduled procedure shown in the SoA.

EOS: LSLV (Visit 3/contact) 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 and/or participant's parent(s)/LAR who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the eDiary, attend study site visits, ability to access and utilize a phone or other electronic communications). INC#1

  Note: for participants in case of physical incapacity that would preclude the self-completion of the eDiary, either (i) site staff can assist the participant (for activities performed during site visits) (ii) or the participant may assign a caregiver to assist him/her with this activity (for activities performed at home). However, at no

time will the site staff or caregiver evaluate the participant's health status while completing eDiaries or make decisions on behalf of the participant.

- Written or witnessed informed consent obtained from the participant/participant's parent(s)/LAR(s) (participant must be able to understand the informed consent) prior to performance of any study-specific procedure. INC#2

  Written informed assent obtained from the participant (participant must be able to understand the informed assent) if he/she is less than the legal age* prior to performance of any study-specific procedure.

  **The legal age is determined according to local regulations in each participating country. In case the legal age is achieved during the conduct of the study, an additional written informed consent from the participant should be obtained at the time of the legal age.*

5.1.1. Specific inclusion criteria for all participants in Cohort 1 and Cohort 3

- A male or female participant 18-49 YOA at the time of the study intervention administration. INC#3
- Participants should be diagnosed with at least 1 of the following medical conditions if considered medically stable* by the investigator: INC#4

  **A stable condition is defined as a disease not requiring significant change (based on the investigator's opinion) in therapy or worsening during the 3 months before enrollment.*

  - Chronic cardiopulmonary disease resulting in activity restricting symptoms or use of long-term medication:
    - Chronic obstructive pulmonary disease (COPD)
      - Global Initiative for Chronic Obstructive Lung Disease (GOLD) Grade 2-4
    - Asthma
      - Patient on Maintenance and Reliever Therapy (MART) OR with at least one rescue treatment per week (excluding exercise asthma)
    - Cystic fibrosis
    - Other chronic respiratory diseases: lung fibrosis, restrictive lung disease, interstitial lung disease, emphysema or bronchiectasis
    - Chronic heart failure:
      - A minimum of class II symptoms according to New York Heart Association classification of heart failure
    - Pre-existing CAD (CAD not otherwise specified)

        - Physician diagnosis of CAD based on electrocardiogram, exercise stress test, nuclear stress test, cardiac computed tomography scan or cardiac angiogram (more than the presence of hypercholesterolemia)
    - Cardiac arrhythmia
        - Patient diagnosed with a cardiac arrythmia that require medical support either pharmacologically or with a medical device
- Diabetes mellitus: types 1 or 2 with active treatment for the past 6 months
- Other diseases at increased risk for RSV disease
    - Chronic kidney disease
        - G2-G3 disease (Glomerular Filtration Rate between 30 and 90 ml/min/1.73 m^2)
    - Chronic moderate to severe liver disease
    - Neurologic or neuromuscular conditions (for specific exclusion criteria, see Section 5.2.1)

- Female participants of non-childbearing potential may be enrolled in the study. Nonchildbearing potential is defined as premenarche, hysterectomy, bilateral oophorectomy, bilateral salpingectomy or post-menopause. INC#5
- Female participants of childbearing potential may be enrolled in the study, if the participant:
    - has practiced adequate contraception from 1 month prior to study intervention administration, and
    - has a negative pregnancy test on the day of study prior to intervention administration, and
    - has agreed to continue adequate contraception for at least 1 month after completion of the study intervention administration. INC#6

Refer to Section 10.4.1 for definitions of woman of childbearing potential and non-childbearing potential, and Section 10.4.2 on adequate contraception.

5.1.2. Specific inclusion criteria for all participants in Cohort 2

- A male or female participant ≥60 YOA at the time of the study intervention administration. INC#7
- 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 medically stable* by the investigator. INC#8

  **A stable condition is defined as disease not requiring significant change (based on the Investigator's opinion) in therapy or 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#9

5.2. Exclusion criteria

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

5.2.1. Medical conditions

- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., current malignancy, human immunodeficiency virus) or immunosuppressive/cytotoxic therapy (e.g., medication used during cancer chemotherapy, organ transplantation, or to treat autoimmune disorders), based on medical history and physical examination (no laboratory testing required). EXC#1
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study intervention (For details on components of study intervention administered, refer to *Arexvy* SmPC/Prescribing Information [Arexvy Summary of Product Characteristics, 2023; Arexvy Prescribing Information, 2023] and Table 9 in Section 6.1). EXC#2
- Unstable* chronic illness. EXC#3

  **Unstable condition is defined as a disease that does not fall under the definition of stable disease in Section 5.1.1.*
- Any history of dementia or any medical condition that moderately or severely impairs cognition. EXC#4

  Note: If deemed necessary for clinical evaluation, the investigator can use tools such as Mini-Mental State Exam, Mini-Cog or Montreal Cognitive Assessment (to determine cognition levels of the participant).
- Recurrent or uncontrolled neurological disorders or seizures. Participants with medically controlled active or chronic neurological diseases can be enrolled in the study as per investigator assessment, provided that their condition will allow them to comply with the requirements of the protocol (e.g., completion of the diary cards, attend study site visits). Study participants may decide to assign a caregiver to help them complete the study procedures. EXC#5
- Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study (e.g., life-threatening disease). EXC#6
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe. EXC#7
- 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#8

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine, or medical device) other than the study intervention during the period beginning 30 days before the dose of study intervention (Day -29 to Day 1), or planned use during the study period (up to Visit 3/ contact, Month 6). EXC#9
- Planned or actual administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after the dose of study intervention administration*, with the exception of inactivated, subunit and split influenza vaccines or COVID-19 vaccines which can be administered up to 14 days before or from 14 days after the study intervention administration. EXC#10

  Note: In case an emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is used according to the local governmental recommendations and that the Sponsor is notified accordingly.
- Previous vaccination with any RSV vaccine, including investigational RSV vaccines. EXC#11
- Chronic administration of immune-modifying drugs (defined as more than 14 consecutive days in total) and/or administration of long-acting immune-modifying treatments or planned administration at any time up to the EOS. EXC#12
  - Up to 3 months prior to the study intervention administration:
    - For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent. Inhaled, topical and intra-articular steroids are allowed.
    - Administration of immunoglobulins and/or any blood products or plasma derivatives
  - Up to 6 months prior to study intervention administration: long-acting immune-modifying drugs including among others immunotherapy (e.g., TNF-inhibitors), monoclonal antibodies, antitumoral medication.

5.2.3. Prior/Concurrent clinical study experience

- Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or invasive medical device). EXC#13

5.2.4. Other exclusions

5.2.4.1. Other exclusions for all participants

- History of chronic alcohol consumption and/or drug abuse as deemed by the investigator to render the potential participant unable/unlikely to provide accurate safety reports or comply with study procedures. EXC#14
- Bedridden participants. EXC#15

- Planned move during the study period that will prohibit participating in the study until study end. EXC#16
- Participation of any study personnel or their immediate dependents, family, or household members. EXC#17

5.2.4.2. Other exclusions for Cohort 1 and Cohort 3

- Pregnant or lactating female participant. EXC#18
- Female planning to become pregnant or planning to discontinue contraceptive precautions within 1 month after study intervention administration. EXC#19

5.3. Lifestyle considerations

No restrictions are required.

5.4. Screen failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs related to study procedures/concurrent GSK medication.

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

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

- Acute disease and/or fever at the time of enrollment and/or study intervention administration. Refer to the SoA in Section 1.3 and Section 8.3.1.2 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.).
- Participants with known COVID-19 positive contacts may be dosed at least 14 days after the exposure, provided that the participant remains symptom-free, and at the discretion of the investigator.
- In case of administration of inactivated and subunit influenza vaccines and COVID-19 vaccines: postponement of study intervention administration within given protocol timelines and prior to the end of the study enrollment period, to allow

respect of at least 14 days interval between flu/COVID-19 vaccination and study intervention administration.

- In case of administration of any other vaccines, 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 30 days interval between other vaccination and study intervention administration.

All efforts should be made so that blood sample is taken on the same date as vaccination. The following procedures must be repeated prior to the delayed study intervention administration:

- Blood sampling (applicable for Part A only)
- Urine for pregnancy testing
- Body temperature and vital signs
- Physical examination
- Re-check contradictions, warnings, and precautions to study intervention
- Re-check inclusion/exclusion criteria

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

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

The definition of study intervention is provided in the Definition of Terms.

6.1. Study intervention(s) administered

Study intervention administered is mentioned in Table 9 below. Refer to Section 4.1 for study intervention administration schedule.

Table 9 Study Intervention administered

Study intervention name:	**RSVPreF3 OA Investigational Vaccine**	
Study intervention formulation:	RSVPreF3 (120 µg)	AS01E: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injections
Presentation:	Powder for suspension for injection; Vial	Suspension for suspension for injection; Vial
Type:	Investigational	
Product category:	Biologic	
Route of administration:	IM	
Administration site:		
• **Location**	Deltoid	
• **Directionality**	Upper	
• **Laterality ****	Non-Dominant	
Number of doses to be administered:	1	
Volume to be administered by dose *:**	0.5 mL	
Packaging and labeling:	Refer to the pharmacy manual for more details	
Manufacturer:	GSK	

GSK=GlaxoSmithKline Biologicals SA; IM=Intramuscular; MPL=Monophosphoryl lipid A; OA=Older adults

* 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 intervention. Appropriate medical treatment and equipment must be readily available during the observation period in case of anaphylaxis or 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, and cup for urine collection.
- Instructions for medical device use are provided in Laboratory Manual and Pharmacy Manual.
- Complaints related to medical devices should be reported to GSK as detailed in the 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

All participants will receive 1 dose of the RSVPreF3 OA investigational vaccine at Visit 1 (Day 1).

The assignment of clinical trial supplies will be performed using a GSK RTSM system.

6.3.3. Intervention allocation to the participant

The subject level study intervention assignment activity is conducted using a GSK RTSM system.

Participants in Part A will be enrolled into 2 different cohorts.

- Participants 18-49 YOA at increased risk for RSV disease will be enrolled into Cohort 1 in 3 disease categories (cardiopulmonary conditions, diabetes mellitus and other disease categories), with approximately 25% of participants with cardiopulmonary conditions and approximately 25% of participants with diabetes mellitus. The remaining approximately 50% can be distributed freely across the above 2 disease categories as well as include participants with chronic renal or liver disease or neurological or neuromuscular disease. In terms of the sex as well approximately 35% of male participants, approximately 35% of female participants and remaining 30% can be distributed freely across the 2 categories will be enrolled to Cohort 1.
- Participants in Cohort 2 will be enrolled in 2 age categories (60-69 YOA and ≥ 70 YOA), with approximately 40% of participants 60-69 YOA and approximately 30% of participants ≥ 70 YOA. The remaining 30% can be distributed freely across the 2 age categories. In terms of the sex as well approximately 35% of male participants, approximately 35% of female participants and remaining 30% can be distributed freely across the 2 categories will be enrolled to Cohort 2.

Participants in Part B will be enrolled into 1 cohort.

- Participants 18-49 YOA at increased risk for RSV disease (Cohort 3) will be enrolled in 3 disease categories (cardiopulmonary conditions, diabetes mellitus and other disease categories), with approximately 25% of participants with cardiopulmonary conditions and approximately 25% of participants with diabetes mellitus. The remaining approximately 50% can be distributed freely across the above 2 disease categories as well as include participants with chronic renal or liver disease or neurological or neuromuscular disease. In terms of the sex approximately 35% of

male participants, approximately 35% of female participants and remaining 30% can be distributed freely across the 2 categories.

The RTSM system will assign the study intervention number. Recruitment caps are managed by the RTSM system.

When RTSM system is not available, please refer to the Pharmacy Manual for instructions.

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

CCI

6.4. Blinding

This is an open-label study.

6.5. Study intervention compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date of the dose as well as kit number administered in the clinic will be recorded in the source documents.

A record of the quantity of RSVPreF3 OA investigational vaccine administered to each participant must be maintained and reconciled with study intervention and compliance records.

6.6. Dose modification

Not applicable.

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

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

During the study conclusion visit, the investigator will ask each participant/participant's parent(s)/LAR(s) if they are interested in participating/allowing the participant to join any potential booster or long-term evaluation studies. If a participant/participant's parent(s)/LAR(s) are not interested in joining any potential booster or long-term evaluation studies the reason for refusal will be documented, when available, in the participant's eCRF.

6.8. Treatment of overdose

Not applicable.

6.9. Prior and concomitant therapy

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

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

- All concomitant medication including vaccines/products, except vitamins and dietary supplements, administered during the 30-day period after the dose of study intervention (Day 1 to Day 30).
- All concomitant medication leading to elimination from the analysis, including products/vaccines. Please refer to the Section 5.2.2 for further details.
- All concomitant medication which may explain/cause/be used to treat an SAE/pIMD/AESI including vaccines/products, as defined in Section 8.4.1 and Section 10.3.5. These must also be recorded in the Expedited AE Report (as applicable).
  - 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 in the absence of ANY symptom and in anticipation of a reaction to the study intervention administration.
- Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:
  - Reason for use
  - Dates of administration including start and end dates
  - Dosage information including dose and frequency
- Any antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination needs to be recorded on the eCRF.

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

Medications that are contraindicated for use in this study are stipulated in the exclusion criteria in Section 5.2.2.

Table 10 describes prohibited medications (that could impact evaluation of participants baseline status, safety and efficacy assessments) and the required washout period prior to study intervention administration. Generally, these medications are prohibited until after study end (Visit 3/contact, Month 6), unless otherwise stated below.

Medications that are not stipulated in the exclusion criteria or listed in Table 10 may be used based on the discretion of the investigator (after careful evaluation whether or not the medication could impact evaluation of the clinical trial objective or the safety of the participant).

Table 10 Prohibited medications and washout period

Prohibited medications	Washout period
Investigational or non-registered product	30 days prior to first dose until Visit 3 (Part A) and contact (Part B)
Vaccine	30 days prior to first dose until 30 days after study administration (Visit 1)[1]
Immune-modifying drugs >14 consecutive days in total	3 months prior to first dose until Visit 3 (Part A)/Contact (Part B)[2]
Long-acting immune-modifying treatments (e.g., immunotherapy (e.g., TNF-inhibitors), monoclonal antibodies, antitumoral medication)	6 months prior to first dose until Visit 3 (Part A)/ Contact (Part B)
Immunoglobulins and/or any blood products or plasma derivatives[2]	3 months prior to first dose until Visit 3 (Part A)/ Contact (Part B)

[1] Any vaccine. However, for COVID-19 and inactivated/subunit/split influenza vaccines (fully licensed or with EUA), this time window can be decreased to 14 days before and after each dose. If emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is recommended and/or organized by the public health authorities outside the routine immunization program, the time period of 30 days described above can be reduced, if necessary for that vaccine, provided it is used according to the local governmental recommendations and that the Sponsor is notified.

[2]For corticosteroids, this will mean prednisone equivalent ≥20 mg/day, or equivalent. Please note: Inhaled, topical and intra-articular steroids are allowed.

Refer to Table 11 for an overview of the timing for recording of concomitant medication during the study.

Table 11 Timing of collection of concomitant medication to be recorded

	Dose 1		Study conclusion (Visit 3/ contact at Month 6)
	Day 1	Day 30	
All concomitant medication including vaccines/products, except vitamins and dietary supplements			
All concomitant medication including products/vaccines leading to elimination from the analysis			
All concomitant medication including vaccines/products which may explain/cause/be used to treat an SAE/AESI (pIMD and AF*)			
Any prophylactic medication			

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Not applicable to this study.

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 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 event SAEs/AESIs
Lost to follow-up	Unknown Other, Specify
Protocol deviation	

Reasons	Additional items/Sub-reasons
Investigator Decision	Specify
Pregnancy	
Site Terminated by Sponsor	
Study Terminated by Sponsor	
Withdrawal by Participant	Burden of Procedure Participant Relocated Pandemic Other, Specify
Death	
Other	Specify

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE/AESI until the event is resolved, stabilized, otherwise exaplained, or the participant is lost to follow up (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 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 in 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.
- Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team becomes aware of them. In case of doubts of immediate safety concerns regarding the inclusion of a possible participant, inclusion should be postponed until a decision can be made.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria prior to study intervention administration. The investigator will maintain a log of all participants screened. All relevant information, such as confirmation of eligibility and reasons for screening failure will be mentioned in this screening log. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- If allowed by country regulation/ethics, study visits may be conducted remotely (by a HHS professional or site's own staff) and/or virtually (secure video conferences, phone calls, or a web portal and/or mobile application), as per the SoA.
- 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 in Part A (Cohort 1 and 2) over the duration of the study, related to procedures in this study, will not exceed 45 mL and CCI [redacted] Repeat or unscheduled samples may be taken once at every timepoint for technical issues with the samples.
- Study participants may decide to assign a caregiver to help them fulfill the study procedures.
- It is preferred to have all visits on-site. However, during special circumstances (e.g., pandemic, patients for whom the transfer to the clinic has become very difficult), the specific guidance from local public health, if applicable, and other competent authorities regarding the protection of individuals' welfare must be applied and consulted with the sponsor. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:
  - For Part A, Visit 3 may be conducted at the participant's home (by the site staff), if appropriate. Biological sample at Visit 3 may be collected at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use. CCI [redacted]

CCI [redacted]

  - For Parts A and B, if the eDiary device has been provided by GSK it may be transmitted from and to the site by courier service if allowed by local regulations and or collected at home.

- Impact of visits performed outside of the site's location on the PPS for immunogenicity will be determined on a case-by-case basis.

8.1. Administrative 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/parent(s)/LAR(s) and/or review of the participant's medical records. Record any relevant pre-existing conditions, signs and/or symptoms present prior to the study intervention/study start in the eCRF.

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

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

8.1.3. Measure height and weight

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

8.1.4. Smoking status and smoking exposure history

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

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

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

8.2. Immunogenicity assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA. Immunogenicty assessments will be performed for participants in Part A only (Cohort 1 and Cohort 2).

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

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

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

Sample testing will be done in accordance with the recorded consent of the individual participant/participant's parent(s)/LAR(s).

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 45 mL (approximately 15 mL at each visit) will be collected from all study participants in Part A (Cohort 1 and Cohort 2) during the entire study period.

Refer to SoA in Section 1.3 for information on volumes collected for different assessments.

CCI [redacted]

Table 12 Biological samples (Part A)

Sample type	Quantity	Unit	Timepoint	Subset name*
Blood for humoral response	~15	mL	Visit 1 (Day 1) Visit 2 (Day 31) Visit 3 (Month 6)	All participants (Part A)
CCI [redacted]				

CCI [redacted].

* Refer to Section 6.3 for subset description.

Blood sample at Visit 1 (Day 1) should be collected prior to study intervention administration.

8.2.2. Laboratory assays

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

Table 13 Laboratory assays (Part A)

Test Classification	System	Component	Challenge	Method	Laboratory
Humoral immunity (antibody determination)	Serum	RSV-A neutralizing titer		Neutralization	GSK*
	Serum	RSV-B neutralizing titer		Neutralization	GSK*
CCI [redacted]					GSK*

CCI [redacted]; GSK=GlaxoSmithKline Biologicals SA; ICS=Intracellular cytokine staining; CCI [redacted]
RSV=Respiratory syncytial virus; CCI [redacted]; CCI [redacted].

CCI [redacted]

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

Immunological read-outs are described in Table 14.

Table 14 Immunological read-outs (Part A)

Blood sampling time point		Subset name	No. of participants	Component
Type of contact and time point	Sampling time point			
Humoral immunity (on serum samples)				
Visit 1 (Day 1)	Pre-Adm	All participants	~850	RSV-A neutralizing titer RSV-B neutralizing titer
Visit 2 (Day 31)	Day 31	All participants	~850	RSV-A neutralizing titer RSV-B neutralizing titer
Visit 3 (Month 6)	Month 6	All participants	~850	RSV-A neutralizing titer RSV-B neutralizing titer
CCI [redacted]				

CCI [redacted]

Pre-Adm=Pre-study intervention administration; RSV=Respiratory syncytial virus; CCI [redacted]

CCI [redacted]

8.2.4. Immunological correlates of protection

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

8.3. Safety assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.3.1. Pre-study intervention administration procedures

8.3.1.1. Physical examination

History directed physical examination will be performed for each participant.

If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to 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.

8.3.1.2. Vital signs

At a minimum, oral or axillary temperature, pulse rate, respiratory rate, and blood pressure will be recorded.

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

Vital signs are to be taken after at least 10 minutes of rest and before blood collection for laboratory tests and will consist of systolic/diastolic blood pressure, heart rate and respiratory rate by counting the number of breaths for 1 minute.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Collected information needs to be recorderd in the eCRF.

8.3.1.3. 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.

8.3.2. Post-study intervention administration procedures

8.3.2.1. Physical examination

Physical examination at each study visit after the study intervention administration will be performed only if the participant/participant's parent/LAR(s) indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate. Should there be an underlying condition or illness that is diagnosed in any of these visits, this will be adequatly recorded in eCRF.

8.3.3. Warnings and precautions to administration of study intervention

Refer to *Arexvy* SmPC/Prescribing Information [Arexvy Summary of Product Characteristics, 2023; Arexvy Prescribing Information, 2023].

Warnings and precautions to administration of study intervention must be checked at Visit 1 (Day 1) as specified in SoA.

8.3.4. Safety monitoring and Committee

- Participant safety will be continuously monitored by the Medical Monitor, designated Safety Lead (or delegate) and 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.

8.4. 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 or pIMD and other safety information and remain responsible for following up all AEs (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, or the participant's legally authorized representative).

Investigator safety reports must be prepared for 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 time points 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 15 Collection and reporting of safety information

Event	Pre-adm* Day 1	Adm			6 months post-intervention and study conclusion
		Day 1	Day 4#	Day 30	Month 6
Solicited administration site and systemic solicited AEs					
Unsolicited AEs†					
All SAEs and AESIs (including pIMDs and AF†) and fatal SAEs†					
SAEs related to study participation** or concurrent GSK medication/ vaccine					
Pregnancy					
AEs/SAEs leading to withdrawal from the study					
Intercurrent medical conditions***					

AF=Atrial fibrillation; Pre-adm=pre-study intervention administration; Adm=study intervention administration; AE=Adverse event; SAE=Serious adverse event; pIMD=Potential immune-mediated disease.

* Corresponds to the day when informed consent/informed assent is obtained (Day 1, prior to study intervention administration).

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

*** 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.

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

Day 4 is not a visit/contact at site.

The shaded region in the table indicates time period of data collection.

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 poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section 8.4.1.

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/participants' parent(s)/LAR(s) 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 [and AEs of special interest (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. AESIs

pIMDs and AF are the AESIs collected during the study.

Collecting and reporting timeframes for AESIs:

- pIMDs: To be reported from Day 1 (after administration of study intervention) up to study end (6 months after administration of study intervention).
- Atrial fibrillation:
  - AF Non-serious AEs: to be reported from Day 1 (after administration of study intervention) up to Day 30.
  - AF SAEs: to be reported from Day 1 (after administration of study intervention) up to study end (6 months after administration of study intervention).

8.4.4.1. Potential immune-mediated diseases

pIMDs are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 16.

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 below 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 preexisting chronic condition (if it exacerbated following vaccination) in the eCRF.

Table 16 List of potential immune-mediated diseases (pIMDs)

Blood disorders and coagulopathies	Cardio-pulmonary inflammatory disorders	Endocrine disorders
• Antiphospholipid syndrome • Autoimmune aplastic anemia • Autoimmune hemolytic anemia, including: – Warm antibody hemolytic anemia – 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”	• Idiopathic Myocarditis/Pericarditis, including: – Autoimmune / Immune-mediated myocarditis – Autoimmune / Immune-mediated pericarditis – Giant cell myocarditis • Idiopathic pulmonary fibrosis, including: – Idiopathic interstitial pneumonia (Interstitial lung disease, Pulmonary fibrosis, Immune-mediated pneumonitis) – Pleuroparenchymal fibroelastosis (PPFE) • Pulmonary alveolar proteinosis (PAP) – Frequently used related terms include: “pulmonary alveolar lipoproteinosis”, “phospholipidosis”	• Addison’s disease • Autoimmune / Immune-mediated thyroiditis, including: – Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) – Atrophic thyroiditis – Silent thyroiditis – Thyrotoxicosis • Autoimmune diseases of the testis and ovary, including: – Autoimmune oophoritis – Autoimmune ovarian failure – Autoimmune orchitis • Autoimmune hyperlipidemia • Autoimmune hypophysitis • Diabetes mellitus type I • Graves’ or Basedow’s disease, including: – Marine Lenhart syndrome – Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy • Insulin autoimmune syndrome

		• Polyglandular autoimmune syndrome, including: – Polyglandular autoimmune syndrome type I, II and III
Eye disorders	**Gastrointestinal disorders**	**Hepatobiliary disorders**
• Ocular Autoimmune / Immune-mediated disorders, including: – 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	• Autoimmune / Immune-mediated pancreatitis • Celiac disease • Inflammatory Bowel disease, including: – Crohn's disease – Microscopic colitis – Terminal ileitis – Ulcerative colitis – Ulcerative proctitis	• Autoimmune cholangitis • Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis
Musculoskeletal and connective tissue disorders	**Neuroinflammatory/neuromuscular disorders**	**Renal disorders**
• Gout, including: – Gouty arthritis • Idiopathic inflammatory myopathies, including: – Dermatomyositis – Inclusion body myositis – Immune-mediated necrotizing myopathy – Polymyositis • Mixed connective tissue disorder • Polymyalgia rheumatica (PMR) • Psoriatic arthritis (PsA) • Relapsing polychondritis • Rheumatoid arthritis, including: – Rheumatoid arthritis associated conditions – Juvenile idiopathic arthritis – Palindromic rheumatism – Still's disease – Felty's syndrome	• Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants, including: – 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) – Noninfective encephalitis/ encephalomyelitis / myelitis – Postimmunization encephalomyelitis • Guillain-Barré syndrome (GBS)*, including:	• Autoimmune/Immune-mediated glomerulonephritis, including: – IgA nephropathy – IgM nephropathy – C1q nephropathy – Fibrillary glomerulonephritis – Glomerulonephritis rapidly progressive – Membranoproliferative glomerulonephritis – Membranous glomerulonephritis – Mesangioproliferative glomerulonephritis – Tubulointerstitial nephritis and uveitis syndrome

• Sjogren's syndrome • Spondyloarthritis, including: – Ankylosing spondylitis – Juvenile spondyloarthritis – Keratoderma blenorrhagica – Psoriatic spondylitis – Reactive Arthritis – Undifferentiated spondyloarthritis • Systemic Lupus Erythematosus, including: – Lupus associated conditions (e.g., Cutaneous lupus erythematosus, Lupus nephritis, etc.) – Complications such as shrinking lung syndrome (SLS) • Systemic Scleroderma (Systemic Sclerosis), including: – Raynaud's syndrome – Systemic sclerosis with diffuse scleroderma – Systemic sclerosis with limited scleroderma (also known as CREST syndrome)	– Variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN) • Idiopathic cranial nerve palsies/paresis and inflammations (neuritis), including: – 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), including: – 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, including: – Ocular myasthenia – Lambert-Eaton myasthenic syndrome • Narcolepsy (with or without presence of unambiguous cataplexy) • Peripheral inflammatory demyelinating neuropathies and plexopathies, including – 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), including: – Acute partial transverse myelitis (APTM) – Acute complete transverse myelitis (ACTM)	
Skin and subcutaneous tissue disorders	**Vasculitis**	**Other (including multisystemic)**
• Alopecia areata • Autoimmune / Immune-mediated blistering dermatoses, including: – Bullous Dermatitis – Bullous Pemphigoid – Dermatitis herpetiformis – Epidermolysis bullosa acquisita (EBA) – Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease – Pemphigus • Erythema multiforme • Erythema nodosum • Lichen planus, including: – Liquen planopilaris • Localised Scleroderma (Morphoea) – Eosinophilic fasciitis (also called Shulman syndrome) • Psoriasis • Pyoderma gangrenosum • Reactive granulomatous dermatitis, including: – Interstitial granulomatous dermatitis – Palisaded neutrophilic granulomatous dermatitis • Stevens-Johnson Syndrome (SJS), including: – Toxic Epidermal Necrolysis (TEN) – SJS-TEN overlap • Sweet's syndrome, including: – Acute febrile neutrophilic dermatosis • Vitiligo	• Large vessels vasculitis*, including: – 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: – Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) – Behcet's syndrome – Buerger's disease (thromboangiitis obliterans) – Churg–Strauss syndrome (allergic granulomatous angiitis) – Erythema induratum (also known as nodular vasculitis) – Henoch-Schonlein purpura (also known as IgA vasculitis) – Microscopic polyangiitis – Necrotizing vasculitis – Polyarteritis nodosa – Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) – Granulomatosis with polyangiitis	• 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, including: – 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: – Kawasaki's disease – Multisystem inflammatory syndrome in adults (MIS-A) – Multisystem inflammatory syndrome in children (MIS-C) • Overlap syndrome • Raynaud's phenomenon • Sarcoidosis, including: – 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 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 as AE or SAE 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/pregnancies/AESIs

- Prompt notification by the investigator to the sponsor of an SAE/pregnancy/AESI 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 17 Timeframes for submitting SAE, pregnancy 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 AEs Report	24 hours*	electronic AEs Report
Pregnancies	24 hours*	electronic pregnancy report	24 hours *	electronic pregnancy report
pIMDs	24 hours**	electronic AEs Report	24 hours*	electronic AEs Report
Serious AF***	24 hours**	Electronic AEs Report + AF follow-up questionnaire	24 hours*	Electronic AEs Report + AF follow-up questionnaire

* 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 Expedited AEs Report and in the specific AF follow-up questionnaire. Non-serious AF will be reported as non-serious adverse event eCRF screen and in the AF follow-up questionnaire.

8.4.6. Pregnancy

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

- Details of all pregnancies in female participants will be collected after the start of study intervention and until EOS.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor 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/pregnant female partner and the neonate and the information will be forwarded to the sponsor. See Table 17 for reporting timeframes.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.5. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will continue to be monitored after study intervention.

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

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

8.4.8. Participant card

The investigator (or designee) must provide the participant/participant's parent(s)/LAR(s) with a "participant card" containing information about the clinical study. The participant/participant's parent(s)/LAR(s) 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/LAR/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up.

8.5. Pharmacokinetics

Not applicable to this study.

8.6. Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity assessments

Immunogenicity is described in Section 8.2.

8.10. Health economics or medical resource utilization and health economics

Not applicable in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

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

Table 18 Study objectives and null hypothesis

Objectives	Null hypothesis
Primary (Part A)	
• To demonstrate the NI of the humoral immune response in participants 18-49 YOA at increased risk for RSV disease compared to OA (≥60 YOA) for the RSV-A strain after RSVPreF3 OA investigational vaccine administration.	• **Null hypothesis 1 (H1):** The anti-RSV-A GMT ratio RSV-OA (≥60 YOA) over RSV-A-AIR (18-49 YOA) is >1.5 or the SRR difference (RSV-OA [≥60 YOA] minus RSV-A-AIR [18-49 YOA]) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favor of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.
• To demonstrate the NI of the humoral immune response in participants 18-49 YOA at increased risk for RSV disease compared to OA (≥60 YOA) for the RSV-B strain after RSVPreF3 OA investigational vaccine administration.	• **Null hypothesis 2 (H2):** The anti-RSV-B GMT ratio RSV-OA (≥60 YOA) over RSV-A-AIR (18-49 YOA) is >1.5 or the SRR difference (RSV-OA [≥60 YO]) minus RSV-A-AIR [18-49 YOA]) is >10% at 1 month post RSVPreF3 OA vaccine administration. This must be rejected in favor of the alternative hypothesis that the GMT ratio is ≤1.5 and the SRR difference is ≤10%.

A=Adults; AIR=At increased risk; GMT=Geometric mean titer; H1=Null hypothesis 1; H2=Null hypothesis 2; NI=Non-inferiority; OA=Older adults; RSV=Respiratory syncytial virus; SRR=Seroresponse rate; YOA=Years of age.

9.2. Analysis sets

Table 19 Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened Set	All participants who were screened for eligibility.	Study Population
Enrolled Set	All participants who entered the study (who were allocated a treatment number or received study intervention or underwent a post screening study procedure). Note: screening failures (who never passed screening) and participants screened (met eligibility) but never enrolled into the study are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Exposed Set (ES)	All participants who received the study intervention. Analysis per group is based on the administered intervention.	Study population, Reactogenicity, Safety
Per-Protocol Set (PPS)*	All eligible participants who received the study intervention as per protocol, had immunogenicity results pre- and post-dose, complied with blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. Analysis per group is based on the administered intervention.	Immunogenicity

*Contribution of participants to PPS will be defined by timepoint

9.2.1. Criteria for elimination from analyses

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

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

9.3. Statistical analyses

SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Supportive analyses and demography summaries will be described in the SAP.

9.3.1. Primary endpoints/estimands analysis (Part A)

Primary estimand analysis will be performed on the Per-Protocol Set (PPS) for participants in Part A.

RSV-A and RSV-B neutralizing group GMT ratio at 1 month after the RSVPreF3 OA vaccine administration will be computed for RSV-OA (≥60 YOA) cohort over RSV-A-AIR (18-49 YOA) cohort, with 95% CI, using an CCI [redacted] on log10-transformed titers for each neutralization assay. The model will include the group RSV-OA (≥60 YOA) and RSV-A-AIR (18-49 YOA) and the baseline log10-transformed titer as covariate.

RSV-A and RSV-B neutralizing group SRR differences at 1 month after the RSVPreF3 OA vaccine administration will be computed for RSV-OA (≥60 YOA) cohort minus RSV-A-AIR (18-49 YOA) cohort, with 95% CI. The 95% CI will be derived using the method of CCI [redacted] 1985. SRR is defined as the proportion of participants having a fold increase in neutralizing titers (post-study intervention administration over pre-study intervention administration) ≥4.

Missing data will not be imputed.

9.3.1.1. Success criteria for non-inferiority and testing sequence

In order to control the global type I error at 2.5% (1-sided), the primary objective will be assessed using a hierarchical testing. NI will be first tested for RSV-A strain and, only if NI has been demonstrated, will the NI be tested for RSV-B strain.

NI for RSV-A strain will be claimed to be successful if the upper limit of the 95% CI for the RSV-A neutralizing group GMT ratio will be ≤1.5 and the upper limit of 95% CI for the RSV-A neutralizing group SRR difference will be ≤10%.

NI for RSV-B strain will be claimed to be successful if NI has been demonstrated for RSV-A strain and if the upper limit of the 95% CI for the RSV-B neutralizing group GMT ratio will be ≤1.5 and the upper limit of 95% CI for the RSV-B neutralizing group SRR difference will be ≤10%.

9.3.2. Secondary endpoints/estimands analyses

The estimand analysis for immunogenicity will be performed on the PPS, for participants in Part A.

For each timepoint with blood sample collection for humoral immune response and for RSV-A/B neutralizing titers, the following analysis will be performed by group:

- Percentage of participants with neutralizing titers equal to or above the technical assay cut-off and their exact 95% CI will be tabulated.
- GMTs and their 95% CI will be tabulated and represented graphically.
- Distribution of neutralizing titers will be displayed using reverse cumulative curves.
- MGI, i.e., geometric mean of ratios of neutralizing titers of post vaccination time point over pre-vaccination (Day 1), will be tabulated with 95% CI.
- SRR and 95% CI will be tabulated.

The estimand analysis for safety will be performed on the ES, for participants in Parts A and Part B. Descriptive analysis by group will be summarized as follows:

- Percentage of participants reporting each solicited administration site event (any grade, Grade 3 and resulting in medically attended visit) with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days).
- Percentage of participants reporting each solicited systemic event (any grade, Grade 3 and resulting in medically attended visit) with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days).
- Percentage of participants reporting unsolicited AEs within 30 days after study intervention administration (i.e., the day of study intervention administration and 29 subsequent days) by MedDRA Primary System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT). Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit.

- Percentage of participants reporting SAEs and AESIs (including pIMDs and AF) after study intervention administration (Day 1) up to study end (6 months after study intervention administration) by MedDRA Primary SOC, HLT and PT.
- Percentage of participants reporting SAEs and AESIs (including pIMDs and AF) related to study intervention administration after study intervention administration (Day 1) up to study end (6 months after study intervention administration) by MedDRA Primary SOC, HLT and PT.
- Percentage of participants reporting any fatal SAEs after study intervention administration (Day 1) up to study end (6 months after study intervention administration).

9.4. Interim analyses

9.4.1. Sequence of analysis

The analyses will be performed stepwise:

- **Day 31 (Part A):** A first analysis will be performed on all immunogenicity, reactogenicity and safety data available and as clean as possible, when data for at least primary and secondary endpoints up to Visit 2 (Day 31) are available for all participants in Part A. This analysis will be considered as final for the primary endpoints.
- **Month 6 (Part A):** If required, a safety analysis can be performed when safety data up to Month 6 are available and as clean as possible, for all participants in Part A.
- **Day 31 (Part B):** If required, a safety analysis can be performed when safety data up to Visit 2 (Day 31) are available and as clean as possible, for all participants in Part B. This analysis may be combined with Month 6 safety analysis for Part A.

  Month 6 (Part A): If required an immunogenicity analysis can be performed when all data for secondary endpoints up to study conclusion (Visit 3, Month 6) are available and as clean as possible, for all participants in Part A.
- An **EOS** analysis will be performed when all immunogenicity and safety data up to study conclusion (Visit 3/Contact, Month 6) will be available for all participants in Part A and Part B.
- If the data of different analyses become available around the same timepoint, these analyses can be combined into one analysis.

9.5. Pre-dose sample size determination

The target sample size for the study is approximately 850 participants for Part A: 425 participants in Cohort 1 (RSV-A-AIR [18-49 YOA group]) and 425 participants in Cohort 2 (RSV-OA [≥60 YOA group]), to obtain at least 722 evaluable participants (361 participants in the RSV-A-AIR [18-49 YOA] cohort and 361 participants in the RSV-OA [≥60 YOA] cohort) for the evaluation of the primary objectives, assuming that approximately 15% of the enrolled participants will not be evaluable.

Participants who withdraw from the study will not be replaced.

The power to demonstrate the primary NI objectives following the hierarchical testing procedure described in Section 9.3.1 is presented in Table 20.

Table 20 Power for primary objectives of non-inferiority of the humoral immune response after RSVPreF3 OA vaccine between the RSV-A-AIR (18-49 YOA) Cohort 1 to RSV-OA (≥ 60 YOA) Cohort 2 for 361 evaluable participants per group

Objective	Standard deviation (SD) of log10 titers / SRR (%)	Non-inferiority margin	Type II Error	Power[1]
NI for RSV-A strain				
GMT RSV-A	SD=0.45	1.5	0.05	99.95%
SRR RSV-A	SRR=81.6%[2]	10%	6.92	93.08%
Global power for RSV-A strain				**93%**
NI for RSV-B strain				
GMT RSV-B	SD=0.45	1.5	0.05	99.95%
SRR RSV-B	SRR=78.7%[2]	10%	9.56	90.44%
If non-inferiority is demonstrated for RSV-A, global power for RSV-B strain				**90%**

NI=Non-inferiority; SRR=Seroresponse rate; GMT=Geometric mean titer; RSV=Respiratory syncytial virus
[1]Pass 2019 1-sided alpha=2.5% for each endpoint (GMT ratio and SRR difference), two-Sample T-Tests for Non-Inferiority assuming equal variance for group GMT ratios and CCI for Non-Inferiority tests for group SRR difference, Non-inferiority limit=0.176 (=log10(1.5)) for group GMT ratios
[2]Reference from RSV OA=ADJ-006

For the evaluation of reactogenicity and safety, the sample size of 1025 participants in combined Cohorts 1 and 3 (RSV-A-AIR group) has 64% and 87% probability of observing at least one vaccinated participant with AE if the true AE incidence rate is 0.1% and 0.2% respectively. This probability increases to at least 95% for true AE incidence rates ≥0.3%.

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.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, 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/participants' parent(s)/LAR(s) and answer all questions regarding the study.
- Potential participants/participants' parent(s)/LAR(s) must be informed that their participation is voluntary. They or their LARs 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 investigator must obtain assent from the minor participant in addition to the consent provided by the participants' parent(s)/LAR(s) when a minor can assent to participate in a study. The investigator is also accountable for determining a minor's

capacity to assent to participation in a research study according to the local laws and regulations.

- In accordance with local laws and regulations, participants who become legally emancipated during the study, i.e., reach the legal age of consent, must be reconsented.
- 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/participant's parent(s)/LAR(s) must be reconsented to the most current version of the ICF(s)/IAF during their participation in the study.
- A physical copy of the ICF(s)/IAF must be provided to the participant/participant's parent(s) or their LAR.
- In accordance with local laws and regulations, participants who become legally emancipated during the study, i.e., reach the legal age of consent, must be reconsented.
- The participant/participant's parent(s)/LAR(s) must provide consent by signing an ICF/IAF, which summarizes the study, includes a consent statement and provides documentation that the participant agrees to continue participating in the study.

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 PI 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

- The study is planned to be conducted at sites in multiple countries. The recruitment plan will be defined by each participating site. Recruitment will be tracked using RTSM system.
- 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 in the participating sites across participant 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.
- When the target number of participants is reached in each cohort, further enrollment of participants in that cohort will be stopped. If needed, the maximum number of participants in a particular cohort may be adapted during the study.

- The procedures for participants identification/recruitment (e.g., referral letters, advertisements etc.) must be approved by the IRB/IEC together with the material intended for participants identification/recruitment and participants use.

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/participants' parent(s)/LAR(s) must be informed that their/the minor participants's 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/participants' parent(s)/LAR(s), that their/the minor partcipant'sdata will be used as described in the informed consent/assent.
- The participant/participants' parent(s)/LAR(s) must be informed that their/the minor participant's 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 Treatment Code 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 eCRFs 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 lectronically 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 rom 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 the 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 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

10.2.1. RSV-A and RSV-B neutralization assays

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

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

CCI

CCI

[redacted]

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 NOT 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:
- 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

- **Definition of solicited event**

- Solicited events are predefined events administration site events and systemic events for which the participant/ participant's parent(s) /LAR(s) is specifically questioned, and which are noted by the participant/ participant's parent(s) /LAR(s) in their eDiary.

Table 21 Solicited administration site

Pain at administration site
Redness (Erythema) at administration site
Swelling at administration site

Table 22 Solicited systemic events

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

Note: Participants/participants' parent(s)/LAR(s) will be instructed to measure and record the oral/axillary temperature in the evening. If additional temperature

measurements are taken at other times of the day, participants/participants' parent(s)/LAR(s) will be instructed to record the highest temperature in the eDiary.

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/ participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include both serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants/ participant's parent(s)/LAR(s) 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/ participant's parent(s) /LAR(s) 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/participant's parent(s)/LAR(s) will be collected during an interview with the participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit.

10.3.5. Recording, assessment and follow-up of AE, SAE, 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.

- An eDiary will be used in this study to capture solicited administration site or systemic events. The participant/participant's parent(s)/LAR(s) should be trained on how and when to complete the eDiary.
- Anyone who measures administration site or systemic events and who will record the event in the eDiary, e.g., the study caregiver, should have received a caregiver information letter explaining the role of the caregiver prior to completing the eDiary. This training must be documented in the participant's source record.
- For each solicited and unsolicited AE the participant experiences, the participant/ participant's parent(s)/LAR(s) will be asked if they/their child 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 eDiary and in the participant's eCRF as part of normal AE reporting (for solicited and unsolicited AEs). If the collection of solicited AEs was not possible for any reasons via the eDiary and solicited AEs were reported to the investigator by the participant, then it would be possible for it to be reported directly to the site staff and submitted (e.g., via the eCRF). 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/participant's parent(s)/LAR(s) is making entries in the eDiary, their identity must be documented in the participant's source record.
- The completed eDiary will be collected and verified during discussions with the participant/participant's caregiver(s) on Visit 2.
- All solicited events that occur during the four days following administration of the dose of the study intervention (Day 1 to Day 4) must be recorded into the eDiary, irrespective of intensity. An automatic reminder to complete the eDiary will be sent to the participants during this time frame. Daily eDiary compliance will be checked by the investigator or delegate on the eDiary portal. In case of non-compliance, the investigator should contact the participant to remind the importance of daily entries. All other AEs occurring within this time frame should be recorded into the appropriate section of the eCRF, irrespective of their intensity or whether or not they are considered related to the study intervention.
- After review and verbal discussion of the eDiary entries with the participant/participant's parent(s)/LAR(s), if there are clear eDiary errors the investigator will complete his/her own assessment in the relevant sections of the eCRF.
- Note: eDiary may be completed by a minor participant under the supervision of the participant's parent(s)/LAR(s) provided the minor is capable of assessing and reporting the information to be recorded on eDiary. The ultimate accountability for completion of the eDiary remains with the participant's parent(s)/LAR(s). The investigator should discuss this accountability with the participant's parent(s)/LAR(s).
- The investigator or delegate should verify the reported information during a discussion with the minor participant preferably in the presence of their parent(s)/LAR(s).

- Return of the eDiary device is not applicable if the participant has BYOD but verification of the recorded data should always take place.
- Any unreturned eDiary will be sought from the participant/participant's parent(s)/LAR(s) through telephone call(s) or any other convenient procedure.
- Data on solicited events reported in the eDiary will be electronically transferred to the eDiary vendor, where it can be monitored by appropriately qualified site staff and sponsor staff through a web-based portal.
- Refer to the eDiary Manual for more information regarding the use of eDiary**.**

10.3.5.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE, AESI, SAE 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 23 Intensity scale for solicited events

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

Event	Intensity grade	Parameter
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia (muscle pain)	0	None/Normal**
	1	Mild: Myalgia present but does not interfere with activity
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia (joint pain)	0	None/Normal**
	1	Mild: Arthralgia present but does not interfere with activity
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

* Refer to the SoA (Section 1.3) for the definition of fever and the preferred location for temperature measurement.
**For participants already experiencing some of the solicited systemic events prior to vaccine administration, 'None/Normal' corresponds to 'similar to baseline' and only discomfort above baseline is to be reported as ≥1.

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

Table 24 Intensity scale of administration site redness (Erythema)/swelling, and fever

Intensity grade	**Redness** (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 judgment.

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

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, pregnancies or any other events of interest

- 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, and nonserious AESI (as defined in the Section 8.4.4), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.
- Other nonserious AEs must be followed until EOS or until the participant is lost to follow-up.

Follow-up during the study

AEs/AESIs 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 paper pregnancy follow-up report/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 pregnancy 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 8.4.7).

10.3.5.7. Reporting of SAEs, AESIs and pregnancies

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) or to the GSK/medical monitor by telephone.
- 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/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the GSK/medical monitor.
- In rare circumstances and in the absence of email/facsimile 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: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. WOCBP Definition

Women in the following categories are considered WOCBP (fertile):

- Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.
- 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:

- Premenarchal: Tanner stage 1 (prepubertal)

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 follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, 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

- 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 25).

Table 25 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]
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

10.5.1. Germany

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

For this study, there is no intention to conduct specific analyses investigating the relationship between gender and the safety, immunogenicity and efficacy of the investigational RSVPreF3 OA vaccine. Recruitment will include both males and females. To not expose pregnant women and their fetuses/children to an investigational vaccine, females enrolled in this study will either be of nonchildbearing potential (i.e., hysterectomy, bilateral oophorectomy, bilateral salpingectomy or post-menopause), or if she is of childbearing potential, she must have a negative pregnancy test and use appropriate methods of contraception for the study duration (refer to the study protocol, Section 5.1 "Inclusion criteria" and Section 5.2 "Exclusion criteria"). Women who are pregnant, planning to become pregnant or breastfeeding are excluded from this study.

10.5.2. Japan

Regulatory and ethical considerations

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

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

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

Study period

Study Period is included in Exhibit.

Study administrative structure

Sponsor information, List of Medical Institutions and Investigators are included in Exhibit.

10.5.3. South Africa

As per regulatory requirement and due to high prevalence of HIV infection, all participants from South Africa with unknown HIV status (unknown or previously tested negative) will be counselled and tested for HIV infection, using the South African Health

Products Regulatory Authority (SAHPRA) approved test kits prior to enrolment. If HIV result is positive, these participants will be excluded as per Section 5.2.1 Medical Conditions exclusion criterion 1.

10.6. Appendix 6: Grading scales for chronic diseases in scope of the AIR population

10.6.1. GOLD classification

Stages of COPD quantify the severity of the disease. COPD is classified into 4 classes [GOLD, 2020].

GOLD Class	Intensity	Definition
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

10.6.2. New York Heart Association Classification of heart failure

Stages of chronic heart failure quantify the severity of the disease. CHF is classified into 4 classes [NYHA].

NYHA Class	Definition	Limitation	Example
I	Ordinary physical activity does not cause undue fatigue, dyspnoea, or palpitations.	None	Can complete any activity requiring ≤7 MET: • Carry 11 kg up 8 steps • Carry objects weighing 36 kg • Shovel snow • Spade soil • Ski • Play squash, handball, or basketball • Jog or walk 8 km/hour.
II	Ordinary physical activity causes fatigue, dyspnoea, palpitations, or angina.	Mild	Can complete any activity requiring ≤5 MET: • Sexual intercourse without stopping • Garden • Roller skate • Walk 7 km/hour on level ground • Climb one flight of stairs at a normal pace without symptoms.
III	Comfortable at rest; less than ordinary physical activity causes fatigue, dyspnoea, palpitations, or angina.	Moderate	Can complete any activity requiring ≤2 MET: • Shower or dress without stopping • Strip and make a bed • Clean windows • Play golf • Walk 4 km/hour.
IV	Symptoms occur at rest; any physical activity increases discomfort.	Severe	Cannot do or cannot complete any activity requiring ≥2 MET; cannot do any of the above activities.

MET = Metabolic equivalent of task, a measure of how much energy is expended compared to remaining at rest.

10.6.3. Chronic kidney disease classification

Stages of CKD quantify the severity of the disease. CKD is classified into 5 stages [CKD, 2021].

- Stage 1 (G1): Normal GFR (≥90 mL/min/1.73 m^2) plus either persistent albuminuria or known structural or hereditary renal disease.
- Stage 2 (G2): GFR 60 to 89 mL/min/1.73 m^2
- Stage 3a (G3a): 45 to 59 mL/min/1.73 m^2
- Stage 3b (G3b): 30 to 44 mL/min/1.73 m^2
- Stage 4 (G4): GFR 15 to 29 mL/min/1.73 m^2
- Stage 5 (G5): GFR < 15 mL/min/1.73 m^2

GFR (in mL/min/1.73 m^2) in CKD can be estimated by the CKD-EPI creatinine equation: 141 × (serum creatinine) -1.209× 0.993 age. The result is multiplied by 1.018 if the patient is female, and by 1.159 if the patient is African American. For female African Americans, the result is multiplied by 1.018 × 1.159 (1.1799). Alternatively, GFR can be estimated using timed (most commonly 24 hours) urine creatinine clearance using measured serum and urine creatinine; this equation tends to overestimate GFR by 10 to 20%. It is used when serum creatinine assessment may not be as accurate (e.g., in patients who are sedentary, very obese, or very thin). Serum cystatin C is an alternative endogenous GFR marker used as a confirmatory test in people with nonrenal factors affecting serum creatinine level (e.g., extremely high, or low muscle mass, exogenous creatine intake, amputations or neuromuscular diseases, and high protein or exclusively plant-based diets). GFR is calculated using CKD-EPI cystatin C equation.

The CKD-EPI formula is more accurate than the MDRD and Cockcroft-Gault formulas, particularly for patients with a GFR near normal values. The CKD-EPI equation yields fewer falsely positive results indicating chronic kidney disease and predicts outcome better than the other formulas.

11. REFERENCES

Arexvy Prescribing Information. AREXVY (Respiratory Syncytial Virus Vaccine, Adjuvanted) suspension for intramuscular injection, 2023. Accessed in October 2023 at https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Arexvy/pdf/AREXVY.PDF

Arexvy Summary of Product Characteristics. Arexvy powder and suspension for suspension for injection, Respiratory Syncytial Virus (RSV) vaccine (recombinant, adjuvanted), 2023. Accessed in October 2023 at https://www.ema.europa.eu/en/documents/overview/arexvy-epar-medicine-overview_en.pdf

Bao K, Reinhardt RL. The differential expression of IL-4 and IL-13 and its impact on type-2 immunity. *Cytokine.* 2015;75(1):25-37. doi: 10.1016/j.cyto.2015.05.008.

Barbas CF, Crowe JE, Cababa D, et al. Human monoclonal Fab fragments derived from a combinatorial library bind to respiratory syncytial virus F glycoprotein and neutralize infectivity. *Proc Natl Acad Sci USA*. 1992;89(21):10164-8.

Bates JT, Keefer CJ, Slaughter JC, et al. Escape from neutralization by the respiratory syncytial virus-specific neutralizing monoclonal antibody palivizumab is driven by changes in on-rate of binding to the fusion protein. *Virology*. 2014;454-455:139-44. doi: 10.1016/j.virol.2014.02.010.

Borchers AT, Chang C, Gershwin ME, et al. Respiratory syncytial virus – a comprehensive review. *Clin Rev Allergy Immunol*. 2013;45(3):331-79.

Boyman O, Sprent J. The role of interleukin-2 during homeostasis and activation of the immune system. *Nat Rev Immunol.* 2012;12(3):180-90.

Branche AR, Saiman L, Walsh EE, et al. Change in functional status associated with respiratory syncytial virus infection in hospitalized older adults. *Influenza Other Respir Viruses*. 2022a;16(6):1151-60.

Branche AR, Saiman L, Walsh EE, et al. Incidence of Respiratory Syncytial Virus Infection Among Hospitalized Adults, 2017-2020. *Clin Infect Dis*. 2022b;74(6):1004-1011.

Chattopadhyay PK, Yu J, Roederer M. A live-cell assay to detect antigen-specific CD4+ T cells with diverse cytokine profiles. *Nat Med.* 2005;11(10):1113-7.

Dieussaert I, et al. RSV prefusion F protein-based maternal vaccine-preterm birth and other outcomes. *N.Eng J Med*. 2024;390(11):1009-1021.

Falsey AR, Hennessey PA, Formica MA, et al. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med*. 2005;352(17):1749-59.

Frentsch M, Arbach O, Kirchhoff D, et al. Direct access to CD4+ T cells specific for defined antigens according to CD154 expression. *Nat Med.* 2005;11(10):1118-24.

GOLD COPD. Pocket guide to COPD diagnosis, management, and prevention. A guide for health care professionals. 2020 Edition. Accessed 14 June 2022. https://goldcopd.org/wp-content/uploads/2020/03/GOLD-2020-POCKET-GUIDE-ver1.0_FINAL-WMV.pdf

Haralambieva IH, Ovsyannikova IG, Pankratz VS, et al. The genetic basis for interindividual immune response variation to measles vaccine: new understanding and new vaccine approaches. *Expert Rev Vaccines*. 2013;12(1):57–70.

Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, Reed C, Grijalva CG, Anderson EJ, Courtney DM et al: Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med*. 2015, 373(5):415-427.

Kollmann TR. Variation between populations in the innate immune response to vaccine adjuvants. *Front Immunol*. 2013;4:81. doi: 10.3389/fimmu.2013.00081.

Korn T, Bettelli E, Oukka M, et al. IL-17 and Th17 Cells. *Annu Rev Immunol.* 2009;27:485-517.

Leroux-Roels I, Davis MG, Steenackers K, et al. Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F (RSVPreF3) Candidate Vaccine in Older Adults: Phase 1/2 Randomized Clinical Trial. *J Infect Dis*. 2023;227(6):761-772.

McDonald JU, Rigsby P, Dougall T, et al. Establishment of the first WHO International Standard for antiserum to Respiratory Syncytical Virus: Report of an International collaborative study. *Vaccine*. 2018;36(50):7641-7649. doi: 10.1016/j.vaccine.2018.10.087.

McDonald JU, Rigsby P, Dougall T, et al. Expansion of the 1st WHO international standard for antiserum to respiratory syncytial virus to include neutralisation titres against RSV subtype B: An international collaborative study. *Vaccine*. 2020;38(4):800-807. doi: 10.1016/j.vaccine.2019.10.095.

Melgar M, Britton A, Roper LE, et al. Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023. *MMWR Morb Mortal Wkly Rep* 2023;72:793–801.

Moris P, Van Der Most R, Leroux-Roels I, et al. H5N1 influenza vaccine formulated with AS03 A induces strong cross-reactive and polyfunctional CD4 T-cell responses. *J Clin Immunol.* 2011; 31(3):443-54.

MSD Manual. Chronic Kidney Disease (CKD). Updated October 2021. Accessed 14 June 2022. https://www.msdmanuals.com/professional/genitourinary-disorders/chronic-kidney-disease/chronic-kidney-disease?query=chronic%20kidney%20disease%20stages

MSD Manual. New York Heart Association (NYHA) Classification of Heart Failure. Accessed 14 June 2022. https://www.msdmanuals.com/professional/multimedia/table/new-york-heart-association-nyha-classification-of-heart-failure

Papi A, Ison MG, Langley JM, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. *N Engl J Med*. 2023;388(7):595-608. doi:10.1056/NEJMoa2209604.

Pérez-Losada M, Posada D, Arenas M, et al. Ethnic differences in the adaptation rate of HIV gp120 from a vaccine trial. *Retrovirology*. 2009;6:67.

Samten B, Thomas EK, Gong J, Barnes PF. Depressed CD40 ligand expression contributes to reduced gamma interferon production in human tuberculosis. *Infect Immun.* 2000;68(5):3002-6.

Schoenborn JR, Wilson CB. Regulation of interferon-gamma during innate and adaptive immune responses. *Adv Immunol.* 2007;96:41-101.

Sedger LM, McDermott MF. TNF and TNF-receptors: From mediators of cell death and inflammation to therapeutic giants - past, present and future. *Cytokine Growth Factor Rev.* 2014;25(4):453-72.

Shi T, Vennard S, Jasiewicz F, et al. Disease burden estimates of respiratory syncytial virus related acute respiratory infections in adults with comorbidity: A systematic review and meta-analysis. *J Infect Dis*. 2021;15;jiab040. doi: 10.1093/infdis/jiab040.

Stubbe M, Vanderheyde N, Goldman M, et al. Antigen-specific central memory CD4+ T lymphocytes produce multiple cytokines and proliferate in vivo in humans. *J Immunol.* 2006;177(11):8185-90.

Wölfl M, Kuball J, Eyrich M, et al. Use of CD137 to study the full repertoire of CD8+ T cells without the need to know epitope specificities. *Cytometry A.* 2008;73(11):1043-9.

Signature Page for 222253 TMF-19110695 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 03-May-2024 07:45:19 GMT+0000