CLINICAL STUDY PROTOCOL

Primary Study Intervention	GlaxoSmithKline Biologicals SA (GSK)'s investigational respiratory syncytial virus (RSV) vaccine BIO RSV OA=ADJ (GSK3844766A)
Other Study Intervention	Placebo: Saline solution
Study Identifier	221265 (RSV OA=ADJ-024)
Approval Date	19 Apr 2024
Title	A Phase 3, randomized, placebo-controlled, observer-blind study in India to evaluate immune response, reactogenicity and safety of a single intramuscular dose of RSVPreF3 OA investigational vaccine when administered to older adults ≥60 years of age and adults 50-59 years of age at increased risk of respiratory syncytial virus lower respiratory tract disease.
Brief Title	A study on the immune response and safety of an RSV OA vaccine in India when given to older adults 60 years of age and above and adults 50-59 years of age at increased risk of respiratory syncytial virus lower respiratory tract disease.
Sponsor	GlaxoSmithKline Biologicals S.A. Rue De L'Institut 89 1330 Rixensart Belgium
Sponsor signatory	Nadia Meyer 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	221265 (RSV OA=ADJ-024)
Approval date	19 Apr 2024
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Investigator name	_____
Signature	_____
Date of signature (DD Month YYYY)	_____

Protocol Amendment Summary Of Changes Table

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment -1	19 Apr 2024
Original Protocol	6 December 2023

Amendment -1 (19 Apr 2024)

Overall rationale for the current Amendment:

The protocol is amended based on feedback received on 12 March 2024, following a meeting with the Subject Expert Committee (SEC) of India held on 27 February 2024. The purpose of this amendment is to increase the sample size for both cohorts (Cohort 1 [Older adults] and Cohort 2 [Adults-AIR]) included in this study.

Atrial fibrillation (AF) is added as Adverse Events of Special Interest (AESI) in this amendment. In safety analysis of the efficacy study (RSV OA=ADJ-006) (data lock point [DLP] of 30 April 2022), a numerical imbalance was observed within 30 days post-vaccination, with 10 events of AFs (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. These safety data were reviewed by the project safety review team (SRT) and the independent data monitoring committee (IDMC), and no safety signals were identified. However, GSK is of the opinion that a detailed assessment of all AF cases is required. Therefore, AF will be considered as an AESI.

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

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

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

1.2 Schema		This change has been made as per regulatory feedback.
2.2 Background	Updated Information about 50-59AIR submission to FDA.	This change has been made to update on submission of 50-59AIR data elsewhere.
4.1 Overall design	New sample size has been updated. Added wording on dosing schedule.	This change has been made as per regulatory feedback. This change has been made to align with other studies.
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.
6.9 Prior and concomitant therapy	Updated the information on Atrial fibrillation and prohibited medications and washout period.	This change has been made to align with other RSV OA studies.
7.2 Participant discontinuation/withdrawal from the study	Added 'stabilized, otherwise explained, or the participant is lost to follow up' wording.	This change has been made to align with other RSV OA studies.
8.3.1.1 Physical examination	Visit 2 physical examination wording has been deleted as it is not a part of pre-study intervention administration procedure.	This change has been made to align with other RSV OA studies.
8.3.2.1 Physical examination	Physical examination at Visit 2 (Day 31) wording has been added as it is a part of post-study intervention administration procedure.	This change has been made to align with other RSV OA studies.
1.3 Schedule of activities 8.4.1 Time period and frequency for collecting AE, SAE, and other safety information. 8.4.3 Follow-up of AEs and SAEs 8.4.4 Adverse events of special interest (AESI) 8.4.4.2 Atrial fibrillation (AF) 8.4.5 Regulatory reporting requirements for SAEs, AESIs and pregnancies 10 Supporting documentation and operational considerations	Atrial fibrillation has been added as an AESI in all safety related sections.	Atrial fibrillation has been included as an AESI in line with other RSV OA studies to further characterise atrial fibrillation events.
8.4.1.1 Potential immune-mediated Diseases (pIMDs)	The list of pIMDs in table 11 has been updated.	Based on new MedDRA version 26.1 the list of pIMDs has been updated.

9.1 Statistical hypothesis	Wording updated.	Updated to improve clarity of the statement.
9.5 Pre-dose sample size determination	Sample size information has been updated.	This change has been made as per regulatory feedback.
10.5.3 Chronic kidney disease classification	Added in the Grade for CKD classification.	To be consistent with inclusion criteria.
11 References	Added references.	
List of abbreviations and definition of terms	Added the AF abbreviation and the definition for enrolled participant.	Updates to align with GSK standards for protocol template.
Throughout protocol	Administrative and editorial changes were made to align table numbers, formatting, and crossreferences.	To maintain consistency with template guidance.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AAION	Arteritic Anterior Ischemic Optic Neuropathy
ACTM	Acute Complete Transverse Myelitis
ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
AHEI	Acute Hemorrhagic Edema of Infancy
AIR	At Increased Risk
ALT	Alanine Aminotransferase
AMSAN	Acute Motor and Sensory Axonal Neuropathy
ANCA	Anti-Neutrophil Cytoplasmic Antibody
APTM	Acute Partial Transverse Myelitis
ARI	Acute Respiratory Illness
AS01	Adjuvant System 01
ATCC	American Type Culture Collection
CAD	Coronary Artery Disease
CHF	Chronic 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

Abbreviation	Definition
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
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
EBA	Epidermolysis Bullosa Acquisita
ECG	Electrocardiogram
eCRF	Electronic Case Report form
EEC	European Economic Commission
EoS	End-of-Study
ERD	Enhanced Respiratory Disease
ES	Exposed Set
FEV	Forced Expiratory Volume
FSFV	First Subject's First Visit
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline Biologicals SA
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HLT	High Level Term
HRT	Hormonal Replacement Therapy
IB	Investigator Brochure
ICE	Intercurrent Events
ICF	Informed Consent Form
ICH	International Council on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICSR	Individual Case Safety Reports
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITP	Idiopathic thrombocytopenic purpura
LABD	Linear IgA-mediated Bullous Dermatosis
LRTD	Lower Respiratory Tract Disease
LSLV	Last Subject's Last Visit
MART	Maintenance and Reliever Therapy
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MET	Metabolic Equivalent of Task
MGI	Mean Geometric Increase

Abbreviation	Definition
MIS-A	Multisystem Inflammatory Syndrome in Adults
MIS-C	Multisystem Inflammatory Syndrome in Children
MMN	Multifocal Motor Neuropathy
MMSE	Mini-Mental State Examination
MoCA	Mini-Cog or Montreal Cognitive Assessment
MPL	Monophosphoryl lipid A
MS	Multiple Sclerosis
NYHA	New York Heart Association
OA	Older Adults
PCD	Primary Completion Date
PI	Personal Information
pIMD	Potential Immune-Mediated Disease
PPFE	Pleuroparenchymal fibroelastosis
PPS	Per-Protocol Set
PT	Preferred Term
QS-21	*Quillaja saponaria* Molina, fraction 21
QTL	Quality Tolerance Limit
RS	Reynolds Syndrome
RSV	Respiratory Syncytial Virus
RTSM	Randomization and Trial Supply Management
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction

Abbreviation	Definition
SJS	Stevens-Johnson Syndrome
SLS	Shrinking Lung Syndrome
SoA	Schedule of Activities
SOC	System Organ Class
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
ULN	Upper Limit of Normal
USADE	Unanticipated Serious Adverse Device Effect
VAED	Vaccine Associated Enhanced Disease
VAERD	Vaccine Associated Enhanced Respiratory Disease
VMED	Vaccine-Mediated Enhanced Disease
WOCBP	Woman of Childbearing Potential
WONCBP	Woman of Nonchildbearing Potential
YOA	Years of Age

Definition of Terms

Term	Definition
Adverse Drug Reaction	An adverse event where a causal relationship between a medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. a. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorized
Adverse event	Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Adverse event of special interest	An adverse event of special interest (serious or nonserious) 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.

Term	Definition
	In an observer-blind study, the participant, the site and sponsor personnel involved in the clinical evaluation of the participants are blinded while other study personnel may be aware of the treatment assignment. In a single-blind study, the investigator(s) and/or their staff are aware of the intervention assignment, but the participant is not.
Caregiver	A 'caregiver' is someone who • lives in the close surroundings of a participant and has a continuous caring role or • has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol-specified procedures.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Co-administered (concomitant) products	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Comparator	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
Current smoker	A person who is currently smoking or who has stopped smoking within 6 months before study start.

Term	Definition
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.
Intercurrent medical condition	A condition that has the capability of altering the immune response to the study vaccine or is confirmed to have an alteration of the participant's initial immune status.
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Invasive medical device	A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.
Investigational medicinal/vaccine 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,

Term	Definition
	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.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.

Term	Definition
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
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).
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.

Term	Definition
	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.
Suspected Unexpected Serious Adverse Reaction (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.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, randomized, placebo-controlled, observer-blind study in India to evaluate immune response, reactogenicity and safety of a single intramuscular dose of RSVPreF3 OA investigational vaccine when administered to older adults ≥60 years of age and adults 50-59 years of age at increased risk of respiratory syncytial virus lower respiratory tract disease.

Brief Title: A study on the immune response and safety of an RSV OA vaccine in India when given to older adults 60 years of age and above and adults 50-59 years of age at increased risk of respiratory syncytial virus lower respiratory tract disease.

Rationale: Refer to Section 2.1.

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

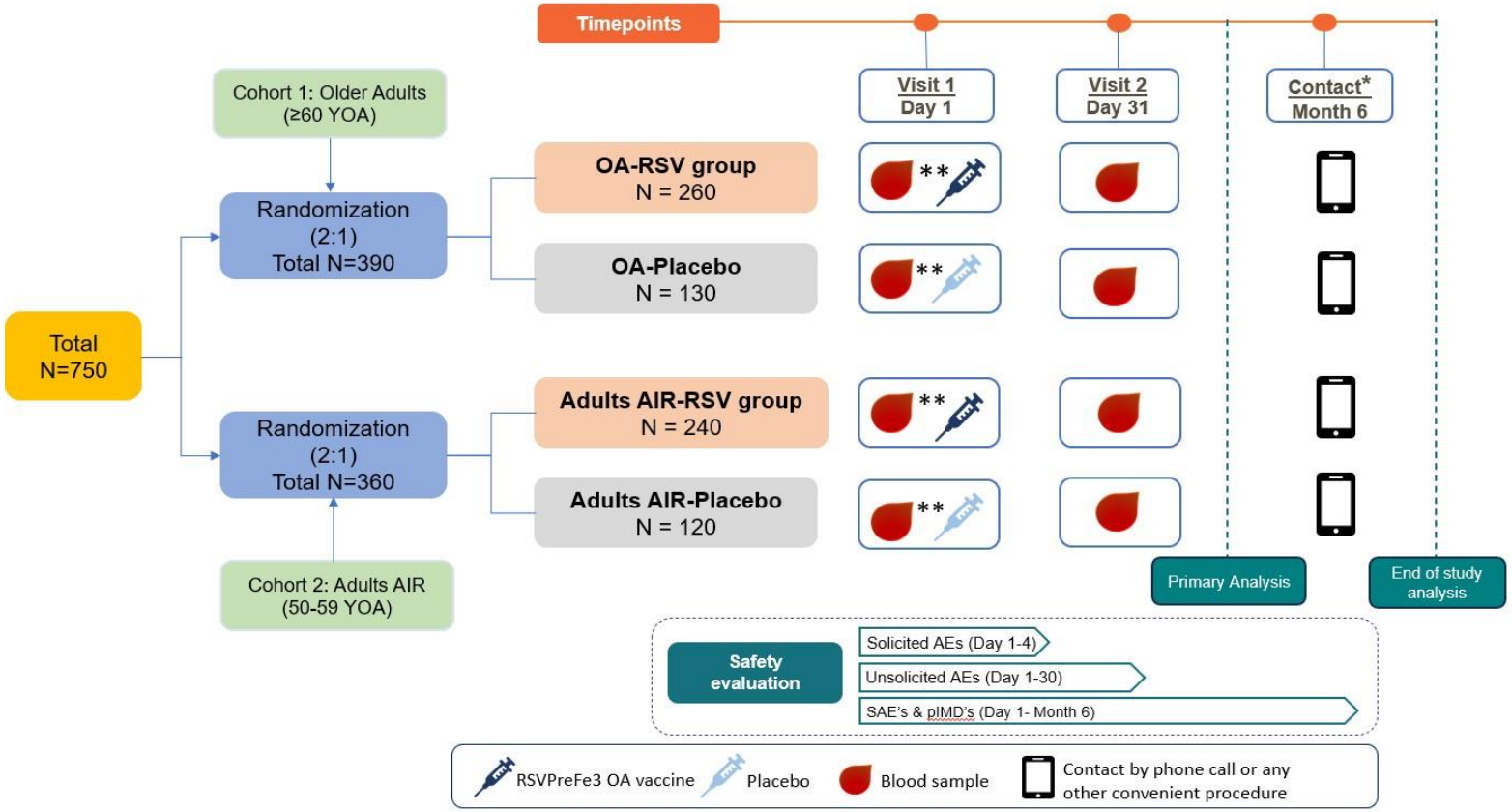
Overall Design: Refer to Sections 1.2 and 4.1.

Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Schema

Figure 1 Study design overview



N: Number of participants; OA: Older adults; AEs: Adverse events; SAEs: Serious adverse events; pIMDs: potential immune-meditated diseases; YOA: Years of age.
AIR: At increased risk-Participants with underlying medical conditions such as chronic pulmonary and cardiovascular disease, diabetes mellitus types 1 and 2, chronic liver and renal diseases.
* Contact by telephone call or any other convenient procedure for the safety follow-up will take place 6 months after study intervention administration.
**Blood sample at Visit 1 (Day 1) should be collected prior to study intervention administration.

1.3. Schedule of activities (SoA)

Table 1 Schedule of Activities

Type of contact Timepoints	Visit 1 Day 1	Visit 2[1] Day 31	Contact[2] Month 6	Notes
Informed consent	●			See Section 10.1.3 for details.
Distribution of 'Participant card'	○			See Section 8.4.8 for details.
Inclusion and exclusion criteria	●			See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria.
Check with participant if he/she will appoint a caregiver and distribute caregiver information letter, when applicable	○	○		See Section 4.1.2 for more information.
Baseline and Demographic assessments				
Collect demography data	●			See Section 8.1.1 for more information.
Medical and vaccination history	●			See Section 8.1.2 for more information.
Physical examination	○	○[a]		See Section 8.3.1.1 for more information.
Record height and weight	●			See Section 8.1.3 for more information.
Record smoking status and smoking exposure history (including electronic smoking devices)	●			See Section 8.1.4 for more information.
Vital signs	●			See Section 8.3.1.2 for more information.
Screening conclusion	●			See Section 8.3.1.2 for more information.
Clinical specimen for laboratory assessments				
Urine pregnancy test (only for women of childbearing potential in Cohort 2)[3]	●			See Section 8.3.1.3 for more information.
Blood sampling in all participants for humoral immune response assessment (~10 mL)[4]	●	●		See Section 8.2.1 for more information.
Study intervention administration				
Check contraindications, warnings and precautions to vaccination	○			See Section 7.1.1 for more information.
Check criteria for temporary delay for enrollment and/or study intervention administration	○			See Section 5.5 for more information.
Randomization (study group and intervention number allocation)	●			See Section 6.3 for more information.
Body temperature before study intervention administration[5]	●			See Section 8.3.1.2 for more details.
Administration of study intervention (including 30-minute post-vaccination observation)	●			See Section 6.1 for more information.
Recording of administered study intervention number	●			

Type of contact Timepoints	Visit 1 Day 1	Visit 2[1] Day 31	Contact[2] Month 6	Notes
Safety assessments				
Setup eDiary	○			See Section 10.3.5.1 for more information
Training participant/caregiver on use of eDiary	○			See Section 10.3.5.1 for more information
Recording of solicited administration site and systemic events (Days 1–4 post-study intervention adminstration) in the eDiary	▲			See Section 10.3.5 for more information.
Review of eDiary[6]		○		See Section 10.3.5.1 for more information
Recording of unsolicited AEs (Days 1-30 post-study intervention administration)[7]	●	●		See Section 10.3.5 for more information.
Record concomitant medications/vaccinations	●	●	●	See Section 6.9 for more information.
Record intercurrent medical conditions	●	●	●	See Section 9.2.1 for more information.
Recording of SAEs, pIMDs[7] and pregnancy	●	●	●	See Section 10.3.5 for more information.
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[8]	●	●	●	See Section 10.3.5 for more information.
Recording of AEs/SAEs leading to withdrawal from the study	●	●	●	See Section 7.2 for more information.
Return of eDiary device or assist participant to delete application[9]		○		See Section 10.3.5.1 for more information.
Contact for safety follow-up			●	See Section 8.3.2.1 for more inforamtion.
Study conclusion			●	See Section 4.4 for more information.

AE, Adverse event;SAE, serious adverse event; pIMD, potential immune mediated disease.
Note: The double-line border following Day 31 indicates the analyses which will be performed on all data (i.e. data that are as clean as possible) obtained up to Day 31.
● Is used to indicate a study procedure that requires documentation in the individual eCRF.
○ Is used to indicate a study procedure that does not require documentation in the individual eCRF.
○ [a] If deemed necessary by the investigator.
▲ Is used to indicate a study procedure recorded in eDiary.
[1]Visit 2 should preferably be done on-site but if deemed necessary (during special circumstances such as the COVID-19 pandemic), this study visit can be replaced by a home visit conducted by authorized staff. Any information from the participant required according to study procedures and not collected during the home visit can be obtained by means of a phone call conducted by the site staff.
[2]Six months after study intervention administration. For this contact, multiple formats (e.g., e-mail, text message, fax or phone call) can be proposed by the study site.
[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]Blood sampling at Visit 1 should be performed prior to study intervention administration.
[5]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.
[6]Designated site staff should review the eDiary frequently during the active event collection period to assess participant/caregiver compliance and monitor reported events to ensure correct data are provided/missed data are recorded.

[7]Atrial fibrillation (AF) will be considered as adverse events of special interest (AESI) in this study and will be additionally reported in the AF follow-up questionnaire (electronic or paper) in eCRF. The reporting of non-serious AF will be performed according to the unsolicited AE reporting period. The reporting of AF meeting the SAE definition (serious AF) will be performed according to the SAE reporting period.

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

[9]Return of the e-Diary device is not applicable if the participant has a “Bring Your Own” e-device.

Table 2 Intervals between study visits

Interval	Planned visit interval	Allowed interval range
Visit 1 (Day 1)→ Visit 2 (Day 31)	30 days	30-42 days
Visit 1 (Day 1)→ Contact (6 months post-study intervention administration)	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 a RSVPreF3 OA vaccine against RSV-associated (subtypes A and B) disease in adults. The vaccine was first approved for use in adults ≥ 60 YOA in the US in May 2023, under the tradename *Arexvy.* The vaccine is also approved in the EU and other countries.

The purpose of the current study is to evaluate the immunogenicity and safety of a single dose of investigational RSVPreF3 OA vaccine in Indian older adults ≥60 YOA and Indian adults 50-59 YOA at increased risk of RSV-LRTD.

2.2. Background

RSV is a ribonucleic acid virus of the *Pneumoviridae* family that causes ARI in humans [Afonso, 2016]. There are 2 subtypes of RSV - RSV A and RSV B - circulating with other respiratory viruses. Overall, the peak activity of RSV mainly occurs during the rainy season and winter period in India, and some correlation with low temperatures has been observed [Broor, 2018; Ghia, 2021]. RSV causes upper and lower respiratory tract infections in people of all ages with the risk of serious infection increasing in young children, OA and adults at high-risk due to presence of comorbidities.

Despite most initial and severe infections occurring during early childhood, RSV is increasingly recognized as a common cause of respiratory illness in adults [Branche, 2022; Jain, 2015]. A worldwide systematic review and meta-analysis to assess the global burden of RSV-ARI in adults ≥ 65 YOA found the estimated number of RSV-ARI cases in industrialized countries to be 1.5 million (95% CI, 0.3-6.9) in 2015 with an incidence of 6.7 cases/1,000 person-years (data for developing countries were missing). Of 1.5 million RSV-ARI cases approximately 14.5% (214 000 episodes; 95% CI,100 000–459 000) were admitted to hospitals [Shi, 2020]. A recently conducted systematic literature review and meta-analysis on RSV burden of disease in adults aged ≥ 60 years found the estimated RSV-ARI attack rate to be 1.62% (95% CI: 0.82-3.08) and hospitalization due to RSV-ARI to be 0.15% (95% CI: 0.09-0.22) which translates to approximately 5.2 million cases of RSV-ARI and 470 000 cases of hospitalizations in adults ≥ 60 YOA in high income countries based on 2019 population [Savic, 2023].

In populations of patients with chronic comorbidities, the incidence of RSV infections is increased, leading to a greater need for medical care and hospitalization. A major US study reported incidence of RSV-related hospitalizations amongst high-risk patients of different age groups. Overall, the RSV-hospitalization rates ranged from 7.7-11.9, 33.5-57.5 and 136.9-255.6 per 100 000 population for 18-49, 50-64 and ≥ 65 YOA, respectively. In the 50-64 year old age group, those with COPD had 6.3-6.4 times higher RSV-hospitalisation rates than those without COPD. In the same age group, the RSV-hospitalisation rates were 2.3-3.6 times higher for those with asthma compared to those without asthma, and 3.4-3.6 times higher for patients with diabetes compared to those without diabetes. 50–64-year-olds with CAD had 3.7-4.4 times higher hospitalisation rates than those without CAD. Those with CHF in the 40-59 year old age group had increased hospitalization rates of 13.3-18.8 times higher compared to those without CHF, the highest increase in hospitalization rates out of all the chronic comorbidities [Branche, 2022]. Chronic liver and kidney disorders are also associated with increased risk for severe RSV disease [Melgar, 2023].

India is a major contributor to the global burden of RSV disease resulting in hospitalization of young children [Li, 2021]. RSV has been reported to be one of the most common causes of ARI and severe ARI in India, with RSV positivity rates varying between 5% and 22% across studies [Broor, 2018; Saxena, 2017; Chadha, 2022]. However, these studies have primarily focused on children and data on RSV-LRTD in adults and OA in India are limited.

Currently, two vaccines have been licensed outside of India for prevention of RSV infections in adults ≥ 60 YOA; *Arexvy* (manufactured by GSK) and *Abrysvo* (manufactured by Pfizer Inc).

There is no preventive vaccination available in India against the RSV infection. The mainstay of treatment is symptomatic or supportive treatment which includes oxygen and corticosteroid therapy.

In a pivotal global Phase 3 efficacy study in adults aged ≥ 60 years, the RSVPreF3 OA investigational vaccine demonstrated overall vaccine efficacy of 82.6% (96.95% CI: 57.9-94.1) against RSV-LRTD [Papi, 2023]. The vaccine induced both humoral and cell-mediated immune response and showed a clinically acceptable safety profile [Schwarz,2023].

A GSK study [NCT05590403] to evaluate immune response and safety of RSVPreF3 OA investigational vaccine in adults 50-59 YOA, including those who are at increased risk of RSV-LRTD, versus adults ≥ 60 YOA is ongoing in the US, Argentina, Canada, Germany, Netherlands, Poland, Spain and Japan. The primary endpoints evaluating non-inferiority of humoral response to RSV vaccine and SRR at one month post-vaccination in adults 50-59 YOA (with and without comorbidities associated with RSV-LRTD) compared to adults ≥ 60 YOA have been successfully met. The safety profile in 50-59 YOA groups is consistent with the profile observed in adults ≥ 60 YOA.

To date there is no licensed vaccine for the prevention of RSV-associated diseases in adults 50-59 YOA and age extension applications are under regulatory assessments in US, EU and several other countries.

Currently, the RSVPreF3 OA investigational vaccine is not approved for use in India. To meet the requirement of the Indian regulatory authority for licensure and to evaluate the immunogenicity and safety of RSVPreF3 OA investigational vaccine in the Indian population, the current study has been planned.

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

2.3. Benefit/risk assessment

2.3.1. Risk assessment

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

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 administration site events will be collected and reviewed up to Day 4.

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
Local reactions at site of blood draw	Pain, erythema/redness, 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

In parallel with the RSVPreF3 OA clinical development program, another RSV vaccine development program was initiated by GSK, with the objective to prevent RSV-associated lower respiratory tract illness in neonates and infants during their first 6 months of life, through immunization of pregnant women with a single dose of the investigational RSV maternal vaccine candidate.

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 vaccine candidate for older adults (RSV PreF3 OA vaccine) contains the same RSV antigen as the RSV maternal vaccine candidate but the RSVPreF3 OA vaccine is

combined with GSK's established $AS01_E$ 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 taking into account the low incidence of spontaneous pregnancies in this age group [Salihu, 2003], GSK has assessed that WOCBP as of 50-59 YOA 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 vaccination in this study. Study participants will be adequately informed of the risks associated with pregnancy as the informed consent contains specific information regarding the RSV Maternal study.

The RSVPreF3 OA vaccine trials in participants ≥60 YOA are closely monitored for safety with all available safety data reviewed internally. In addition, the Phase 3 RSV OA=ADJ-006 clinical study is monitored by an IDMC on an ongoing basis. The IDMC has not raised any concern for safety in the OA population. The RSVPreF3 OA vaccine has not been studied in pregnant women to date.

2.3.2. Benefit assessment

The participants may not directly benefit from participating in this study. For those receiving the RSVPreF3 OA investigational vaccine, they may have the benefit of being protected against RSV-associated disease. In a pre-specified efficacy interim analysis of an ongoing Phase 3 trial in adults aged 60 years and above, the primary objective was met with a high vaccine efficacy during the first RSV season and no unexpected safety concerns were observed (refer to IB).

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).

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

2.3.3. Overall benefit-risk conclusion

The RSVPreF3 OA investigational vaccine is in clinical development. Considering the measures taken to minimize the risk to participants in this study, the potential risks are justified by the potential benefits of receiving the vaccine and the value of information to be gained which will contribute to clinical development of this vaccine in India.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the humoral immune response following administration of a single dose of the RSVPreF3 OA investigational vaccine.	• RSV-A and RSV-B neutralizing titers pre-study intervention administration and at 1 month after study intervention administration.
Secondary	
To evaluate the safety and reactogenicity following administration of a single dose of the RSVPreF3 OA investigational vaccine.	• Occurrence of each solicited administration site event with onset within 4 days after study intervention administration (i.e., the day of study intervention administration and 3 subsequent days). • 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 after study intervention administration (Day 1) up to study end (Month 6). • Occurrence of pIMDs after study intervention administration (Day 1) up to study end (Month 6).

OA: Older adult; RSV: Respiratory syncytial virus; AE: Adverse event; SAE: Serious adverse event; pIMD: Potential immune-mediated Disease.

PRIMARY ESTIMAND

The primary clinical question of interest is to evaluate humoral immunogenicity of a single dose of RSVPreF3 OA investigational vaccine administered in older adults ≥60 YOA, and in adults aged 50-59 YOA at increased risk of RSV-LRTD in the Indian population, when participants have not used prohibited medication nor received prohibited concomitant vaccines, and participants have not developed a prohibited medical condition.

The primary estimand is described by the following attributes:

- **Population:** Indian OA ≥60 YOA and adults aged 50-59 YOA at increased risk of RSV-LRTD at the time of study intervention administration.
- **Endpoint (variable):** RSV-A and RSV-B neutralizing titers (expressed in ED60) measured at baseline (Day 1) and 1 month (Day 31) after the study intervention administration, fold increase in RSV-A and RSV-B neutralizing titers from Day 1 to Day 31, seroresponse in RSV-A and RSV-B neutralizing titers from Day 1 to Day 31.
- **Treatment condition:** RSVPreF3 OA investigational vaccine or Placebo at Day 1.

- **Intercurrent Events (ICEs) and strategies:** A hypothetical strategy will be used to manage the intercurrent events. Data collected after ICEs will be excluded from the analysis.

  The following intercurrent events will lead to data exclusion from the assessment of immunogenicity:

  - Medical condition forbidden by the protocol.
  - Vaccine and/or medication forbidden by the protocol.

- **Population level summary:** GMT with 95% CI at Day 1 (baseline) and at Day 31, MGI with 95% CI at Day 31, and SRR with 95% CI at Day 31 will be summarized separately for RSV-A/B antigen and by treatment group.

  MGI is defined as the geometric mean of the within-participant ratios of post-vaccination titers over pre-vaccination titers.

  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.

Rationale for estimand: The above estimand addresses the objective of evaluating humoral immunogenicity in Indian OA ≥ 60 YOA and adults aged 50-59 YOA at increased risk of RSV-LRTD after administration of a single dose of RSVPreF3 OA investigational vaccine without confounding of other medications/vaccinations/medical condition on the target population since the impact of developing medical condition forbidden by protocol and use of forbidden medications and vaccinations is anticipated to modify the vaccine effect.

SECONDARY ESTIMANDS

Attributes					Summary measure
Treatment	Population	Endpoint (Variable)	Intercurrent events		
			Description	Handling strategy	
RSVPreF3 OA investigational vaccine or Placebo at Day 1.	Indian adults aged 50-59 YOA at increased risk of RSV-LRTD and ≥ 60 YOA at the time of study intervention administration.	• Occurrence of each solicited administration site event with onset within 4 days after study intervention administration. • Occurrence of each solicited systemic event with onset within 4 days after study intervention administration. • Occurrence of unsolicited AEs within 30 days after study intervention administration. • Occurrence of SAEs after study intervention administration (Day 1) up to study end (Month 6). • Occurrence of pIMDs after study intervention administration (Day 1) up to study end (Month 6).	Taking prohibited medication /vaccine or forbidden 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 treatment group who report each of the endpoints.

AE, Adverse event; pIMD, Potential immune-mediated Disease; SAE, Serious adverse event.

4. STUDY DESIGN

4.1. Overall design

Refer to Figure 1 provided in Section 1.2.

Experimental design: Phase 3, randomized, placebo-controlled, observer-blind study.

Study groups and randomization: Approximately 750 eligible participants aged ≥60 YOA and 50-59 YOA at increased risk of RSV-LRTD will be enrolled in 2 cohorts, as follows:

Cohort 1 (Older adults): Approximately 390 eligible participants aged ≥ 60 YOA will be enrolled and randomly assigned (2:1) to 2 study groups, as follows:

- **OA-RSV group:** participants will receive a single dose of the RSVPreF3 OA investigational vaccine on Visit 1 (Day 1).
- **OA-Placebo group:** participants will receive a single dose of placebo (saline) on Visit 1 (Day 1).

Cohort 2 (Adults-AIR): Approximately 360 eligible participants aged 50-59 YOA at increased risk of RSV-LRTD will be enrolled and randomly assigned (2:1) to 2 study groups, as follows:

- **Adults-AIR-RSV group:** participants will receive a single dose of the RSVPreF3 OA investigational vaccine on Visit 1 (Day 1).
- **Adults-AIR-Placebo group:** participants will receive a single dose of placebo (saline) on Visit 1 (Day 1).

Cohorts and age categories for Cohort 1 will be considered as stratification factors. Enrollment rules will be applied for the proportion of participants enrolled within disease categories (Cohort 2) and within each age category of 60-69, 70-79 and ≥ 80 YOA (Cohort 1). Refer to Section 4.1.1.

Duration of study: The total duration of the study, per participant, will be approximately 6 months.

Sampling schedule: Two blood samples (approximately 10 mL each) will be collected from all participants to evaluate the immune response to the investigational RSVPreF3 OA vaccine on Day 1 (pre-intervention) and Day 31 (1 month post-study intervention).

PCD: The PCD will be when the last participant completes Day 31, as per SoA.

Blinding strategy: The study will be conducted in an observer-blind manner from study start-up to Day 31 analysis, beyond which the study will be considered single-blind. Refer to Section 6.4 for details.

Data collection: eCRF will be used. Solicited AEs will be collected using an eDiary device.

EoS: Refer to Section 4.4 for details.

Safety monitoring: The study will be monitored by an SRT. Refer to Section 10.1.6 for details.

Dosing schedule: Participants will receive a single dose of the investigational study intervention (RSVPreF3 OA or Placebo) at Visit 1 (Day 1).

The description of the vaccine(s)/product is presented in Table 4.

4.1.1. Enrollment rules

Cohort 1 (Older adults)

Participants will be enrolled in 3 age categories reflecting an approximate age distribution and disease burden in the general population. It is therefore intended to enroll:

- Approximately 40% of participants 60-69 YOA
- Approximately 30% of participants 70-79 YOA
- Approximately 10% of participants ≥80 YOA
- The remaining 20% can be distributed freely across the 3 age categories.

Cohort 2 (Adults-AIR)

Enrollment rules will ensure adequate representation of the different diseases (see Section 5.1.1). It is therefore intended to enroll:

- Approximately 25% of participants with chronic pulmonary diseases
- Approximately 25% of participants with chronic cardiovascular diseases
- Approximately 25% of participants with diabetes mellitus (type 1 and type 2)
- The remaining 25% can be distributed freely across the above 3 disease categories as well as include participants with chronic renal or liver disease.

Both cohorts

When the target number of participants is reached in a particular disease or age category, further enrollment of participants in that category will be stopped. If needed, the maximum number of participants in a particular disease or age category may be adapted during the study. Additionally, an effort should be made to recruit approximately equal number of participants from each sex.

Details of recruitment strategy are provided in Section 10.1.4.

4.1.2. Caregiver support

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

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

Caregivers may help the study participants with performing some practical study procedures such as receiving or making phone calls to site staff, planning study visits,

transcribing responses to diaries, transportation to and from the study site etc. However, at no time, the caregiver should evaluate the participant's health status while answering diaries or make decisions on behalf of the participant. At the first study visit (Visit 1) the site staff should inform the participant of the possibility to appoint a caregiver. Then at the subsequent study visit (Visit 2) the site staff should check again with the participant if he/she wishes to appoint a caregiver or if there were or will be changes of caregiver.

4.2. Scientific rationale for study design

RSV is associated with serious illness in OA and high-risk adults, including those with chronic lung and heart disease or other comorbidities which may lead to increased risk of RSV-LRTD. The efficacy of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV-LRTD caused by RSV A and/or RSV B in OA ≥60 YOA has been demonstrated in the global Phase 3 clinical study RSV OA=ADJ-006. High RSV-A and RSV-B neutralizing titers were also observed in study participants who received the RSVPreF3 OA investigational vaccine (refer to IB). A separate global Phase 3 study has demonstrated non-inferiority of humoral response and SRR following a single dose of the RSVPreF3 OA investigational vaccine in 50-59 YOA adults (with and without increased risk of RSV-LRTD) compared with adults ≥60 YOA.[Ferguson, 2024]

Immune protection against RSV in older people is incompletely understood and probably multifactorial. Older adults with low serum neutralizing titers have been reported to be at greater risk of developing symptomatic RSV infection and of hospitalization than those who have high antibody titers [Falsey, 1998; Walsh, 2004]. The immunogenicity endpoints in this study will therefore be relying on virus neutralization assays against RSV-A and RSV-B subtypes.

The current study is designed as a Phase 3, observer-blind, placebo-controlled study to evaluate the immune response of RSVPreF3 OA investigational vaccine in adults aged ≥60 YOA and 50-59 YOA at increased risk of RSV-LRTD in the Indian population. Reactogenicity and safety will also be evaluated in all study participants.

4.2.1. Rationale for the use of placebo

As there is currently no licensed RSV vaccine available in India, a placebo group (receiving saline solution) will be used as control for the safety/reactogenicity assessments and to maintain study blinding.

4.2.2. Rationale for study blinding

Given the difference in reconstitution and visual appearance of the RSVPreF3 OA investigational vaccine and the saline solution used as placebo, double blinding is not possible, and the study will be conducted in an observer-blind manner for all participants (until Day 31 analysis). Please refer to Definition of Terms for the definition of observer blind.

Further information on blinding and unblinding is provided in Section 6.4.

4.2.3. Participant input into design

Not applicable.

4.3. Justification for dose

A single dose (0.5 mL) of the licensed formulation (120 µg RSVPreF3/AS01$_E$) 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 all periods of the study including the last visit or the last scheduled procedure/contact shown in the SoA.

LSLV (contact at Month 6) 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.

Adherence to the inclusion and exclusion criteria specified in the protocol is essential.

5.1. Inclusion criteria

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

- Participants, who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the eDiary, return for follow-up visits, ability to access and utilize a phone or other electronic communications). INC#1

  Note: In case of physical incapacity that would preclude the self-completion of the eDiary, either site staff can assist the participant (for activities performed during site visits) or the participant may assign a caregiver to assist him/her with this activity (for activities performed at home). However, at no time will the site staff or caregiver evaluate the participant's health status while completing the eDiary or make decisions on behalf of the participant. Refer to Definition of Terms for the definition of caregiver.

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

5.1.1. Specific inclusion criteria for all participants in Cohort 1 (Older adults)

- Male or female, ≥ 60 YOA at the time of the study intervention administration. INC#3
- Participants who are medically stable in the opinion of the investigator at the time of study intervention administration. Participants with chronic stable medical conditions with or without specific treatment, such as diabetes mellitus, hypertension, or cardiac disease, are allowed to participate in this study if considered by the investigator as medically stable. INC#4

  A stable medical 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 enrolment.
- Participants living in the general community or in an assisted-living facility that provides minimal assistance can be enrolled, such that the participant is primarily responsible for self-care and activities of daily living. INC#5

5.1.2. Specific inclusion criteria for all participants in Cohort 2 (Adults-AIR)

- Male or female, 50-59 YOA at the time of the study intervention administration. INC#6
- Participants should be diagnosed with at least 1 of the following medical conditions and considered medically stable by the investigator: INC#7

  A stable medical 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 pulmonary disease resulting in activity restricting symptoms or use of long-term medication:
    - Chronic obstructive pulmonary disease (COPD)
      - Global Initiative for Chronic Obstructive Lung Disease (GOLD) Grade 2-4 (see Section 10.5.1)
    - Asthma
      - Patient on Maintenance and Reliever therapy (MART) with treatment at least once per week (excluding exercise asthma)
    - Cystic fibrosis
    - Other chronic respiratory diseases: lung fibrosis, restrictive lung disease, interstitial lung disease, emphysema, or bronchiectasis
  - Chronic cardiovascular disease:
    - Chronic heart failure (CHF)

  - A minimum of class II symptoms according to New York Heart Association classification of heart failure (see Section 10.5.2)
- Pre-existing coronary artery disease (CAD not otherwise specified)
  - Physician diagnosis of CAD based on electrocardiogram, exercise stress test, nuclear stress test, cardiac computed tomography scan or cardiac angiogram (more than the presence of hypercholesterolemia)
- Cardiac arrhythmia
  - Patient diagnosed with a cardiac arrythmia that requires medical support either pharmacologically or with a medical device.

- Diabetes mellitus: type 1 or type 2 with active treatment for the last 6 months
- Other diseases at increased risk for RSV-LRTD disease:
  - Chronic kidney disease
    - G2-G3 disease (Glomerular Filtration Rate between 30 and 90 ml/min/1.73 m^2 – see Section 10.5.3)
  - Chronic liver disease

- Female participants of non-childbearing potential may be enrolled in the study. Non-childbearing potential is defined as hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or post-menopause. INC#8
- Female participants of childbearing potential may be enrolled in the study if the participant: INC#9
  - has practiced adequate contraception from 1 month prior to study intervention administration, and
  - has a negative pregnancy test on the day of and prior to study intervention administration, and
  - has agreed to continue adequate contraception for at least 1 month after the study intervention administration.

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

5.2. Exclusion criteria

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

5.2.1. Medical Conditions

- History of any reaction or hypersensitivity likely to be exacerbated by any component of the study interventions (for details of the components of the RSVPreF3 OA investigational vaccine refer to *Arexvy* SmPC/Prescribing Information [*Arexvy* package insert, 2023; *Arexvy* summary of product

characteristics, 2023] and Table 4), including a known history of severe allergic reaction (e.g., anaphylaxis). EXC#1

- Any confirmed or suspected immunosuppressive or immunodeficient condition, resulting from disease (e.g. current malignancy, human immunodeficiency virus) or immunosuppressive/cytotoxic therapy (e.g., medication used during cancer chemotherapy, organ transplantation, or to treat autoimmune disorders), based on medical history and physical examination (no laboratory testing required). EXC#2
- Unstable chronic illness. EXC#3
- Recurrent history or uncontrolled neurological disorders or seizures. Participants with medically-controlled active or chronic neurological diseases can be enrolled in the study as per investigator assessment, provided that their condition will allow them to comply with the requirements of the protocol (e.g. completion of the eDiary, attend phone call/study site visits). EXC#4
- Any history of dementia or any medical condition that moderately or severely impairs cognition. EXC#5

  Note: If deemed necessary for clinical evaluation, the investigator can use tools such as Mini-Mental State Examination (MMSE), Mini-Cog or Montreal Cognitive Assessment (MoCA) to determine cognition levels of the participant.
- Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study (e.g., life-threatening disease). 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 invasive medical device) other than the study interventions during the period beginning 30 days (Day -29 to Day 1) before the dose of study interventions or their planned use during the study period (Day 1 up to Month 6). EXC#9

  Note: EEC directive 93/42/EEC defines an invasive medical device as 'A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body'.
- Previous vaccination with licensed or investigational RSV vaccine. EXC#10
- 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 (fully licensed or with emergency use authorization [EUA]) which can be administered up to 14 days before or from 14 days after the study intervention administration. EXC#11

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

- Chronic administration of immune-modifying drugs (defined as more than 14 consecutive days in total) and/or planned use of long-acting immune-modifying treatments at any time up to the end of the study. EXC#12
  - Up to 3 months prior to the study intervention administration:
    - For corticosteroids, this will mean prednisone equivalent ≥ 20 mg/day for adult participants. Inhaled and topical steroids are allowed.
    - Administration of immunoglobulins and/or any blood products or plasma derivatives.
  - Up to 6 months prior to study intervention administration: long-acting immune-modifying drugs including among others immunotherapy (e.g., TNF-inhibitors), monoclonal antibodies, antitumoral medication.

5.2.3. Prior/Concurrent Clinical Study Experience

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

5.2.4. Other Exclusion Criteria

5.2.4.1. Other Exclusion Criteria 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
- Participation of any study personnel or their immediate dependents, family, or household members. EXC#15
- Planned move during the study conduct that prohibits participation until study end. EXC#16
- Bedridden participants. EXC#17

5.2.4.2. Other Exclusion Criteria for cohort 2 (Adults-AIR)

- Pregnant or lactating female participant. EXC#18
- Female participant planning to become pregnant or planning to discontinue contraceptive precautions. EXC#19

5.3. Lifestyle considerations

Not applicable.

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, information from any previous trials with the same IP, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number for every screening/rescreening event. Previously assigned participant numbers are to be recorded in the participants' eCRF.

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

Enrollment/study intervention administration may be postponed during the enrollment period until transient conditions cited below are resolved:

- Acute disease and/or fever at the time of enrollment and/or study intervention administration. Refer to the SoA (Section 1.3) for definition of fever and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled and/or dosed at the discretion of the investigator.
- Participants with symptoms suggestive of active COVID-19 infection (e.g. fever, cough, etc.). The return to the site of the participant 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 within the past 14 days may be vaccinated at the discretion of the investigator at least 14 days after the exposure if the participant remains symptom free.
- In case of administration of inactivated, subunit and split influenza vaccines or COVID-19 vaccines: Postponement of study vaccine administration within given protocol timelines to allow respect of the 14 day-interval between flu or COVID-19 vaccination and study vaccine administration.
- Other issues (e.g., technical or administrative) preventing dose administration on day of visit.

- All efforts should be made so that blood sample is taken on the same date as vaccination. For Visit 1, if the planned study intervention administration is delayed, blood sampling does not need to be repeated if it was obtained during enrolment visit. The following procedures must be repeated prior to the delayed study intervention administration:
  - Urine pregnancy test
  - Body temperature and vital signs
  - Physical examination
  - Re-check contraindications, warnings, and precautions to study intervention
  - Re-check inclusion/exclusion criteria

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

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

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

6.1. Study interventions administered

Table 4 Study Interventions Administered

Study intervention name	RSVPreF3 OA investigational vaccine		Placebo
Study intervention formulation	RSVPreF3 (120 µg)	AS01$_E$: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injections	NaCl (0.9%); Water for injections
Presentation	Powder for suspension for injection (Vial)	Suspension for suspension for injection (Vial)	Solution for injection (syringe)
Type	Investigational		Control
Product category	Biologic		Combination product
Route of administration	IM		
Location	Deltoid		
Laterality	Non-dominant**		
Number of doses to be administered	1		1
Volume to be administered by dose ***	0.5 mL		At least 0.5 mL****
Packaging and labeling	Refer to the pharmacy manual for more details		
Manufacturer	GSK		

AS01$_E$ = Adjuvant System 01; QS-21 = *Quillaja saponaria* Molina, fraction 21; MPL = Monophosphoryl lipid A.
*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 reconstitution
****The volume of the saline pre-filled syringe may be between 0.6 and 0.8 mL. The full volume is to be injected.

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

6.1.1. Medical devices

- The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are placebo prefilled syringes. Other medical devices (not manufactured by or for GSK) provided for use in this study are thermometer for body temperature measurement, materials for study intervention administration and syringes.
- Instructions for medical device use are provided in Laboratory Manual and Pharmacy Manual.
- All device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.7) and appropriately managed by GSK.

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 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

Participants 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

Eligible participants in Cohort 1 and Cohort 2 will be randomly assigned in a 2:1 ratio at Visit 1 (Day 1) to receive RSVPreF3 OA investigational vaccine or Placebo.

The assignment of clinical trial supplies will be performed using GSK Randomization and Trial Supply Management (RTSM) system.

6.3.3. Intervention allocation to the participants

The order of study intervention assignment is generated (permuted block randomization) and stratified by cohort and age categories in Cohort 1 using a GSK RTSM system. The subject level study intervention assignment activity is conducted using a GSK RTSM system.

Participants will be enrolled into 2 different cohorts.

- Participants in Cohort 1 will be enrolled in 3 age categories (60-69 YOA, 70-79 YOA and ≥80 YOA).
- Participants 50-59 YOA and at increased risk of RSV-LRTD will be enrolled into Cohort 2 in 4 disease categories (Chronic pulmonary diseases, Chronic cardiovascular diseases, Diabetes mellitus types 1 and 2 and Other disease categories).

The RTSM system will assign randomization number and corresponding study group at time of randomization as well as the study intervention number at time of each study intervention administration. 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.

6.4. Blinding

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

Refer to pharmacy manual regarding details of the tasks that can be performed by the unblinded study personnel. The unblinded study personnel are allowed to transcribe source data (as detailed in Section 10.1.9) into the eCRF without interpretation or generation of data.

The laboratory in charge of the sample testing will be blinded to the intervention assignment in participants. Codes will be used to link the participant and study (without any link to the intervention attributed to the participant) to each sample. There will be no link between the study intervention groups and the identity of the participant.

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

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

6.4.1. Emergency unblinding

This is an observer-blind study in which participants/ the site and sponsor personnel involved in the clinical evaluation of the participants are blinded to study intervention. The RTSM will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may, at the investigator's discretion, contact GSK to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

If the investigator is unable to access RTSM, they can contact the GSK helpdesk based on the information provided in the pharmacy manual.

A physician other than the investigator (e.g., an emergency room physician) or participant /participant's caregiver or family member may also request emergency access to the participant's study intervention information as per participant card.

A participant may continue in the study if that participant's intervention assignment is unblinded. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.

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

assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5. Study intervention compliance

As this is an observer-blind study, vaccine preparation and administration will be done by authorized medical personnel who will not participate in any of the study clinical evaluation assays. Study intervention administration will be performed under medical supervision. The date and time of study intervention administration will be recorded in the source documents.

6.6. Dose modification

Not applicable.

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

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

6.8. Treatment of overdose

Not applicable.

6.9. Prior and concomitant therapy

At each study visit/contact, the investigator or delegate should question the participant about any 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, ongoing at Visit 1 and/or administered during the 30-day period after the dose of study intervention (Day 1 to Day 30).
  - Reason for use
  - Dates of administration including start and end dates
  - Dosage information including dose and frequency
- All concomitant medication leading to elimination from the analysis, including products/vaccines. Please refer to the Section 5.2.2 for further details.
- All concomitant medication which may explain/cause/be used to treat an SAE/pIMD including vaccines/products, as defined in Section 8.4 and Section 10.3.5.7. These must also be recorded in the Expedited AE Report.

- For all AF AESIs (including serious and non-serious), concomitant drugs which could be associated with development or worsening of AF must be reported in the AF follow-up questionnaire.
- Any prophylactic medication (e.g., analgesics, antipyretics) administered on the day of study intervention administration (Day 1) in the absence of ANY symptom and in anticipation of a reaction to the study intervention administration.
- Any antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination need 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 5 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 contact at month 6, unless otherwise stated below.

Medications that are not stipulated in the exclusion criteria or listed in Table 5 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 5 Prohibited medications and washout period

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

[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 the dose of study intervention. 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 and topical steroids are allowed.

Refer to Table 6 for an overview of the timing for recording of concomitant medication during the study.

Table 6 Timing of collection of concomitant medication to be recorded.

	Dose 1 Day 1	Day 30	Study conclusion (Contact at Month 6)
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			

pIMD = Potential immune-mediated Disease; SAE = Serious adverse event; AESI: Adverse event of special interest; AF=Atrial Fibrillation.

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.

7.1.1. Contraindications to subsequent study intervention administration

Not applicable.

Refer to Section 5.2 for the list of contraindications to study intervention administration at Day 1 (Visit 1).

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.

The participant will be permanently discontinued from the study intervention and the study at that time.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. If the participant withdraws

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

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

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

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

Participants who are withdrawn from the study because of AE/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 explained, 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 within the allowed interval, 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, contact with next-of-kin, 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, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status of the participant is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- 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. Subjects who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria.
- 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.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- The maximum amount of blood collected from each participant over the duration of the study, related to procedures in this study, will not exceed 20 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

- Study participants may decide to assign a caregiver to help them fulfill the study procedures. Please refer to Section 4.1.2 for details.
- It is preferred to have all visits on-site. However, during special circumstances (e.g., COVID-19 pandemic), 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:
  - Visit 2 may be conducted at the participant's home (by the site staff), if appropriate. Biological sample at Visit 2 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.
- 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 and baseline procedures

8.1.1. Collection of demographic data

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

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

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

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

8.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history by interviewing the participant and/or review of the participant's medical records. Record any 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* 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. Record 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.

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

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

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

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

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

8.2.1. Biological Samples

An overall blood volume of 20 mL will be collected during the entire study period. Refer to Table 7 and SoA for information on volumes collected for different assessments.

Table 7 Biological samples

Sample type	Quantity	Unit	Timepoint	Subset
Blood	~10	mL	Visit 1 (Day 1) and Visit 2 (Day 31)	All participants
Urine for pregnancy test	-	-	Visit 1 (Day 1)	WOCBP

WOCBP, woman of childbearing potential.
Blood sample and urine sample for pregnancy testing 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 8 Laboratory assays

Test Classification	System	Component	Method	Laboratory
Humoral immunity	Serum	RSV-A neutralizing titer	Neutralization	GSK*
		RSV-B neutralizing titer		

*GSK laboratory refers to the Vaccines Clinical Laboratory and Assay Portfolio (Vx CL&AP) in Rixensart, Belgium; Wavre, Belgium. Vx CL&AP may delegate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Siena, Italy or to a CRO.
RSV, respiratory syncytial virus.

Please refer to Section 10.2 for a brief description of the assays performed in the study.

The addresses of clinical laboratories used for sample analysis are provided in a separate document accompanying this study protocol.

GSK clinical laboratories have established a Quality System supported by procedures. The activities of GSK clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

8.2.3. Immunological read-outs

Table 9 Immunological read-outs

Blood sampling timepoint		Subset name	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Visit 1 (Day 1)	Pre-study intervention administration	All participants	750	RSV-A and RSV-B neutralizing titers
Visit 2 (Day 31)	Day 31 (1 month post dose 1)	All participants	750	RSV-A and RSV-B neutralizing titers

RSV, respiratory syncytial virus.

8.2.4. Immunological correlates of protection

No generally accepted immunological correlate of protection has been demonstrated so far for the antigens used in the study intervention.

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 at Visit 1 (Day 1 pre-study intervention administration).

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

8.3.1.2. Vital signs

Resting vital signs should be checked at Visit 1 (Day 1 pre-study intervention administration). Vital signs are to be taken before blood collection for laboratory tests and will consist of systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest by counting the number of breaths for 1 minute. Collected information needs to be recorded in the eCRF.

If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. Vital signs will be re-taken in case of delayed vaccination. Refer to the Section 5.5 for the list of criteria for temporary delay of study intervention administration.

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).

8.3.1.3. Pregnancy testing

Female participants of childbearing potential must perform a urine pregnancy test before the administration 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 Visit 2, Day 31 will be performed only if the participant indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate. Should there be an underlying condition or illness that is diagnosed in any of these visits, this will be adequately recorded in eCRF.

8.3.2.2. Safety contact at 6 months post-study intervention administration

Six months after the study intervention administration, each participant must be contacted to check if he/she has experienced any SAEs or pIMDs since study intervention administration, and to collect information on concomitant medications/vaccinations.

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

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

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

8.3.3. Warnings and precautions to administration of study intervention

Refer to Arexvy SmPC/Prescribing Information [*Arexvy* package insert, 2023; *Arexvy* summary of product characteristics, 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 and other safety information, and remain responsible for following up all AEs, and AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver).

Investigator safety reports must be prepared for 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 and Section 10.6.

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

All AEs will be collected from the start of study intervention administration until the timepoints specified in the SoA.

All SAEs will be collected from the start of study intervention administration until the time points specified in the SoA.

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 study intervention 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., study intervention, 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 10 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†, all pIMDs 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***					

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

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

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 and Section

10.6. 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 and Table 10.

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

8.4.2. Method of detecting AEs and SAEs

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contact. All SAEs 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 and Section 10.6.4.4.

8.4.4. Adverse Events of Special Interest (AESI)

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)

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 11.

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

The investigator(s) must exercise their medical/scientific judgment to determine whether other diseases have an autoimmune origin (i.e., pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD. In addition, the investigator should categorize each pIMD either as a new onset condition (if it started following vaccination) or as an exacerbation of a pre-existing chronic condition (if it exacerbated following vaccination) in the eCRF.

Table 11 List of pIMDs

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

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

Medical Concept	Additional Notes
	• Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis • Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease • Felty's syndrome
Sjögren's syndrome	
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blenorrhagica • Psoriatic spondylitis • Reactive Arthritis • Undifferentiated spondyloarthritis
Systemic Lupus Erythematosus	• Includes Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)
Systemic Scleroderma (Systemic Sclerosis)	• Includes Raynaud's syndrome systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants	Includes the following: • Acute necrotising myelitis • Bickerstaff's brainstem encephalitis

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

Medical Concept	Additional Notes
	• Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
Lichen planus	• Includes liquen planopilaris
Localised Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Takayasu's arteritis
Medium sized and/or small vessels vasculitis	Including but not limited to: • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Behcet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis) • Erythema induratum (also known as nodular vasculitis) • Henoch-Schonlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis

Medical Concept	Additional Notes
	• Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Granulomatosis with polyangiitis
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• Frequently used related terms include : "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"
Goodpasture syndrome	• Frequently used related terms include : "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"
Immune-mediated enhancement of disease	• Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	Including but not limited to: • Kawasaki's disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Raynaud's phenomenon	
Sarcoidosis	• Includes Loefgren syndrome
Susac's syndrome	

8.4.4.2. Atrial fibrillation (AF)

AEs of AF are considered as AESI in this study.

In the efficacy study (RSV OA=ADJ-006), at the time of safety analysis 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) [Papi,2023]. To further characterize events of AF, AF will be considered as an AESI.

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

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

8.4.5. Regulatory reporting requirements for SAEs, AESIs and pregnancies

- Prompt notification by the investigator to the sponsor of an SAE/AESI /pregnancy 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 12 Timeframes for submitting SAE, AESI and pregnancy reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*	electronic 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 in the non-serious adverse event eCRF screen and in the AF follow-up questionnaire.

8.4.6. Pregnancy

Female participants who become pregnant after 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 and the neonate and the information will be forwarded to the sponsor. See Table 12 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 8.4.4.2. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- 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, pIMDs, pregnancies

Table 13 Contact information for reporting SAEs, pIMDs, pregnancies

Study contact for questions regarding SAEs, pIMDs, pregnancies and SAEs linked to device deficiencies Contact GSK's local and/or medical contacts
Contacts for reporting SAEs, pIMDs, 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 with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back-up.

8.4.9. Medical device deficiencies

Medical devices are being provided for use in this study as the study intervention. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.6.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.6 of the protocol.

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Section 10.6.

8.4.9.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The medical device deficiency report form will be sent to the sponsor by email. If email is unavailable, then alternative method should be utilized.
- The sponsor will be the contact for the receipt of device deficiency reports.

8.4.9.4. Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the

legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.5. Pharmacokinetics

Pharmacokinetics is not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamics is not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity assessments

Immunogenicity is described in Section 8.2.

8.10. Health economics or medical resource utilization and health economics

Not applicable for this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypothesis

The primary objective, as outlined in Section 3, will be addressed using an estimation approach with no hypothesis testing.

9.2. Analysis sets

Table 14 Analysis sets

Analysis set	Description	Analysis evaluated
Screened Set	All participants who were screened for eligibility.	Study population
Enrolled Set	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). NOTE: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed to reach the target enrollment) are excluded from the Enrolled Set as they did not enter the study.	Study population
ES	All participants who received the study intervention. Analysis per group is based on the administered intervention.	Safety, Reactogenicity
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

The 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 primary and secondary endpoints. Supportive analyses and demography summaries will be described in the SAP.

9.3.1. Primary endpoint/estimand analysis

Primary estimand analysis will be performed on the PPS for immunogenicity.

For each timepoint with blood sample collection for humoral immune response and for each assay (RSV-A/B neutralization), 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. GMTs will be computed by taking the anti-logarithm of the arithmetic mean of the log_{10}-transformed titers.
- Distribution of neutralizing titers will be displayed using reverse cumulative curves.
- MGI, i.e., geometric mean of ratios of neutralizing titers of post-primary vaccination time point (Day 31) over pre-primary vaccination (Day 1), will be tabulated with 95% CI. CIs for MGI will be based on a back transformation of CI for the mean of the difference between log_{10}-transferred values, assuming that log-transformed values are normally distributed with unknown variance.
- SRR and 95% CI will be tabulated. 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.
- Any missing data will not be imputed.

9.3.2. Secondary endpoints/estimands analyses

The estimands analysis for safety will be performed on the ES. A descriptive analysis by group will present a summary of:

- Percentage of participants reporting each solicited administration site event with onset within 4 days after study intervention administration (i.e. the day of study intervention administration and 3 subsequent days).
- Percentage of participants reporting each solicited systematic event with onset within 4 days after study intervention administration (i.e. the day of study intervention administration and 3 subsequent days).
- Percentage of participants reporting unsolicited AEs within 30 days after study intervention administration (i.e. the day of study intervention administration and 29 subsequent days) by MedDRA Primary SOC, HLT and PT.
- Percentage of participants reporting SAEs 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 pIMDs after study intervention administration (Day 1) up to study end (6 months after study intervention administration) by MedDRA Primary SOC, HLT and PT.

9.4. Interim analyses

9.4.1. Sequence of analyses

The following analysis will be performed stepwise:

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

  Refer to Section 6.4 for details on the blinding strategy.

- **Month 6, EoS**: An EoS analysis will be performed when data for the secondary endpoints up to study end/Month 6 Contact are available for all participants. This analysis will be considered as final for those endpoints.

9.5. Pre-dose sample size determination

The target sample size for the study is to enrol approximately 750 participants: i.e., approximately 390 participants in Cohort 1 (≥ 60 years of age, OA) and approximately 360 participants in Cohort 2 (50-59 years of age, AIR). Participants will be randomized in a 2:1 ratio within each cohort. Assuming approximately 15% attrition rate, approximately 220 participants in OA-RSV group, 110 participants in OA-Placebo group, 200 participants in Adults-AIR-RSV group and 100 participants in Adults-AIR-Placebo group are expected to be evaluable for the primary objective.

9.5.1. Evaluation of humoral response at Day 31 (primary objective)

Mean Geometric Increase (MGI, Day 31 over Day 1) in RSV-A and RSV-B neutralizing titers (ED60)

Table 15 presents the power to show that the LL of the 95% CI for MGI at one month (Day 31) after RSV vaccination is above a defined threshold, for a range of thresholds and MGI, in the OA-RSV group and in the Adults-AIR-RSV group. MGI is defined as the geometric mean of the within-participant ratios of post-vaccination titers (at Day 31) over pre-vaccination titers.

In the pivotal efficacy study RSV OA=ADJ-006, an MGI of 10.2 (95% CI, 9.5-11.0) and 8.6 (95% CI, 8.0-9.2) was observed at one month after RSV vaccination for RSV A and RSV B neutralizing titers respectively. For 220 evaluable participants in RSV OA vaccination group, the study has at least 99% power to show that the LL of 95% CI for MGI is greater than or equal to 5-fold increase if the true MGI is at least 8-fold.

In the study RSV OA=ADJ-018, an MGI of 11.63 (95% CI, 10.52-12.86) and 9.05 (95% CI, 8.23-9.94) was observed in Adults-AIR-RSV group at one month after RSV vaccination for RSV A and RSV B neutralizing titers respectively. For 200 evaluable

participants in Adults-AIR-RSV vaccination group, the study has at least 99% power to show that the LL of 95% CI for MGI is greater than or equal to 5-fold increase if the true MGI is at least 8-fold.

Table 15 Power that the LL of the 95% CI for MGI in RSV-A/B neutralizing titers (ED60) at 1 month (Day 31) after RSV vaccination is above a defined threshold, for a range of thresholds and MGI.

Summary measure	Number of evaluable participants	Threshold	True MGI (Day 31 over Day 1)	Power (%)
MGI (fold increase of post vaccination Day 31 titers over pre-vaccination titer)	220 (OA-RSV group)	LL of 95% CI for MGI ≥4	8-fold	>99.9
			9-fold	>99.9
			10-fold	>99.9
		LL of 95% CI for MGI ≥5	8-fold	>99.9
			9-fold	>99.9
			10-fold	>99.9
		LL of 95% CI for MGI ≥6	8-fold	97.5
			9-fold	>99.9
			10-fold	>99.9
		LL of 95% CI for MGI ≥7	8-fold	44.5
			9-fold	92.9
			10-fold	99.8
	200 (Adults-AIR-RSV group)	LL of 95% CI for MGI ≥4	8-fold	>99.9
			9-fold	>99.9
			10-fold	>99.9
		LL of 95% CI for MGI ≥5	8-fold	>99.9
			9-fold	>99.9
			10-fold	>99.9
		LL of 95% CI for MGI ≥6	8-fold	99.0
			9-fold	>99.9
			10-fold	>99.9
		LL of 95% CI for MGI ≥7	8-fold	51.2
			9-fold	96.3
			10-fold	>99.9

Power computed using PASS 2019 software, Paired T-Tests for Superiority by a Margin, 1-sided alpha=2.5%; assuming a SD of 0.47 in OA RSV group and 0.41 in Adults-AIR-RSV group.

As reference, a SD of 0.47 and 0.45 for RSV-A and RSV-B antigen respectively was observed in the pivotal efficacy RSV OA=ADJ -006 study in terms of MGI in RSV A/B neutralizing titers at Day 31 compared to baseline. A MGI of 10.2 and 8.6 for RSV-A and RSV-B respectively was observed in the same study. A SD of 0.41 and 0.39 for RSV-A and RSV-B antigen respectively was observed in RSV OA=ADJ -018 study in terms of MGI in RSV A/B neutralizing titers at Day 31 compared to baseline. MGI of 11.63 and 9.05 for RSV-A and RSV-B respectively was observed in the same study in the Adults-AIR-RSV group.

Seroresponse rate (SRR) in RSV-A and RSV-B neutralizing titers (ED60) from Day 1 to Day 31

Table 16 presents the power to show that the Lower Limit (LL) of the 95% CI for SRR at one month (Day 31) after RSV vaccination is above a defined threshold, for a range of thresholds and SRR, in the OA-RSV group and in the Adults-AIR-RSV group. 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.

In RSV OA=ADJ-006, the pivotal efficacy study, a SRR of 81.6% (95% CI, 78.9-84.2) and 78.7% (95% CI, 75.8-81.4) was observed at one month after RSV vaccination for RSV A and RSV B neutralizing titers respectively. For 220 evaluable participants in RSV OA vaccination group, the study has at least 99% power to show that the LL of 95% CI for SRR is above 60% if the true SRR is at least 75%.

In RSV OA=ADJ-018, a SRR of 86.9% (95% CI, 82.8-90.3) and 81.6% (95% CI, 77.1-85.6) was observed in Adults-AIR-RSV group at one month after RSV vaccination for RSV A and RSV B neutralizing titers respectively. For 200 evaluable participants in Adults-AIR-RSV vaccination group, the study has at least 99% power to show that the LL of 95% CI for SRR is above 60% if the true SRR is at least 75%.

Table 16 Power that the LL of the 95% CI for SRR in RSV-A/B neutralizing titers (ED60) at 1 month (Day 31) after RSV vaccination is above a defined threshold, for a range of thresholds and SRR.

Summary measure	Number of evaluable participants	Threshold	True SRR (%)	Power (%)
SRR in RSV A / RSV-B neutralizing titers at Day 31 over pre-vaccination	220 (OA-RSV group)	LL of 95% CI for SRR ≥60%	75	99.7
			80	>99.9
			85	>99.9
		LL of 95% CI for SRR ≥65%	75	87.8
			80	99.9
			85	>99.9
		LL of 95% CI for SRR ≥67%	75	71.0
			80	99.1
			85	>99.9
		LL of 95% CI for SRR ≥70%	75	35.3
			80	92.2
			85	>99.9
		LL of 95% CI for SRR ≥72%	80	77.8
			85	99.7
		LL of 95% CI for SRR ≥75%	80	40.6
			85	96.0
	200 (Adults-AIR-RSV group)	LL of 95% CI for SRR ≥60%	75	99.6
			80	>99.9
			85	>99.9
		LL of 95% CI for SRR ≥65%	75	85.5
			80	99.8
			85	>99.9
		LL of 95% CI for SRR ≥67%	75	66.3
			80	98.4
			85	>99.9
		LL of 95% CI for SRR ≥70%	75	34.6
			80	90.6
			85	99.9
		LL of 95% CI for SRR ≥72%	80	73.6
			85	99.5
		LL of 95% CI for SRR ≥75%	80	33.5
			85	92.8

Power computed using PASS 2019 software, Non-Inferiority Test for one proportion, 1-sided alpha=2.5%;
A SRR of 81.6% and 78.7% for RSV A and RSV B neutralizing titers was observed in RSV OA=ADJ-006 (212494) study. A SRR of 86.9% and 81.6% for RSV A and RSV B neutralizing titers was observed in RSV OA=ADJ-018 (219238) study in the Adults-AIR-RSV group.

9.5.2. Evaluation of reactogenicity and safety

Table 17 presents the probabilities to observe at least one participant with AE by group, for a range of true AE incidence rates.

The sample size of 260 participants in the OA-RSV group and 240 participants in the Adults-AIR-RSV group have, respectively, 72.8% and 70% probabilities of observing at least one vaccinated participant with the AE if the true AE incidence rate is 0.5%. This probability increases to at least 92.7% and 91% respectively for true incidence rates ≥1%.

Table 17 Probability (%) to observe at least one AE for a range of incidence rates.

AE incidence rate (%)	Probability§ (%) to observe at least one vaccinated participant with AE in OA-RSV group (N=260)	Probability§ (%) to observe at least one participant with AE in OA-Placebo group (N=130)	Probability§ (%) to observe at least one vaccinated participant with AE in Adults-AIR-RSV group (N=240)	Probability§ (%) to observe at least one participant with AE in Adults-AIR-Placebo group (N=120)
0.3	54.2	32.3	51.4	30.3
0.4	64.7	40.6	61.8	38.2
0.5	72.8	47.9	70.0	45.2
0.6	79.1	54.3	76.4	51.4
0.7	83.9	59.9	81.5	57.0
0.8	87.6	64.8	85.5	61.9
0.9	90.5	69.1	88.6	66.2
1.0	92.7	72.9	91.0	70.1
2.0	99.5	92.8	99.2	91.1
3.0	100	98.1	99.9	97.4

§Binomial distribution, N=Number of enrolled participants.

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 must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

- Any/Substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial disclosure

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

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that physical informed consent was obtained before the participant was enrolled in the study and the date the physical consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

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 and sex of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Recruitment strategy

- No screening visit is planned for this study. The study is planned to be conducted at multiple sites in India and the recruitment will be competitive. 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 site. In case a site would fall behind in participant recruitment, a redistribution of the enrollment target per site may be made. This would allow the other participating sites to enroll additional participants to ensure full and timely enrollment of the overall targeted number of participants specified in this protocol.
- The proportion of participants recruited into each age group (Cohort 1) and disease category (Cohort 2) will be defined by enrollment rules. When the target proportion of participants is reached in a particular disease or age category, further enrollment in that category will be stopped. If needed the target proportion in a particular disease or age group may be adapted during the study (See Section 4.1.1)
- 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 must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant that their data will be used as described in the informed consent.

- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6. Committees structure

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

10.1.7. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the Quality plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/equivalent summary unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- When copies of source documents are shared externally for review by a central reader mechanism (e.g., endpoint adjudication committee; expert reader), documents are stored by the external body for 25 years.

10.1.9. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Definition of Terms.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Copies of documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g. endpoint adjudication committee; expert reader). The non-exhaustive list of documents shared to inform the central reader may include, discharge summaries, imaging reports, ECG reports etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the investigator sites prior to transfer. Details of the list of documents and the redaction procedure are provided in the site manual or equivalent. These documents will be used by the third party solely for the purpose indicated within this protocol.

10.1.10. Study and site start and closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as FSFV (first ICF signature date).

Study/Site Termination

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

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

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

- For study termination:
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor’s procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
  - Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication policy

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

10.2. Appendix 2: Clinical laboratory tests

RSV-A/B neutralization assay

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

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

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

10.3.1. Definition of AE

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

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. Pre-existing diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

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

- Results in death
- Is life threatening

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

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

- 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 is specifically questioned, and which are noted by the participant in their eDiary.
- The following administration site events will be solicited:
  - Pain at administration site
  - Erythema (redness) at administration site
  - Swelling at administration site
- The following systemic events will be solicited:
  - Fever
  - Headache
  - Myalgia (muscle pain)
  - Arthralgia (joint pain)
  - Fatigue (tiredness)

Note: Participants will be instructed to measure and record the axillary/oral temperature in the evening. If additional temperature measurements are taken at other times of the day, participants will be instructed to record the highest temperature in the 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 who has signed the informed consent. Unsolicited AEs include both serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible

to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

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

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 GSK/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 should be trained on how and when to complete the eDiary.
- Anyone who measures administration site or systemic events and who will record the event in the eDiary should be trained on using the eDiary. This training must be documented in the participant's source record.
- For each solicited and unsolicited AE the participant experiences, the participant will be asked if they received medical attention (defined as unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the participant's 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 caregiver(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 caregiver, if there are clear eDiary errors the investigator will complete his/her own assessment in the relevant sections of the eCRF.
- Return of the eDiary device is not applicable if the participant has "Bring Your Own" e-device.
- Any unreturned eDiary device will be sought from the participant 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 and 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 18 Intensity scales for solicited events in participants.

Event	Intensity grade	Parameter
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities
	2	Moderate: Painful when limb is moved and interferes with everyday activities
	3	Severe: Significant pain at rest. Prevents normal everyday activities
Erythema (redness) at administration site	See Table 19	Greatest surface diameter in mm
Swelling at administration site	See Table 19	Greatest surface diameter in mm
Temperature*	See Table 19	Temperature in °C/°F
Headache	0	None/Normal**
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue (tiredness)	0	None/Normal**
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia (muscle pain)	0	None/Normal**
	1	Mild: Myalgia present but does not interfere with activity
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia (joint pain)	0	None/Normal**
	1	Mild: Arthralgia present but does not interfere with activity
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

* Refer to the SoA (Section 1.3) for the definition of fever and the preferred location for temperature measurement.
**For participants already experiencing some of the solicited systemic events, 'Normal' corresponds to 'similar to baseline' and only discomfort above baseline is to be reported as ≥1.

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

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

Intensity grade	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/pIMD. 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 the study end 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, pIMD or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.7).

10.3.5.7. Reporting of SAEs, AESI 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

- E-mail/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 e-mail/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. Woman of Childbearing Potential (WOCBP)

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

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

3. Premenarchal: Tanner stage 1 (prepubertal)
4. 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.
5. Postmenopausal female

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

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

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 20).

Table 20 Highly effective contraceptive methods

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

Note: 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: Grading scales for chronic diseases in scope of the AIR population

10.5.1. 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

10.5.2. 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.

10.5.3. 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.

10.6. Appendix 6: Medical device AEs, ADEs, SAEs, sADEs, USADEs and device deficiencies: Definitions and procedures for recording, evaluating, follow-up, and reporting in medical device studies

- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.6.1. Definition of medical device AE and ADE

Medical device AE and ADE definition
• A medical device AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2. Definition of medical device SAE, SADE and USADE

A Medical Device SAE is any serious AEs that:
• Led to death
• Led to serious deterioration in the health of the participant, that either resulted in: – A life-threatening illness or injury. 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. – A permanent impairment of a body structure or a body function. – Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. – Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. – Chronic disease (MDR 2017/745).
• Led to fetal distress, fetal death or a congenital abnormality or birth defect
SADE definition
• A SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious ADE that by its nature, incidence, severity or outcome has not been identified in the current version of the IB (see Section 2.3).

10.6.3. Definition of device deficiency

Device deficiency definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.6.4. Recording and follow-up of medical device AE and/or SAE and device deficiencies

10.6.4.1. Medical device AE, SAE, and device deficiency recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK AE/SAE/device deficiency 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.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.
- If the site during the course of the study becomes aware of any serious, nonserious incident (including device deficiencies and malfunctions) related to any GSK non-IMP product they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.

10.6.4.2. Assessment of intensity

Refer to Section 10.3.5.2.

10.6.4.3. Assessment of causality

Refer to Section 10.3.5.3.

10.6.4.4. Follow-up of medical device AE/SAE and device deficiency

- 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/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.6.5. Reporting of medical device SAEs

Medical Device 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 table) 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 table) or to the GSK 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 device 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.

Medical Device SAE Reporting to GSK via Paper Data Collection Tool

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in Section 8.4.7.

10.6.6. Reporting of SADEs

SADE Reporting to GSK

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in Section 8.4.7.

10.6.7. Reporting of medical device deficiencies for associated person

• **Reporting to GSK**
If an Associated Person (i.e. e.g., spouse, caregiver, site staff) experiences a device deficiency, the medical device deficiency information, and any associated AE/SAE information will be reported to GSK. The associated person will be provided with the authorization to contact physician letter. If follow-up information is required, authorization to contact physician (or other licensed medical practitioner) must be signed to obtain consent. • Medical device deficiencies that are not related to an AE or SAE should be reported via email to gsk-rd.complaints@gsk.com, using the medical device deficiency report form. • If the medical device deficiency is related to a nonserious AE and not linked to an SAE, please send the medical device deficiency report form with details of the associated AE via email to gsk-rd.complaints@gsk.com only. • If the device incident is linked to an SAE, please email the medical device deficiency report form, within 24 hours. Refer to Section 8.4.7 for reporting. • GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

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