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	219815 (RSV OA=ADJ-021)
EU CT Number	2023-509455-13-00
Approval Date	15 Feb 2024
Title	A Phase 3, randomized, controlled, partially blind, immuno-bridging study to evaluate immunogenicity, reactogenicity, safety and the occurrence of RSV-associated respiratory tract illness after administration of a single dose of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and older.
Brief Title	A study on the immune response, safety and the occurrence of RSV-associated respiratory tract illness after administration of RSV OA vaccine in adults 60 years and older.
Sponsor	GlaxoSmithKline Biologicals SA Rue De L'Institut 89 B-1330 Rixensart Belgium
Sponsor signatory	Joan Hu Therapeutic Area Leader Vaccine Clinical Development

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	219815 (RSV OA=ADJ-021)
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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	15 Feb 2024
Original Protocol	06 March 2023

Amendment 1 (15 Feb 2024)

Overall rationale for the current Amendment:

The protocol is amended based on feedback received from Notice of Drug Clinical Trial Approval issued by Center for Drug Evaluation (CDE), National Medical Products Administration (NMPA):

- It is recommended to conduct efficacy surveillance (as secondary endpoints) in the study.
- It is recommended to conduct safety evaluation as per Chinese guidelines (Grading Criteria for Adverse Events in Clinical Trials of Preventive Vaccines) and record events of atrial fibrillation (AF) as Adverse Events of Special Interest (AESIs).

In addition, the total sample size of the study population is increased from 1500 to 2600 based on a sensitivity analysis of study power.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
List of Abrreviations and Definitions	Definitions for Serious adverse reaction (SAR) and Suspected unexpected serious adverse reaction (SUSAR) added.	Following the feedback received from EU-CTR, the information is implemented.
Section 1.2: Schema	The study design has been updated to include ARI surveillance in study participants in China.	Based on the feedback received from the CDE, changes were made in the study design to improve the ARI surveillance.
Section 1.3: Schedule of activities (SoA)	The study procedures specific to occurrence of ARI have been added. A table for schedule of activities for ARI surveillance has been added.	Based on the feedback received from the CDE ARI occurrence in the study particular to study participants in China have been added.
Section 2: Introduction	Wording related approval of RSV OA vaccine has been added.	Following RSV OA vaccine approval, specific texts in the protocol has been updated to reflect the same.

Section # and title	Description of change	Brief rationale
Section 3: Objectives, Endpoints and Estimands	A secondary objective specific to occurrence of ARI in study participants in China and its related endpoints have been added.	Based on the feedback received from the CDE ARI occurence in the study particular to study participants in China have been added.
Section 4.2.1 : Case defintions	Case definitions for ARI surveillance have been added	Following feedback received from CDE, ARI surveillance has been included in the study (For study participants in China). This section was updated to include case definitions for ARI surveillance.
Section 5.1 : Inclusion criteria Section 5.2 :Exclusion criteria	Text modified to include additional information on informed consent and study intervention administered.	Following the feedback received from EU-CTR, the information is implemented.
Section 6.1.1. : Medical Devices	A section on Medical Devices has been added to describe all the instructions and procedures involved.	To ensure a consistent data display layout with other studies in the RSV OA project.
Section 8.2.2 : ARI surveillance and methods	An entire section on ARI surveillance has been added to describe all the methods and procedures involved.	Following feedback received from CDE, ARI surveillance has been included in the study. This section was updated to describe all methods and procedures involved in ARI surveillace.
Section 8.2.3. Biological Samples	Total blood volume increased to 45 mL in the RSV Overseas participants.	Based on the feedback received from Customs in China on the shipping requirements, blood volume for sample collection increased.
Section 8.3 :Safety Assessments	Investigator safety reports to be prepared for suspected unexpected serious adverse reactions (SUSARs)	Following the feedback received from the EU-CTR, the information is implemented.
Section 8.4.8 : Medical device deficiencies	A section on medical device deficiencies has been added.	Since placebo (provided in a pre-filled syringe) is considered as a combination product, these sections are applicable and hence included in the protocol.

Section # and title	Description of change	Brief rationale
Section 9 Statistical considerations	RSV OA group [China] / RSV OA group [Overseas] changed to RSV OA group [Overseas]/ RSV OA group [China]. RSV OA group [China] - RSV OA group [Overseas] changed to RSV OA group [Overseas] - RSV OA group [China].	To ensure a consistent data display layout with others studies in the RSV OA project.
Section 9.5: Sample size determination	Sample size is updated to 2600.	Sample size is updated to have a power ≥90% over several different scenarios based on the sensitivity anlaysis of the power (Table 21). This also ensures more study partipants in China data collected.
Section 10.4 : Appendix 4 : Medical device AEs, ADEs, SAEs, sADEs, USADEs and device deficiencies: Definitions and procedures for recording, evaluating, follow-up, and reporting in medical device studies	A section on medical device related events and definitions/procedures for recording/evaluating/follow-up and reporting of these events has been added.	Since placebo (provided in a pre-filled syringe) is considered as a combination product, these sections are applicable and hence included in the protocol.
Throughout the protocol where applicable	Atrial fibrillation has been included as an AESI.	Based on the feedback received from the CDE, AF has been included as an AESI.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AAION	Arteritic anterior ischemic optic neuropathy
ADE	Adverse device effect
AE	Adverse event
AESI	Adverse event of special interest
AF	Atrial fibrillation
ANCA	Anti-neutrophil cytoplasmic antibody
APTM	Acute partial transverse myelitis
ARI	Acute respiratory illness
CD	Community dwelling
CI	Confidence interval
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
CIS	Clinically isolated syndrome
COPD	Chronic obstructive pulmonary disease
CRF/eCRF	Case report form/electronic case report form
CSR	Clinical study report
CTA	Clinical trials application
EBA	Epidermolysis bullosa acquisita
ECG	Electrocardiogram
EMA	European Medicines Agency
EoS	End-of-study
FAS	Full analysis set
FDA	Food and Drug Administration, United States of America
FSFV	First subject first visit

Abbreviation	Definition
GCP	Good clinical practice
GMT	Geometric mean titer
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent ethics committee
ILI	Influenza-like illness
IM	Intramuscular
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional review board
IQR	Inter quartile range
IVRS/IWRS	Interactive voice/web response system
LRTD	Lower respiratory tract disease
LSLV	Last subject last visit
MGI	Mean geometric increase
MI	Myocardial infarction
MS	Multiple Sclerosis
NI	Non-inferiority
NMPA	National Medical Products Administration
OA	Older adult

Abbreviation	Definition
OR	Odds ratio
PCA	Primary completion analysis
PCD	Primary completion date
PI	Personal information
pIMD	Potential immune-mediated disease
PK	Pharmacokinetic
PP	Per protocol
PY	Person year
QTL	Quality tolerance limit
RR	Relative risk
RSV	Respiratory syncytial virus
RTI	Respiratory tract infections
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SmPC	Summary of Product Characteristics
SoA	Schedule of activities
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse reaction
TOC	Table of contents
USADE	Unanticipated serious adverse device effect
VE	Vaccine efficacy
YOA	Years of age

Definition of Terms

Term	Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Adverse event of special interest	An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. 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.
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

Term	Definition
	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.
Combination product	Combination product comprises any combination of: • drug • device • biological product. Each drug, device and biological product included in a combination product is a constituent part.
Community Dwelling Participants:	Participants who live in the community, either independently or with relatives, without the availability of permanent (24 hours a day, 7 days a week) professional on-site assistance with activities of daily living, nursing or medical care.
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.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.

Term	Definition
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Former smoker	A person who stopped smoking for at least 6 months at the time of study start.
Frailty	Frailty is a term used in geriatric medicine to identify older adults who are at increased risk of poor clinical outcomes, such as incident disability, cognitive decline, falls, hospitalization, institutionalization, or increased mortality. Frailty represents a reduction in resistance to stressors leading to increased clinical vulnerability and adverse health outcomes.
Home Healthcare Services	Deployment of mobile health care professional(s) (nurses or phlebotomists) to perform study activities remotely.
Intercurrent medical condition	A condition that has the capability of altering the immune response to the study vaccine or is confirmed to have an alteration of the participant's initial immune status.
Intervention number	A number identifying an intervention to a participant, according to intervention allocation.
Investigational product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.

Term	Definition
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.
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	This is the date that the final participant in the study was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In other words, Primary Completion Achieved is the date of the last contact with the participant when data has been collected/intervention done for the purpose of data collection for analysis of all primary endpoints. In the case of clinical studies with more than 1 primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. This date may occur prior to the study end or be the same date as the study end milestone.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
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.

Term	Definition
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).
Standard of Care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries.
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: “Study intervention” and “study treatment” are used interchangeably unless otherwise specified.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Suspected unexpected serious adverse reaction	A suspected unexpected serious adverse reaction is a serious adverse reaction whose nature, severity or outcome is not consistent with the reference safety information.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, randomized, controlled, partially blind, immuno-bridging study to evaluate immunogenicity, reactogenicity, safety and the occurrence of RSV-associated respiratory tract illness after administration of a single dose of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and older.

Brief Title: A study on the immune response, safety and the occurrence of RSV-associated respiratory tract illness after administration of RSV OA vaccine in adults 60 years and older.

Rationale: Refer to Section 2.1.

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

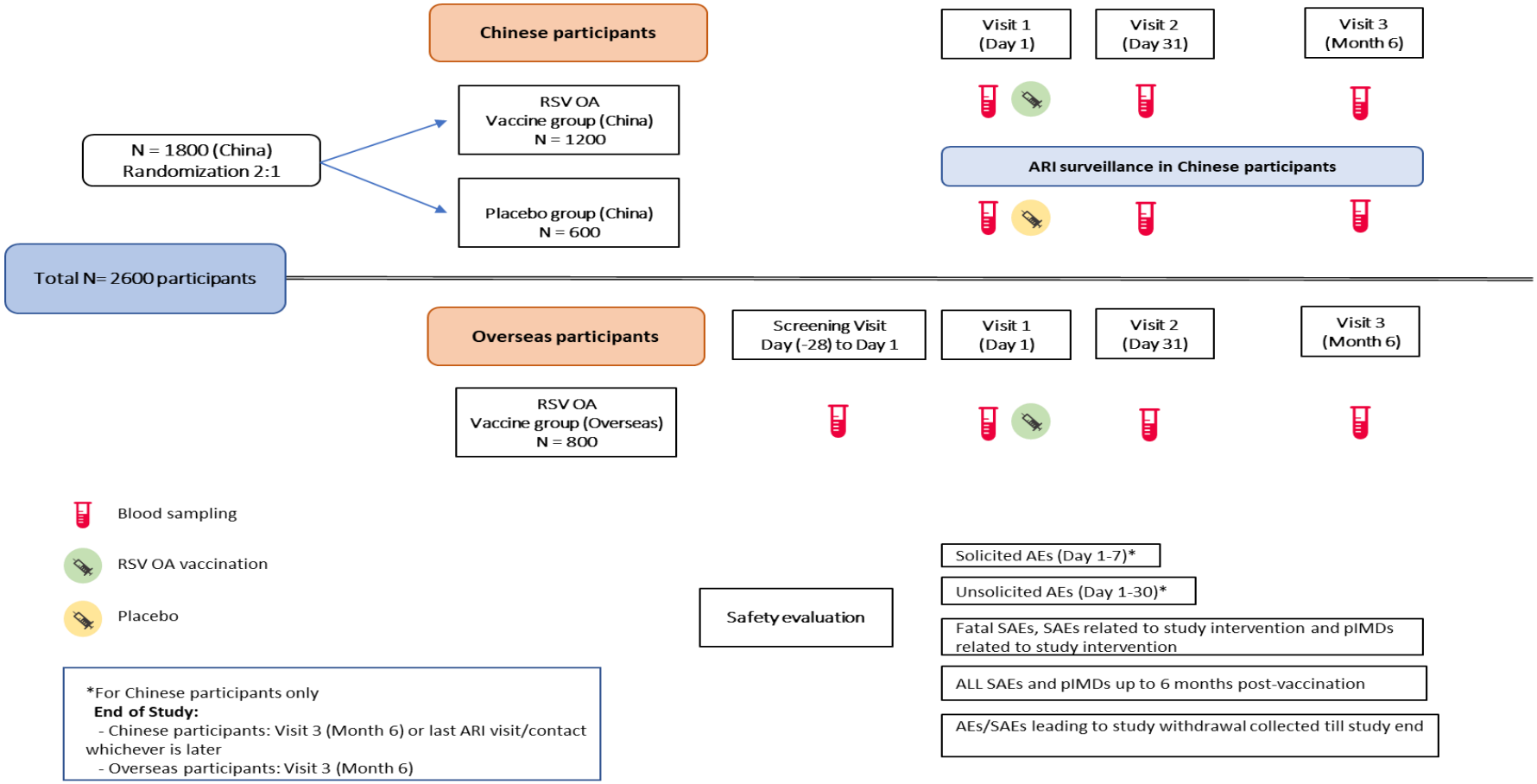
Overall Design: Refer to Section 4.1.

Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Schema

Figure 1 Study design overview



1.3. Schedule of activities (SoA)

Table 1 Schedule of Activities (Study Participants in China)

Type of contact[1]	Visit 1	Visit 2	Visit 3
Timepoint	**Day 1**	**Day 31**	**Month 6**
Informed consent	●		
Inclusion and exclusion criteria	●		
Screening Conclusion	●		
Check with participant if he/she will appoint a caregiver and distribute information letter(s) to caregiver, when applicable	○		
Baseline and demography assessments			
Demography	●		
Measure/record height and weight	●		
Medical and vaccination history[2]	●		
Physical examination	●		
Vital signs	●		
Record oxygen saturation	●		
Lung auscultation	○	○[3]	○[3]
Record smoking status and smoking exposure history (including electronic smoking devices)	●		
Clinical specimens for laboratory assays			
Serology (Blood sampling for neutralization assay [~10 mL each])	●[4]	●	●
Study intervention administration			
Check contraindications, warnings and precautions to vaccination	○		
Check criteria for temporary delay for enrolment and /or study intervention administration	○		
Study group and intervention number allocation	○		
Body temperature before study intervention administration	●		
Administration of study intervention (including 30-minute post-vaccination observation)	●		
Recording of administered study intervention number	●		
ARI surveillance			
Instruct/remind participants of ARI surveillance	○		
Nasal self-swab training with the study participant	○		
Distribution of material for nasal swab collection at home (including instructions)	○	○[3]	○[3]
Safety assessments			
Distribute and instruct participants on the use of paper diary cards for solicited and unsolicited AEs[5]	○		
Return of paper diary cards		○	
Recording of solicited events (Days 1 - 7 post-dosing)	●		

Type of contact[1]	Visit 1	Visit 2	Visit 3
Timepoint	**Day 1**	**Day 31**	**Month 6**
Recording of unsolicited AEs (Days 1- 30 post-dosing)[6]	●	●	
Record any concomitant medications/vaccinations	●	●	●
Record any intercurrent medical conditions	●	●	●
Recording of all SAEs and pIMDs[6]	●	●	●
Recording of AEs/SAEs leading to withdrawal from the study	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[7]	●	●	●
Frailty status			
Assess frailty status with Gait Speed test	●		
Study Conclusion			●[8]

AE: adverse event; AESI: adverse event of special interest; AF: atrial fibrillation; ARI: acute respiratory illness; pIMDs: potential immune-mediated diseases; SAE: serious adverse event.

● is used to indicate a study procedure that requires documentation in the individual eCRF or on web-portal.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF or on web-portal.

1. Study visits should preferably be done on site. For the study contacts, multiple formats can be proposed by the study site. These contacts 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, fax may be used as a screening to check if the participant has anything to report. If the participant answers yes for at least one of the items of interest, a phone call must be done to get the details on the event(s). Receipt of the message must be confirmed by the participant or caregiver, as applicable.
2. Any vaccination administered up to 1 year before administration of the study intervention should be recorded in the eCRF.
3. If deemed necessary by the investigator
4. Blood sampling to be performed before vaccination.
5. A paper diary card will be distributed at Visit 1 (day of vaccination) and will be used for recording solicited AEs on the day of vaccination and for 6 subsequent days (Days 1-7). Another paper diary card will be used for recording unsolicited AEs and concomitant medications/products on the day of vaccination and for 29 subsequent days (Days 1-30) by Chinese participants.
6. Atrial fibrillation (AF) will be considered as adverse event of special interest (AESI) in this study and will be additionally reported in the AF follow-up questionnaire (electronic or paper) in eCRF. The collection of AF will be performed following the AE/SAE reporting periods. The reporting of non-serious AF (Study participants in China only) will be performed according to the unsolicited AE reporting period. The reporting of AF meeting the SAE definition (serious AF) will be performed according to the SAE reporting period.
7. SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to vaccination) up to study end.
8. Study conclusion for participants in China (Visit 3 [Month 6] or last ARI visit/contact whichever is later).

Table 2 Schedule of Activities for ARI surveillance (study participants in China only)

Type of contact	Bi-weekly and monthly contact[1]	Participant call	ARI visit[2]	ARI FU contact[3]	ARI closure contact[3]	Addit. FU contact[4]
ARI surveillance						
Instruct/remind participants of ARI surveillance procedures	○					
Record contact dates	●	●				
Schedule the ARI visit	○[5]	○				
Distribution of new material for nasal self-swab collection (including instructions)			○			
Record date of nasal self-swab collection			●			
Nasal and throat swab sampling by the site staff			●			
Record ARI information	●[5]	●	●	●	●	●
Safety assessments						
Physical examination/Vital signs			●			
Lung auscultation			○			
Record oxygen saturation			●			
Record medications (prescribed/self-treatment) taken to treat ARI or an ARI-related complication			●	●	●	●
Record intercurrent medical conditions	●		●	●	●	●
Recording of all SAEs and AESIs up to 6 months post-vaccination[6]	●		●	●	●	●
Recording of fatal SAEs, SAEs related to study intervention and pIMDs related to study intervention[6]	●		●	●	●	●
Recording of AEs/SAEs leading to withdrawal from the study	●		●	●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[7]	●		●	●	●	●

AE: adverse event; ARI: acute respiratory illness; FU: follow-up; pIMDs: potential immune-mediated diseases; SAE: serious adverse event.

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

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

1. These surveillance contacts will be performed every 2 weeks during the RSV season and every month during the inter-season periods only for study participants in China. Multiple formats can be proposed by the study-site to organize the scheduled contacts. This 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 done to get the details on the event(s). Receipt of the message must be confirmed by the participant or caregiver, as applicable.
2. The ARI visit should preferably be done on-site. If deemed necessary, the visit can be done at home.
3. Each ARI episode will be followed up through an ARI follow-up contact approximately 14 days after ARI onset and an ARI closure contact approximately 28 days after ARI onset, in case the ARI event was still ongoing at the first ARI follow-up contact. These contacts can be done via phone calls.

4. For participants with ARI/complications(s) lasting beyond the ARI closure contact, additional follow-up contacts will be done approximately every 2 weeks (post ARI closure contact) until the resolution of the ARI/complication(s) or study end. These additional follow-up contacts can be done via phone calls.
5. If an ARI is reported during a scheduled surveillance contact, then all the procedures expected at the "participant call" should be performed.
6. 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 collection of AF will be performed following the AE/SAE reporting periods. The reporting of non-serious AF (Study participants in China only) will be performed according to the unsolicited AE reporting period. The reporting of AF meeting the SAE definition (serious AF) will be performed according to the SAE reporting period.
7. SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to vaccination) up to study end.

Table 3 Schedule of Activities (Study participants in Overseas)

Type of contact[1]	Screening Visit	Visit 1	Visit 2	Visit 3
Timepoint	**Day (-28) to Day 1**	**Day 1**	**Day 31**	**Month 6**
Informed consent	●			
Inclusion and exclusion criteria	●	●		
Blood sample for HIV, HBV, HCV and Syphilis (~15 mL)	●			
Screening Conclusion		●		
Check with participant if he/she will appoint a caregiver and distribute information letter(s) to caregiver, when applicable		○		
Baseline and demography assessments				
Demography		●		
Measure/record height and weight		●		
Medical and vaccination history[2]		●		
Physical examination		●		
Vital signs		●		
Record smoking status and smoking exposure history (including electronic smoking devices)		●		
Clinical specimens for laboratory assays				
Serology (Blood sampling for neutralization assay [~10 mL each])		●[3]	●	●
Study intervention administration				
Check contraindications, warnings and precautions to vaccination		○		
Check criteria for temporary delay for enrolment and /or study intervention administration		○		
Study group and intervention number allocation		○		
Body temperature before study intervention administration		●		
Administration of study intervention (including 30-minute post-vaccination observation)		●		
Recording of administered study intervention number		●		
Safety assessments				
Record any concomitant medications/vaccinations		●	●	●
Record any intercurrent medical conditions		●	●	●
Recording of all SAEs and pIMDs[4]		●	●	●
Recording of AEs/SAEs leading to withdrawal from the study		●	●	●
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[5]	●	●	●	●
Frailty status				
Assess frailty status with Gait Speed test		●		
Study Conclusion				●[6]

AE: adverse event; AESI: adverse event of special interest; AF: atrial fibrillation; ARI: acute respiratory illness; pIMDs: potential immune-mediated diseases; SAE: serious adverse event.

● is used to indicate a study procedure that requires documentation in the individual eCRF or on web-portal.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF or on web-portal.

1. Study visits should preferably be done on site. For the study contacts, multiple formats can be proposed by the study site. These contacts 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, fax may be used as a screening to check if the participant has anything to report. If the participant answers yes for at least one of the items of interest, a phone call must be done to get the details on the event(s). Receipt of the message must be confirmed by the participant or caregiver, as applicable.
2. Any vaccination administered up to 1 year before administration of the study intervention should be recorded in the eCRF.
3. Blood sampling to be performed before vaccination.
4. Atrial fibrillation (AF) will be considered as adverse event of special interest (AESI) in this study and will be additionally reported in the AF follow-up questionnaire (electronic or paper) in eCRF. Only serious AF will be collected for study participants in Overseas. The reporting of AF meeting the SAE definition (serious AF) will be performed according to the SAE reporting period.
5. SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained up to study end.
6. Study conclusion for Overseas participants: Visit 3 (Month 6)

Table 4 Intervals between study visits

Interval	Planned visit interval	Allowed interval range
Screening Visit → Visit 1 (RSV OA Vaccine group [Overseas] only)	28 days	Up to 28 days before Visit 1
Visit 1 → Visit 2	30 days	30-42 days
Visit 1 → Visit 3	180 days	180-210 days

Table 5 Intervals between study visits/contacts for ARI surveillance (Study participants in China only)

Interval	Length of interval	Allowed interval
Between each surveillance contact (planned or spontaneous report) during the RSV season[1]	14 days[2]	±3 days[3]
Between each surveillance contact (planned or spontaneous report) during the inter-season periods[1]	30 days[2]	±5 days[3]
ARI visit	At 2 days from ARI onset[4]	2-6 days from ARI onset[4]
ARI follow-up contact	At 14 days from ARI onset[4]	14-18 days from ARI onset[4]
ARI closure contact	At 28 days from ARI onset[4]	28-35 days from ARI onset[4, 5]
Between each additional follow-up contact[6]	At 14 days from last FU contact	±3 days

1. Refer to Section 8.2.2 for details on the surveillance period and methods.
2. Once an ARI event has ended, the scheduled surveillance contacts should resume for that participant. The first surveillance contact should be planned within maximum 14 days after the last ARI follow-up contact during the RSV season and within maximum 30 days after the last ARI follow-up contact during the inter-season periods.
3. For logistical reasons, sites may pre-define the schedule for performing surveillance contacts. In case the site staff reaches the participant outside the schedule, the site may resume to the predefined schedule for the next contact.
4. ARI onset (Day 1) is defined as the first day when the study participant presents at least 2 concomitant ARI symptoms/signs meeting the ARI case definition (see Table 8 in Section 4.2.1).
5. If the ARI event was still ongoing at the first ARI follow-up contact (Day 15), an ARI closure contact should be done approximately 28 days after ARI onset. These contacts can be done via phone calls.
6. Only applicable for participants with ARI/complications(s) lasting beyond the ARI closure contact.

2. INTRODUCTION

2.1. Study rationale

GlaxoSmithKline Biologicals SA (GSK) has developed a new respiratory syncytial virus (RSV) PreFusion protein 3 OA (RSVPreF3 OA) vaccine for the prevention of RSV-associated (subtypes A and B) lower respiratory tract disease (LRTD) disease in adults ≥ 60 years of age (YOA). The vaccine was first approved for use in adults ≥ 60 YOA in the United States (US) on 03 May 2023, under the trade name *Arexvy*. To date, the vaccine is also approved in the European Union, United Kingdom, Canada, Japan, Hongkong and Australia. The assessment in other countries is ongoing.

The purpose of the current study is to evaluate the immunogenicity of the investigational RSVPreF3 OA vaccine in older adults ≥60 YOA in China, in comparison with the immune response generated in overseas population since vaccine efficacy against LRTD has been demonstrated following a single dose of the RSVPreF3 OA vaccine in the global efficacy study RSV OA=ADJ-006. In addition, the safety, reactogenicity and occurrence of ARI (in study participants in China only) after administration of the vaccine will also be assessed as secondary objectives.

2.2. Background

RSV is a ribonucleic acid virus of the Pneumoviridae family that causes acute respiratory illness (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 winter and spring seasons in China, the tropical climate provinces have relative longer RSV season [Luo, 2020]. RSV causes upper and lower respiratory tract infections (RTI) in people of all ages with the risk of serious infection increasing in young children, older adults and adults at high risk due to presence of comorbidities. The RSV infections aged ≥60 YOA, as the second largest population of the total annual RSV infections, usually developed worse outcomes than children [Luo, 2022].

Despite most initial and severe infections occurring during early childhood, RSV is increasingly recognized as a common cause of respiratory illness in adults. Although less than 1% of adults affected are estimated to need admission to hospital [Hall, 2001], RSV is the third most commonly identified viral cause of admission [Falsey, 2005; Thompson, 2003; 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 (95% Confidence Interval (CI), 0.3-6.9) million in 2015 with an incidence of 6.7 cases/1000 person-years (PY, 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. The global number of hospital admissions for RSV-ARI in older adults was estimated at 336 000 (uncertainty range [UR], 186 000–614 000) hospitalizations [Shi, 2019]. Similarly, a systematic analysis to assess the global, regional and national burden of lower respiratory infections in 195 countries, found the incidence of RSV-LRTI in older adults ≥ 70 YOA, to be 6.3 cases/1000 persons [Troeger, 2018]. In another study using data collected as part of a

randomized influenza efficacy study, which was carried out in 14 countries from North America, Europe and East Asia, RSV was detected in 7.4% of older adults ≥ 65 YOA with influenza-like illness (ILI), with values ranging between 0% and 17.1% across countries [Falsey, 2014]. In a 3-year prospective study conducted in the US, RSV was detected in 6.1% of 508 adults ≥ 50 YOA, who were hospitalized due to ARI [Widmer, 2012]. A recently conducted systematic literature review and meta-analysis on RSV burden of disease in adults ≥ 60 YOA in high-income countries, found a pooled estimate of RSV-ARI to be 16.2 (95% CI: 8.4-30.8) cases/1000 persons. The RSV associated hospitalization rate was 0.15% (95% CI: 0.09%-0.22%) and the in-hospital case fatality rate (hCFR) was 7.13% (95% CI: 5.40%-9.36%) [Savic, 2023].

Estimates of incidence and prevalence are mostly available from the US and several countries from Europe. In China, there is no specific RSV surveillance system in place. Since RSV is a well-recognized cause of bronchiolitis in young children, the data on RSV mainly concerns the pediatric population with limited information on the burden of disease in older adults. The population studied is usually a mixture of infants/children and adults with an overrepresentation of children, leading to an underestimation of the full burden of RSV infection in adults ≥ 60 YOA.

Most of the information on the RSV burden of disease (incidence, prevalence) is found through studies done on respiratory viruses overall detected in patients presenting with acute upper or LRTD, ILI or pneumonia and for which different criteria are used for enrolment.

RSV incidence was reported in 3 studies from Hong Kong. The first study reported an RSV-associated incidence proportion in ILI cases of 9.3% among residential care homes during 2006-2007 [Hui, 2008]. The second study assessed RSV-associated ILI incidence in 3 time periods: before, during and after 2009 H1N1 influenza pandemic [Yang, 2015]. In older adults ≥65 YOA, RSV incidence in the post-pandemic period 2010-2013 (0.64/1000 PYs) was higher compared to the pre-pandemic period 2004-2009 (0.41/1000 PYs). Another study reported on incidence rates of respiratory viruses in patients ≥ 65 YOA hospitalized with respiratory infection over a 15-year-period. The average RSV-associated hospitalization rate was 0.57 cases/1000 persons [Chan, 2015].

RSV prevalence is reported in several studies conducted in different parts of China and Hong Kong, mainly performed in the hospital setting. Prevalence of RSV-associated ARI was between 0.3% and 7.4% among people of all ages (GSK, unpublished systematic literature review). Focusing only on reports in older adults aged over 60 years reported with acute upper or lower RTI, prevalence was in the range of 2.0% to 7.4% [Li, 2018; Lu, 2013; Wang, 2018; Ye, 2017]. Prevalence of RSV-associated severe ARI in older adults aged over 60 years was 4.7% [Xu, 2018]. Four studies reporting RSV prevalence among older adults ≥60 YOA presenting with ILI symptoms (i.e. fever was required at enrolment) estimated the prevalence between 2.0% and 2.3% [Ren, 2020, Yang, 2015, Fu, 2015, Ju, 2014].

In patients ≥ 18 YOA hospitalized with RSV infection, lower respiratory complications were reported in 62.7% to 71.9%, cardiovascular complications in 14.3% to 51%. [Lee, 2013; Zhang, 2020a]. Health care use during hospitalization included intensive care

admission (ICU) in 2.1% to 22.1% of the patients admitted with RSV infection and invasive ventilation in 7.9% to 23.5%. The median length of stay ranged from 7 (IQR: 5-14) to 15 (IQR: 11-26) days [Chen, 2021; Lee, 2013; Zhang, 2020a; Zhang, 2020b; Luo, 2022]. In hospitalized adults with RSV or Influenza A infection, cardiovascular complications in RSV cases were significantly higher than in those hospitalized with influenza A infection (Odd ratio [OR]=2.7, 95% CI: 1.2-6.2) [Zhang, 2020]. Focusing only on report in older adults >60 YOA reported ICU admission in 15.1% and invasive ventilation in 7.9% and the in-hospital death in 7.8% [Luo, 2022]. A study reported that RSV infection significantly increased the risk of death in hospitalized patients aged ≥60 years with RTI in two hospitals in China (adjusted OR= 5.38, 95%CI: 1.65-17.51) [Zeng, 2022, Jiang, 2023].

Currently, 2 vaccines have been licensed outside of China for prevention of RSV infections in adults ≥ 60 YOA; *Arexvy* (manufactured by GSK) and *Abrysvo* (manufactured by Pfizer Inc).

However, there are no treatment or preventive vaccination available in China against the RSV infection other than the symptomatic treatment which includes oxygen and corticosteroid therapy. In view of the burden of the disease in this age group, a vaccine is highly needed to protect the vulnerable older adult population from the RSV disease and related complications, hospitalizations and risk of death.

In a large global Phase 3 vaccine clinical trial in adults aged 60 years and above, the vaccine demonstrated overall vaccine efficacy (VE) of 82.6% (96.95% CI, 57.9%-94.1%) against RSV-LRTD. The vaccine induced immune response and was well tolerated with a favorable safety profile.

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 and/or package insert.

Table 6 Risk Assessment

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
RSVPreF3 OA investigational vaccine		
pIMDs	pIMDs are considered a theoretical risk, as for all vaccines containing an adjuvant system.	Refer to Section 8.4.4 for details.
Hypersensitivity reactions (including anaphylaxis)	Previous exposure to components of the vaccine might have induced an immune response that results in an exaggerated or inappropriate reaction.	All participants will remain under observation at the clinical center for at least 30 minutes after study intervention administration or longer if deemed necessary by site personnel. Appropriate medical care must be readily available during this period. Participants with a history of hypersensitivity or severe allergic reaction to any component of the vaccine are excluded from study enrollment.
Syncope (fainting)	Syncope (fainting) can occur following or even before study intervention administration as a psychogenic response to the needle insertion.	Participants who mention experiencing previous episodes of fainting or dizziness before, during or after vaccination, will be asked to lie down during the intervention and remain under observation at the clinical center for at least 30 minutes after study intervention administration or longer if deemed necessary by site personnel. Appropriate medical care must be readily available during this period.
Study procedures		
Local reactions at the injection site	Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, erythema/redness, and swelling.	Physician can implement the measures that they consider necessary. Solicited local AE will be collected and reviewed up to Day 7 following vaccination.
Local reactions at site of blood draw	Pain, redness, irritation, and bruising may occur at the site where blood is drawn.	Physician can implement the measures that they consider necessary.
Syncope (fainting)	Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle insertion.	Participants who mention experiencing previous episodes of fainting or dizziness before, during or after a blood draw, will be asked to lie down during the intervention and remain under observation at the clinical center for at least 30 minutes after blood draw or longer if deemed necessary by site personnel. Appropriate medical care must be readily available during this period.

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

For details of study procedures, dose and study design justification, refer to Section 1.3 and Section 4, respectively.

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 (RSV OA=ADJ-006) in adults aged 60 years and above, the primary objective was met with a high VE during the first RSV season and no unexpected safety concerns were observed (refer to IB).

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

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

2.3.3. Overall benefit-risk conclusion

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

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 7 Objectives and Endpoints

Objectives	Endpoints and estimands
Co-primary Immunogenicity	
To demonstrate the non-inferiority (NI) of humoral immune response in Chinese older adults (OA) enrolled in the RSV OA group (China) compared to OA enrolled in the RSV OA group (Overseas), for the RSV-A strain after the RSVPreF3 OA investigational vaccine administration.	• RSV-A neutralization titres expressed as group GMT ratio (RSV OA group [Overseas] / RSV OA group [China]), 1 month after the RSVPreF3 OA investigational vaccine administration*. • RSV-A neutralization titres expressed as group seroresponse rate (SRR) difference (RSV OA group [Overseas] - RSV OA group [China]), 1 month after the RSVPreF3 OA investigational vaccine administration*.
To demonstrate the NI of humoral immune response in Chinese OA enrolled in the RSV OA group (China), compared to OA enrolled in the RSV OA group (Overseas), for the RSV-B strain after the RSVPreF3 OA investigational vaccine administration.	• RSV-B neutralization titres expressed as group GMT ratio (RSV OA group [Overseas] / RSV OA group [China]), 1 month after the RSVPreF3 OA investigational vaccine administration*. • RSV-B neutralization titres expressed as group SRR difference (RSV OA group [Overseas] - RSV OA group [China]), 1 month after the RSVPreF3 OA investigational vaccine administration*.
Secondary Immunogenicity (descriptive)	
To evaluate the humoral immune response in Chinese OA enrolled in the RSV OA group (China) compared to OA enrolled in the RSV OA group (Overseas), up to 6 months post vaccination.	• RSV-A and RSV-B neutralization titres expressed as GMT, at baseline, 1 month and 6 months after the RSVPreF3 OA investigational vaccine administration. • RSV-A and RSV-B neutralization titers expressed as SRR, 1 month and 6 months after the RSVPreF3 OA investigational vaccine administration.
To evaluate the humoral immune response in Chinese OA enrolled in the RSV OA group (China) compared to historical data generated in the immunogenicity subset of the global efficacy study RSV OA=ADJ-006.	• RSV-A and RSV-B neutralization titres expressed as group GMT ratio (RSV OA=ADJ-006 / RSV OA Vaccine group [China]), 1 month after the RSVPreF3 OA investigational vaccine administration. • RSV-A and RSV-B neutralization titres expressed as group SRR difference (RSV OA=ADJ-006 - RSV OA Vaccine group [China]), 1 month after the RSVPreF3 OA investigational vaccine administration.
Secondary ARI surveillance (Study participants in China only)	
To describe the RSV-confirmed ARI and RSV-confirmed LRTD in RSV OA Vaccine group (China) and Placebo group (China).	Occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI and LRTD, according to the case definition**. In study participants in China with RT-PCR-confirmed RSV A and/or B associated ARI and LRTD cases: • Duration of episodes. • Reported symptoms/signs. • ARI/LRTD severity. • Frailty status.

Objectives	Endpoints and estimands
Secondary Safety	
To evaluate the safety and reactogenicity following the administration of the investigational RSVPreF3 OA vaccine.	For RSV OA group (China) and Placebo group (China): • Percentage of participants reporting each solicited administration site event with onset within 7 days after study intervention administration (i.e., the day of study intervention administration and 6 subsequent days). • Percentage of participants reporting each solicited systemic event with onset within 7 days after study intervention administration (i.e., the day of study intervention administration and 6 subsequent days). • Percentage of participants reporting unsolicited AEs within 30 days after study intervention administration (i.e., the day of study intervention administration and 29 subsequent days). • Percentage of participants reporting SAEs after study intervention administration (Day 1) up to 6 months after study intervention. • Percentage of participants reporting pIMDs after study intervention administration (Day 1) up to 6 months after study intervention. • Percentage of participants reporting SAEs related to study intervention after study intervention administration (Day 1) up to study end. • Percentage of participants reporting pIMDs related to study intervention after study intervention administration (Day 1) up to study end. • Percentage of participants reporting any fatal SAEs after study intervention administration (Day 1) up to study end. For RSV OA group (Overseas): • Percentage of participants reporting SAEs after study intervention administration (Day 1) up to study end (Month 6). • Percentage of participants reporting pIMDs after study intervention administration (Day 1) up to study end (Month 6). • Percentage of participants reporting SAEs related to study intervention after study intervention administration (Day 1) up to study end (Month 6). • Percentage of participants reporting pIMDs related to study intervention after study intervention administration (Day 1) up to study end (Month 6). • Percentage of participants reporting any fatal SAEs after study intervention administration (Day 1) up to study end (Month 6).

AE: Adverse event; ARI: Acute respiratory illness; GMT: Geometric mean titer; LRTD: Lower respiratory tract disease; OA: Older adults; pIMD: potential immune-mediated disease; RSV: Respiratory syncytial virus; SAE: Serious adverse event; SRR: seroresponse rate.

* Co-primary endpoints, NI criteria are defined in Section 9.1. SRR is defined in Section 9.3.1.

Study end in participants in China: Visit 3 (Month 6) or last ARI visit/contact whichever is later.

Study end in Overseas participants: Visit 3 (Month 6)

**Refer to Section 4.2.1 for case definitions.

4. STUDY DESIGN

4.1. Overall design

The study design diagram is provided in Section 1.2.

Experimental design: Phase 3, randomized, controlled, partial blind study.

Study groups and vaccination visits:

The study will aim to enroll approximately 2600 participants, i.e., 1800 participants in China [2:1 randomization allocation between RSV OA group (China) and Placebo group (China)], 800 participants in RSV OA group (Overseas).

Study participants in China will be randomly assigned to the RSV OA group (China) or to the Placebo group (China) (2:1) to receive 1 single dose of investigational RSVPreF3 OA vaccine or Placebo, respectively on Visit 1 (Day 1).

The participants in the RSV OA vaccine overseas group will receive 1 single dose of investigational RSVPreF3 OA vaccine on Visit 1 (Day 1).

Duration of study: The total duration of the study per participant will be approximately 7 months.

Sampling schedule:

For the study participants in RSV OA Vaccine group (Overseas), a blood sample of approximately 15 mL will be collected at screening visit to test for HIV, HBV, HCV and Syphilis.

Three 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-vaccination), Day 31 (post vaccination) and Month 6.

Primary completion date (PCD): The PCD will be when the last participant completes Day 31, as per SoA (Section 1.3).

Blinding: Partially blind. Refer to Section 6.4 for details.

Safety monitoring: GSK's Safety Review Team (SRT) will oversee the safety of the study participants and study conduct (refer to Section 8.3.3).

ARI surveillance: Surveillance for ARI detection will be carried out during the entire study in participants in China, via spontaneous reporting by the participant (starting on the vaccination day [Visit 1]) and via scheduled China site staff contacts (starting from Visit 2 onwards). These contacts will be every 2 weeks during the RSV season and every month during the inter-season periods. For detailed information on activities involved in ARI surveillance, refer to Table 2.

Data collection: Standardized Electronic Case Report Form (eCRF) will be used. Solicited and unsolicited adverse events will be collected using paper diaries.

End of study (EoS): Refer to Section 4.4 for details.

The description of the vaccine(s)/product is presented in Table 9.

4.2. Scientific rationale for study design

RSV is associated with serious illness in older adults and high-risk adults globally and in China. 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 older adults ≥60 YOA has been demonstrated in the global Phase 3 clinical study RSV OA=ADJ-006 (refer to IB). The current study is designed as a Phase 3, partially blind, controlled study to demonstrate the NI of the immune response of RSVPreF3 OA investigational vaccine in older adults in China, compared to older adults in the same age range to be enrolled from overseas countries that participated in the RSV OA=ADJ-006 study. Safety will also be evaluated in all study groups.

The inclusion of a group of participants overseas will allow direct and parallel bridging and comparison for immunogenicity between different populations (China vs Overseas), which is in line with the requirements in draft local guidelines on immunogenicity bridging clinical trial for prophylactic vaccines issued by CDE [CDE, 2022].

Immune protection against RSV in older people is incompletely understood and probably multifactorial. Older adults with low titers of serum NAb have been reported to be at greater risk of developing symptomatic RSV infection and of hospitalization than those who have high antibody titres [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.

Occurrence of RSV-associated ARI and LRTD will also be monitored in all participants in China during the study.

4.2.1. Case definitions

All study participants in China reporting at least 2 ARI symptoms/signs meeting the ARI case definition (see Table 8) will be followed up for ARI assessment. Diagnosis and treatment of each ARI should be performed according to the local standard of care. RT-PCR testing for RSV will be performed at GSK and GSK-designated laboratory. Therefore, all study participants in China with ARI will be requested to follow all study procedures and study contacts defined for the ARI surveillance (i.e., reporting of ARI symptoms/signs, ARI visit and follow-up contacts, etc).

Table 8 Case definitions for ARI and LRTD

Endpoint	Case definition
ARI (Trigger for swabbing)	Presence of: • at least 2 respiratory symptoms/signs for at least 24 hours **OR** • at least 1 respiratory symptom/sign + 1 systemic symptom/sign for at least 24 hours **Respiratory symptoms and signs** - Nasal congestion/rhinorrhea - Sore throat - New or increased sputum - New or increased cough - New or increased dyspnea (shortness of breath) - New or increased wheezing[2] - New or increased crackles/ronchi[3] based on chest auscultation - Respiratory rate ≥ 20 respirations/min[3] - Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[3] - Need for oxygen supplementation[3] **Systemic symptoms and signs** - Temperature ≥ 38.0°C /feverishness[1] - Fatigue - Body aches - Headache - Decreased appetite
RT-PCR-confirmed RSV-ARI [4]	An event meeting the case definition of ARI with at least one RSV-positive swab detected by RT-PCR.[5]
LRTD	Presence of: • at least **2 lower** respiratory symptoms/signs for at least 24 hours including at least **1 lower respiratory SIGN** **OR** • at least **3 lower** respiratory symptoms for at least 24 hours **Lower respiratory symptoms** - New or increased sputum - New or increased cough - New or increased dyspnea (shortness of breath) **Lower respiratory signs** - New or increased wheezing[2] - New or increased crackles/ronchi[3] based on chest auscultation - Respiratory rate ≥ 20 respirations/min[3] - Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90% if pre-season baseline is <95%)[3] - Need for oxygen supplementation[3]
RT-PCR-confirmed RSV-LRTD [4]	An event meeting the case definition of LRTD with at least one RSV-positive swab detected by RT-PCR. [5]
RT-PCR-confirmed severe RSV-LRTD – Definition 1 "Clinical symptomology" [4]	Presence of a LRTD with the following criteria: • at least **2 lower respiratory SIGNS** **AND** • with at least one RSV-positive swab detected by RT-PCR **Lower respiratory signs** - New or increased wheezing[2] - New or increased crackles/ronchi[3] based on chest auscultation - Respiratory rate ≥ 20 respirations/min[3] - Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90% if pre-season baseline is <95%)[3] - Need for oxygen supplementation[3]

Endpoint	Case definition
RT-PCR-confirmed **severe** RSV-LRTD – Definition 2 "Supportive therapy"[4]	Presence of a LRTD with at least one of the following criteria[6]: • Need for oxygen supplementation[3] • Need for positive airway pressure therapy (e.g. CPAP) • Need for other types of mechanical ventilation AND • with at least one RSV-positive swab detected by RT-PCR

ARI: acute respiratory illness; CPCA: continuous positive airway pressure; LRTD: lower respiratory tract disease; RSV: respiratory syncytial virus; RT-PCR: reverse transcription polymerase chain reaction.

1. Feverishness is defined as the feeling of having fever without objective measurement.
2. Reported by study participant or investigator.
3. Reported by investigator.
4. Throat and/or nasal swab samples collected at ARI visits for RT-PCR testing will be collected within 6 days after ARI onset (i.e., up to Day 7).
5. Refer to Section 8.2 for details on the counting of cases that are positive for RSV.
6. In case the participant was already receiving any of these for treating/controlling any pre-existing condition, any significant change or adaptation in the used therapy should be taken into account.

4.2.2. Rationale for the use of placebo

As there is currently no licensed RSV vaccine available in China, a Placebo group (receiving saline solution) will be used as control for safety/reactogenicity assessments.

Participants who received the placebo during the study may be provided with GSK RSVPreF3 OA vaccine after the study is completed and the RSVPreF3 OA vaccine is launched in China, depending on study results, local standards and regulations. Study site will contact the participants when this can be provided.

4.2.3. 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 participants in RSV OA group (China) and Placebo group (China). Please refer to Definition of Terms for the definition of observer blind. Participants enrolled in the RSV OA group (Overseas) will be aware of the intervention they receive, however the sample testing for immunogenicity will be blinded.

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

4.3. Justification for dose

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

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA (Section 1.3).

LSLV (Month 6 for overseas participants; Visit3 [Month 6] or last ARI visit/ contact whichever is later for study participants in China) or Date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints, whichever occurs later. EoS must be achieved no later than 8 months after LSLV. EoS cannot be before LSLV.

5. STUDY POPULATION

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

5.1. Inclusion criteria

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

- Adult male or female of ≥60 YOA at the time of study intervention administration, who live in the community dwelling (CD participants) (see definition of terms for the definition). INC#1
- Participants who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the diary cards, attend regular phone calls/study site visits, perform self-swabbing (study participants in China only), ability to access and utilize a phone or other electronic communications). INC#2

  Note: In case of physical incapacity that would preclude the self-completion of the diary cards, either site staff can assist the participant (for activities performed during site visits) or the participant may assign a caregiver to assist him/her with this activity (for activities performed at home). However, at no time, the site staff or caregiver will evaluate the participant's health status while answering diaries or make decisions on behalf of the participant.
- Participants who are medically stable in the opinion of the investigator at the time of vaccination. Participants with chronic stable medical conditions with or without specific treatment, such as diabetes, hypertension or cardiac disease, are allowed to participate in this study if considered by the investigator as medically stable. INC#3
- 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#4

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 intervention(s) (For details on components of study intervention administered, refer to Table 9 and *Arexvy* [Summary of Product Characteristics, 2023; Prescribing Information, 2023]. EXC#1

- Any clinical conditions for which serum samples would be prohibited for transfer to local central lab for testing. These clinical conditions include hepatitis B, hepatitis C, HIV and Syphilis based on medical history and physical examination (all participants) and laboratory screening tests (overseas participants). EXC#2
- 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#3
- Any history of dementia or any medical condition that moderately or severely impairs cognition. EXC#4
- 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 diary cards, attend regular phone calls/study site visits, perform self-swabbing (study participants in China only). EXC#5
- Significant underlying illness that in the opinion of the investigator would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival to less than 1 year). EXC#6
- Serious or unstable chronic illness. 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

- Previous vaccination with RSV vaccine. EXC#9
- Use of any investigational or non-registered product (drug, vaccine or invasive medical device) other than the study intervention(s) during the period beginning 30 days before the dose of study intervention(s), or their planned use during the study period. 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 study intervention administration, with the exception of COVID-19 and inactivated/subunit influenza vaccines which can be administered up to 14 days before or from 14 days after each study intervention. EXC#11

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

- Administration of long-acting immune-modifying drugs or planned administration at any time during the study period (e.g., infliximab). EXC#12
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 90 days before the study intervention administration or planned administration during the study period. EXC#13
- Chronic administration (defined as more than 14 consecutive days in total) of immunosuppressants or other immune-modifying drugs during the period starting 90 days prior to the study intervention administration or planned administration during the study period. For corticosteroids, this will mean prednisone ≥20 mg/day, or equivalent. Inhaled and topical steroids are allowed. EXC#14

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). Refer to Definition of Terms for the definition of invasive medical device. EXC#15

5.2.4. Other Exclusion Criteria

- 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#16
- Bedridden participants. EXC#17
- Planned move during the study conduct that prohibits participation until study end. EXC#18
- Participation of any study personnel or their immediate dependents, family, or household members. EXC#19

5.3. Caregiver support

Study participants may decide to assign a caregiver to help them fulfilling the study procedures. Please refer to 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's 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 study staff, planning study visits, transcribing responses to diaries, performing the nasal swab (only for study participants in China), 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 time of recruitment, the study staff should inform the participant of the possibility to appoint a caregiver. Then, at each study visit with the exception of the end of study visits, the site staff should check with the participant if he/she wishes to appoint a caregiver or if there were or will be changes in caregiver.

5.4. Lifestyle considerations

Not applicable.

5.5. Screen failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not enrolled into 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 not be rescreened.

Screen number assigned to screen failure participants cannot be reassigned to another participants.

For the overseas arm, if the subjects are positive to any pathogens tested during screening, they will not participate in this study.

5.6. Criteria for temporarily delaying enrollment and/or administration of study intervention

Study vaccine administration may be postponed within the permitted timeframe for study vaccination until transient circumstances cited below are resolved:

- Acute disease and/or fever at the time of vaccination. Fever is defined as a temperature ≥ 37.3°C by axillary route. Oral temperature = axillary temperature + 0.2°C.
- Participants with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be vaccinated at the discretion of the investigator.
- In case of administration of inactivated and subunit influenza vaccines or Coronavirus Disease 2019 (COVID-19) vaccines: Postponement of study vaccine administration within given protocol timelines to allow respect of the 14 day-interval between flu/COVID-19 vaccination and study vaccine administration.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study interventions administered

Table 9 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		Comparator
Product category	Biologics		Combination product
Route of Administration	Intramuscular		Intramuscular
Administration site			
Location	Deltoid		Deltoid
Directionality	Upper		Upper
Laterality	Non-dominant		Non-dominant
Number of doses to be Administered	1		1
Volume to be administered**	0.5 mL		At least 0.5 mL***
Packaging and labelling	Refer to Pharmacy Manual for details		Refer to Pharmacy Manual for details
Manufacturer	GSK		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.
** Refer to the Pharmacy Manual for the volume after reconstitution. 0.5 mL of the reconstituted RSVPreF3 OA vaccine is to be injected.
*** 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, ruler for skin reaction

measurement, materials for study intervention administration, syringes, biological sample collection kits and oximeters.

- Instructions for medical device use are provided in Laboratory Manual and Pharmacy Manual.
- All device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Sections 8.4.6 and 10.4) 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 labelled 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

All participants will be centrally assigned to the study intervention using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

Study intervention will be dispensed at the study visits as summarized in the SoA (Section 1.3).

Returned study intervention should not be re-dispensed to the participants.

Participants who withdraw from the study will not be replaced.

6.4. Blinding

Data from study participants in China 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, ARI surveillance). The study is open-labelled for participants enrolled in the overseas arm.

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 study participants in China. 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 (for study participants in China) from study start and will remain blinded up to study end. The results from the primary analyses (Day 31) may be shared with the principal investigators. The individual data listings and participant treatment assignments will not be provided to the investigators until after the conclusion of the study.

Note that limited members of GSK central study team (CSL, Statistician, Safety Representative, etc.) may be fully/partially unblinded to the study intervention assignment at the time of Day 31 analysis.

6.4.1. Emergency unblinding

This is a partial blind study in which the qualified personnel are blinded to study intervention for participants in China. The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' 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 IVRS/IWRS, 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 1 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

Participants will receive the study intervention, under medical supervision, directly from the investigator or designee.The date and time of the dose administered in the clinic will be recorded in the source documents.

A record of the quantity of study intervention dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.6. Dose modification

Not applicable.

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

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

6.8. Treatment of overdose

Not applicable.

6.9. Prior and concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior 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, except vitamins and dietary supplements, administered during the 30-day period following the administration of study vaccine.
- All concomitant vaccination during the entire study period.
- All concomitant medication including vaccines/products which may explain/cause/be used to treat an SAE/pIMD as defined in Sections 8.4.1 and 8.4.3. These must also be recorded on 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 antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination need to be recorded on the eCRF. An anti-pyretic is considered prophylactic when given in the absence of fever, to prevent fever from occurring.
- All concomitant medications taken for the treatment of an ARI (including prescribed drugs [e.g. antibiotics] and self-treatment) or for an ARI-related complication (Study participants in China only).
- All concomitant medications including vaccines/products leading to discontinuation of the study intervention or an elimination from the analysis (refer to Section 5.2.2 for details).

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

Not applicable.

7.2. Participant discontinuation/withdrawal from the study

A participant 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	AEs requiring expedited reporting to GSK Unsolicited AE* Solicited AE*
Lost to follow-up	Subject Relocated Subject was Incarcerated Other, specify Unknown
Physician Decision	Specify
Protocol Deviation	Specify
Site Terminated by Sponsor	
Study Terminated by Sponsor	
Withdrawal by Participant	Burden of Procedure Participant Relocated Pursue Alternative Treatment COVID-19 Pandemic Other
Other	Specify
Death	

*For study participants in China only

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

7.3. Lost to follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

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 (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Subjects who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management [(e.g., blood count)] and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, contacts, assessments, study intervention distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- Safety/laboratory 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, including any extra assessments that may be required, will not exceed

30 mL for RSV OA Vaccine group (China) and Placebo group (China) and 45 mL for RSV OA Vaccine group (Overseas).

8.1. Administrative and general/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.

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 administration of study intervention in the eCRF.

8.2. Immunogenicity assessment and ARI surveillance

8.2.1. Immunogenicity assessments

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

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

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

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

By default, collected samples will be stored for a maximum of 5 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. If allowed by country regulation/ethics, immunogenicity sampling may be conducted remotely by a Home Healthcare Services professional.

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

8.2.2. ARI surveillance period and methods

Surveillance for detection of ARI episodes will be carried out during the entire study period, via spontaneous reporting by the participant in China (starting on the day of the vaccination* [Visit 1]) and by scheduled site staff contacts (starting from Visit 2 onwards) with different frequencies of contact during the RSV season and the inter-season periods. No ARI surveillance will be conducted for the overseas participants.

* For detailed information on activities involved in ARI surveillance, refer to Table 2.

Swab samples will be taken in all study participants in China meeting pre-specified criteria for ARI case definition (see Table 8). Diagnosis and treatment of each ARI should be performed according to the local standard of care.

8.2.2.1. Nasal self-swab training with the participant in China

At Visit 1, the study participants in China may be invited to practice a nasal self-swab in the presence of site staff to guide them through the instructions and the procedure. The nasal self-swab training can be repeated at any subsequent visit if the participant raises the need for a new training. This swab should be discarded after the training, it should not be sent to the central laboratory.

ARI surveillance starts on the day of vaccination (Visit 1). If the ARI onset (Day 1) occurs after Visit 3 (Month 6), the ARI procedures will not be conducted.

8.2.2.2. Definitions for ARI surveillance

- **ARI onset (Day 1):** will be defined as the first day when the study participant presents **at least 2 concomitant ARI symptoms/signs meeting the ARI case definition** (see Table 8). The ARI case must be confirmed by the investigator/site staff or delegate during the ARI visit.

  Note: The start and end date of each individual symptom and the presence/absence of each sign will be recorded in the eCRF. It may happen that the start date of an individual symptom/sign is before the ARI onset date, if the first symptom/sign started before the second symptom/sign needed to reach the ARI case definition.

- **ARI end:** will be defined as the first day when all ARI symptoms/signs of the participant have returned to baseline or when they diminished significantly as judged by the investigator.
- **New ARI episode:** An ARI episode will be considered as a new episode only after the resolution of the previous one. Between 2 ARI episodes, there must be at least 7 days free of symptoms/signs (or at baseline level) or at least 7 days with significantly diminished symptoms/signs as judged by the investigator.
- **Complications:** The following complications of interest will be collected through the entire study, starting on the Visit 1. The relationship of these complications to an ARI episode will be assessed by the investigator.
  - **Respiratory complications:**
    - **Pneumonia**: A clinical diagnosis of pneumonia based on signs and symptoms, with or without chest radiograph that demonstrates a new or progressive infiltrate.
    - **New diagnosis of COPD or exacerbation of COPD**: A new diagnosis of COPD or, in a participant with previously diagnosed COPD, a worsening of COPD necessitating to increase the dosage or modify the treatment administered.
    - **New diagnosis of asthma or exacerbation of asthma**: A new diagnosis of asthma or, in a participant with previously diagnosed asthma, a worsening of asthma necessitating to increase the dosage or modify the treatment administered.
    - **Other respiratory complications:** Other diagnosis of respiratory illness, including new diagnosis or exacerbation of a pre-existing respiratory disease (e.g., emphysema, chronic bronchitis).
  - Non-respiratory complications:
    - New onset or worsening congestive heart failure (CHF),
    - Myocardial infarction (MI),
    - Stroke,
    - Diabetes,
    - Other non-respiratory complications judged related to an ARI episode by the Investigator.

8.2.2.3. ARI capture and follow-up

ARI episodes will be captured via 2 complementary methods: 1) spontaneous reporting by the study participant in China and 2) scheduled site staff contacts.

Each ARI episode (including if several episodes occur in the same participant) will be assigned a sequential case number. All relevant ARI information will be reported in a specific ARI eCRF screen.

8.2.2.3.1. Spontaneous reporting by the participant

Study participants in China will be instructed to contact spontaneously the investigator/site staff promptly if they experience at least 2 ARI symptoms/signs (see Table 8). The surveillance for ARI will start on the vaccination day (Visit 1). At Visit 1, participants will be provided with instruction material to guide them in the detection of ARI symptoms/signs. At Visit 1, participants will be invited to practice nasal self-swab collection (refer to Section 8.2.2.1).

At each study visit/contact, participants in China should be reminded to contact the investigator/site staff if they experience respiratory symptoms meeting the ARI case definition.

8.2.2.3.2. Scheduled site staff contacts

As of Visit 2 onwards, the site staff will contact the participants in China regularly during the entire study to check if they have experienced any respiratory symptoms meeting the ARI case definition (see Table 8). These contacts will be performed every 2 weeks during the RSV season and every month during the inter-season periods.

The RSV season in China defined for this study are from 1 October to end of April.

Multiple formats can be proposed by the site staff to organize these surveillance contacts. This 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 in China. 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 done to get the details on the event(s). Receipt of the message must be confirmed by the participant or caregiver, as applicable.

At each scheduled contact, study participants in China will be asked if they have experienced:

- Any symptoms/signs meeting the ARI case definition (see Table 8).
- Any of the following respiratory complications:
  - Pneumonia
  - New diagnosis of COPD or exacerbation of COPD
  - New diagnosis of asthma or exacerbation of asthma
  - Other respiratory complications
- Any of the following non-respiratory complications:
  - New onset or worsening congestive heart failure (CHF),
  - Myocardial infarction (MI),
  - Stroke,
  - Diabetes,

  - Other non-respiratory complications judged related to an ARI episode by the investigator,

- Any hospitalization or visit to a healthcare practitioner for a respiratory disease.
- AEs, SAEs, AESIs (including pIMDs and AF)*.

  Note: AEs, SAEs, AESIs (including pIMDs and AF) should be reported to GSK during specified follow-up periods as described in Section 10.3.5.
- Participants will be reminded to contact the site staff in case they experience any ARI symptoms/signs.

If no ARI symptoms/signs are reported during the contact, the investigator/site staff should record date of contact and absence of ARI symptoms/signs in the eCRF. If ARI symptoms/signs are reported, please refer to Section 8.2.2.4.2.

*Note: In this study AF will be collected as AESIs. See definition of AESI in Definition of Terms.

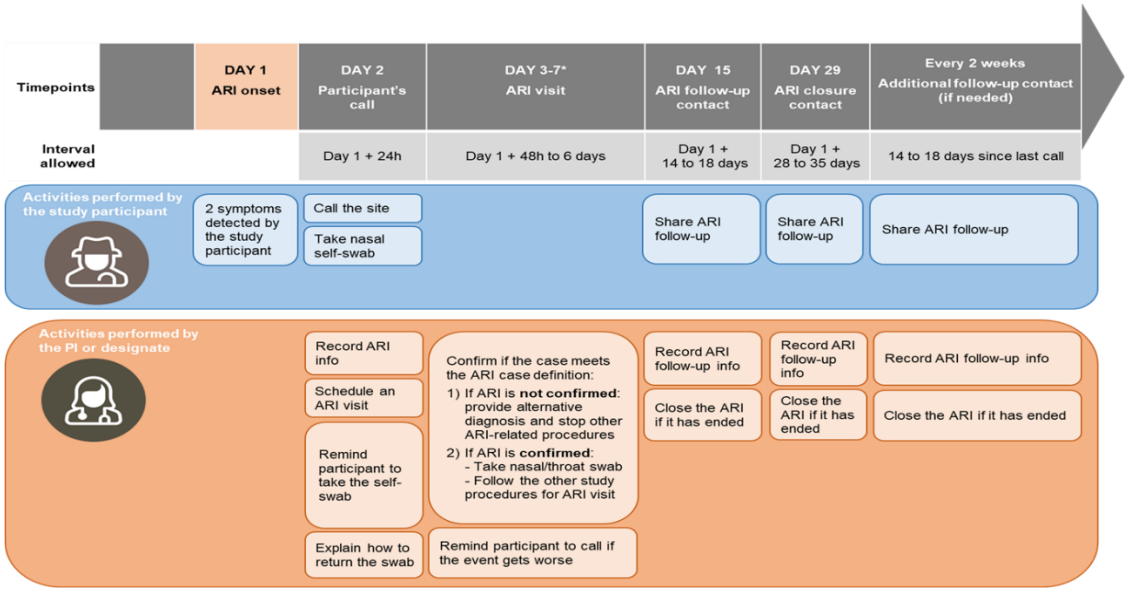
8.2.2.4. ARI procedures

8.2.2.4.1. Primary route to capture ARI episodes

Spontaneous reporting by the study participant in China should be the main route to capture ARI episodes and the related procedures are described in Figure 2 and the sections below.

Note that if an ARI event meets the definition of AE or SAE it should also be reported as AE/SAE according to the specified follow-up periods described in Section 8.4.3.

Figure 2 ARI capture and follow-up



The ARI visit should preferably be done on-site. If deemed necessary, the ARI visit can be done at home. ARI follow-up contacts on Day 15, Day 29 and the additional follow-up contact can be done via phone calls.

In case of at least 2 concomitant ARI symptoms/signs identified by the study participant in China, the following visits and contacts will take place (refer to Table 5 for the intervals allowed for each contact):

- **Participant's call (Day 2):** Within 24 hours of the appearance of at least 2 concomitant ARI symptoms/signs, the participant should call the site staff. During the phone call:
  - **Record ARI symptoms/signs**: The site staff will record the ARI symptoms/signs reported by the participant in the eCRF and record the onset date of each symptom mentioned during the call.
  - **Schedule ARI visit**: The site staff will organize an ARI visit within the per protocol window. (Refer to the note for special circumstances in the ARI visit detailed below).
  - **Reminders for participant procedures**: The participant should be reminded by site staff to take a nasal self-swab. The self-collected swab should be done preferably within 48 hours of ARI onset but not later than 5 days after ARI onset. The participant will be reminded on the storage conditions and return instructions of the swab sample. The self-swab should be returned to the study-site within 2 days after collection or, if not feasible within 2 days, the swab should be returned to site as soon as possible.
- **ARI visit (Days 3-7):** The ARI visit should take place soon after ARI onset, ideally 48 hours after ARI onset, but no later than 6 days after ARI onset. Ideally, and in most cases, the ARI visit should be scheduled at least 1 day after the participant's self-swab (i.e., the nasal self-swab taken by the participant and the nasal and throat swab samples taken by the qualified site staff should not be done on the same day). If for logistical or medical reasons the ARI visit must be scheduled on the same day than the participant call, it is recommended to take the nasal and throat swab during the visit and to omit the self-swab taken by the participant, but this should remain exceptional.

  During the ARI visit the following procedure should be performed (refer also to Table 2 in Section 1.3):

  - **Physical examination, body temperature and vital signs:** refer to Section 8.3.
  - **Pulse oximetry:** refer to Section 8.3.2.4.
  - **Confirmation of ARI:** The investigator or designee will confirm if the event meets the ARI case definition (see Table 8 in Section 4.2.1).

    If the ARI is NOT confirmed, the investigator or designee will record the alternative diagnosis in the eCRF. No other swab sample should be taken and other ARI-related procedures should not be performed. Refer to the lab manual for details on the handling of self-swab samples in case ARI is not confirmed. The management of the participant illness should follow local standard of care.

    If the ARI is confirmed (i.e., the event met the ARI case definition), the investigator or designee will record the ARI information in the eCRF and follow all ARI-related procedures (see Table 2 in Section 1.3). The ARI episode should be treated accordingly to local standard of care.

- **Record ARI information:** The investigator or designee will assess clinical signs and/or symptoms of ARI, record the onset date of each symptom diagnosed/mentioned during the visit and record the presence/absence of each sign detected based on auscultation. The investigator should provide a clinical diagnosis and assess the intensity of the ARI according to the intensity grading provided in.

  If any laboratory testing is performed locally for the identification of respiratory pathogens for the ARI, the date of the testing, method of test, specimen material type, the results and the references of commercial PCR diagnostic kit (if applicable) should be recorded in the eCRF.

Table 10 Intensity grading for ARI/LRTD episode

Mild	=	An ARI/LRTD episode which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
Moderate	=	An ARI/LRTD episode which is sufficiently discomforting to interfere with normal everyday activities.
Severe	=	An ARI/LRTD episode which prevents normal, everyday activities. Such an event would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.

- **Record date of self-swab:** The site staff will record in the eCRF the date when the self-swab was taken by the participant.
- **Nasal and throat swab sampling:** For each ARI reported after the vaccination visit (Visit 1), qualified staff from the study team will collect one swab of cells and secretions from each nostril and one swab from throat. After collection, both swabs will be placed in the same tube. Full details for obtaining nasal and throat sample are provided in the lab manual.

  The swab samples will allow to assess the potential RSV by RT-PCR at a GSK and GSK-designated laboratory.
- **Record treatment prescribed/self-treatment:** Any medication taken for ARI (including self-medication) since ARI onset until resolution of the episode will be recorded in the eCRF with medical indication and start/end dates of the treatment. The same will be applicable to medication(s) prescribed to treat any ARI-related complications.
- **Reminders:** The participants should be reminded to contact the site staff if the ARI worsens. The need for additional visits or contacts for the medical management of the ARI should be assessed by the investigator and follow the local standard of care.
- **Recording of AEs, SAEs and other events of interest:** refer to Section 8.4.
- **Distribution of new material:** At each ARI visit (regardless**,** if the ARI is confirmed or not), the site staff should distribute new self-swabbing material to the study participant for the next ARI episode.

- **ARI follow-up contact (Day 15):** Each ARI episode will be followed up by the investigator/site staff through an ARI follow-up contact (phone call) approximately 14 days after ARI onset.
  - **ARI follow-up information** will be recorded in the eCRF: onset and end date of each symptom (including new symptoms) should be captured. Any update on the diagnosis, the medication taken to treat the ARI and ARI intensity will be recorded. For each ARI the maximum intensity should be recorded.

  If any laboratory testing is performed locally for the identification of respiratory pathogens for the ARI, the date of the testing, method of test, specimen material type, the results and the references of commercial RT-PCR diagnostic kit (if applicable) should be recorded in the eCRF.

  - **Recording of AEs, SAEs and other events of interest**: refer to Section 8.4
- If the ARI ended before the follow-up call, the ARI outcome should be recorded and the scheduled surveillance contacts should resume for that participant.
- **ARI closure contact (Day 29):** If the ARI event was still ongoing at the first ARI follow-up contact, the investigator/site staff will contact again the participant approximately 28 days after ARI onset to check on the resolution of the ARI episode. ARI follow-up information and ARI closure will be recorded and the scheduled surveillance contacts should resume for that participant.
- **Additional follow-up contact:** For participants with complication(s) lasting beyond the ARI closure contact, additional follow-up contacts will be done approximately every 2 weeks post ARI closure contact until the resolution of the ARI/complication(s) or until study end.
- If between the different ARI visit/contacts, the participant was seen by another healthcare provider (HCP) for the ARI, the investigator/site staff should attempt to get maximum information on the ARI episode, diagnosis and results of any laboratory test done for identification of respiratory pathogens.
- **Re-starting scheduled surveillance contacts after ARI end:** Once an ARI event has ended, the surveillance contacts should resume for that participant. The first surveillance contact should be planned:
  - within maximum 14 days after the last ARI follow-up contact if the last FU contact was done during the RSV season.
  - within a maximum of 30 days if it's during the inter-season period.

8.2.2.4.2. Other routes to capture ARI episodes

In some situations, the site staff might be informed of an ARI that was not immediately reported by the study participant in China. The site staff could become aware of these ARI during a surveillance contact, via the participant's call (later than 24 hours after ARI onset), via the participant's caregiver or hospital staff, for example.

If the participant was seen by another HCP for the ARI, the investigator/site staff should attempt to get maximum information on the ARI episode, diagnosis and results of any laboratory test done for identification of respiratory pathogens.

Note that if an ARI event meets the definition of AE or SAE it should also be reported as AE/SAE according to the specified follow-up periods described in Section 8.4.3

a. If, at the time of notification, the ARI is still ongoing and is reported within the interval allowed for ARI visit:

- The site staff should encourage the participant to take a nasal self-swab*. The site staff will organize an ARI visit within the per protocol window. Refer to Section 8.2.2.4.3 for guidance in case of hospitalization during an ARI episode.

  *Note: The self-swab should not be done if the ARI visit is planned on the same day. The nasal and throat swab will be taken during the ARI visit.

- The procedures for the ARI visit and the nasal and throat swab samples as well as the subsequent follow-up contacts should be performed as described in Figure 2 and Section 8.2.2.4.1.

b. If, at the time of notification, the ARI is still ongoing but is reported outside of interval allowed for ARI visit:

- The site staff should document the available ARI information, signs and symptoms in the eCRF but no swab samples should be taken and no ARI visit should be organized. The need for additional visits or contacts for the medical management of the ARI should be assessed by the investigator and follow the local standard of care.
- The procedures for the subsequent follow-up contacts (Day 15 and/or Day 29 and/or additional follow-up calls) should be performed as described in Figure 2 and Section 8.2.2.4.1.

c. If the ARI symptoms/signs are gone at the time of notification:

- The site staff should document the available ARI information, signs and symptoms in the eCRF and close the ARI. No swab samples should be taken and no ARI visit should be organized.

8.2.2.4.3. Hospitalization during an ARI episode

If a study participant in China is hospitalized during an ARI episode, the site staff should make best efforts to collect the relevant information and swab samples for ARI assessment.

Note that if the event also qualifies as a SAE**,** it should be reported to GSK during specified follow-up periods as described in Section 8.4.3.

a. If the participant is hospitalized before the ARI visit:

- The site staff should try to collect a swab sample (either at hospital or at the participant's residence) within 6 days after ARI onset. The swab sample can be either self-collected by the participant (nasal self-swab) or by the site staff (nasal and throat swab).
- Whenever feasible, the other procedures for the ARI visit should be performed within 6 days after ARI onset (see Table 2).
- The investigator or designee should collect relevant information on the hospitalization and ARI episode including diagnosis, ARI signs and symptoms, results of any laboratory test done for identification of respiratory pathogens during the hospitalization and outcome of the hospitalization.
- The subsequent ARI follow-up contacts should be performed as described in Figure 2 and Section 8.2.2.4.1.

b. If the participant is hospitalized after the ARI visit:

- The investigator or designee should collect relevant information on the hospitalization and ARI episode including diagnosis, ARI signs and symptoms, results of any laboratory test done for identification of respiratory pathogens during the hospitalization and outcome of the hospitalization.
- The subsequent ARI follow-up contacts should be performed as described in Figure 2 and Section 8.2.2.4.1.

8.2.2.5. Evaluation of LRTD

All reported ARI cases will be reviewed by blinded, qualified GSK staff members to determine whether certain investigator-reported events meet the definition of LRTD and severe LRTD, using predefined endpoint criteria. This review will be made on clinical criteria (signs/symptoms) and independently of the results of the RSV RT-PCR.

Detailed information on this adjudication process, including data obtained by methodologies which are not protocol-specified or for missing data, will be described in the adjudication charter.

The potential RSV infection will be assessed by RT-PCR testing of swab samples (see Table 12.

8.2.3. Biological samples

An overall volume of 30 mL of blood for RSV OA Vaccine group (China) and Placebo group (China) and 45 mL for RSV OA Vaccine group (Overseas) will be collected during the entire study period. Refer to Table 11 and SoA (Section 1.3) for information on volumes collected for different assessments.

Table 11 Biological samples

Sample type	Quantity	Unit	Timepoints	Subset name
Blood	~15	mL	Screening	RSV OA vaccine group (Overseas only)
Blood	~10	mL	Scheduled (V1, V2 and V3)	All participants
Nasal self-swab specimen	Not Applicable	Not Applicable	Case-driven	All study participants in China reporting at least 2 ARI symptoms/signs meeting the ARI case definition (see Table 8)
Nasal/throat swab specimen collected by qualified site staff	Not Applicable	Not Applicable	Case-driven (ARI visit)	All study participants in China reporting at least 2 ARI symptoms/signs meeting the ARI case definition (see Table 8)

*For the study participants in RSV OA Vaccine group (Overseas), a blood sample of approximately 15 mL will be collected at screening visit to test for HIV, HBV, HCV and Syphilis.

8.2.4. Laboratory assays

All laboratory testing will be performed at a GSK and GSK-designated laboratory.

If applicable, sample management will be done with the support of a Central Laboratory.

For ARI cases identified during the ARI surveillance, the potential RSV infections will be assessed by RT-PCR testing of swab samples.

Table 12 Laboratory assays

Test classification	System	Component	Method	Laboratory
Screening*	Serum	HIV, HBV, HCV and Syphilis	Commercially available Kits	GSK-designated lab
Humoral Immunity Antibody determination)	Serum	RSV-A neutralization titer	Neutralization	GSK and GSK-designated lab
		RSV-B neutralization titer	Neutralization	GSK and GSK-designated lab
Molecular Biology **	Nasal self-swab collected by the study participant in China and nasal/throat swab specimen taken at ARI visit	Respiratory Syncytial Virus A RNA Respiratory Syncytial Virus B RNA	RT-PCR or equivalent	GSK and GSK-designated lab

ARI: acute respiratory illness; CRO: clinical research organization; PCR: polymerase chain reaction; RNA: ribonucleic acid

* For the study participants in the RSV OA Vaccine group (Overseas), a blood sample of approximately 15 mL will be collected at screening visit to test for HIV, HBV, HCV and Syphilis.

** RSV A/B RT-PCR will be performed on all specimen from study participants in China with at least 2 ARI symptoms/signs meeting the ARI case definition as per Table 8 in Section 4.2.1.

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

For neutralization and PCR assays, if feasible and deemed necessary by the Company, those samples may be sent to the Company's lab in Belgium for testing.

8.2.5. Immunological read-outs

Table 13 Immunological read-outs

Blood sampling timepoint		Subset name	No. participants	Component
Type of contact and timepoint	Sampling timepoint			
Screening (Day [-28] to Day 1)	Screening Visit	RSV OA Vaccine group (Overseas)	Approximately 800	HIV, HBV, HCV and Syphilis
Visit 1 (Day 1)	Pre-dose	Immunogenicity	Approximately 2600	RSV-A neutralization RSV-B neutralization
Visit 2 (Day 31)	Post-dose			
Month 6 (Day 181)	Post-dose			

8.2.6. Molecular biology read-outs

Table 14 Molecular biology tests on swab samples

Sampling time point		Subset tested	No. samples tested	Component	Components priority rank
Type of contact and time point	Sampling time point				
Sampling of nasal self-swab	Unscheduled	All study participants in China with at least 2 ARI symptoms/signs*	Case-driven	RSV A/B RNA	1
ARI visit (nasal and throat swabs)	Unscheduled	All study participants in China with at least 2 ARI symptoms/signs*	Case-driven	RSV A/B RNA	1

ARI: acute respiratory illness; RSV: respiratory syncytial virus
* RSV A/B RT-PCR will be performed on all specimen from study participants in China with at least 2 ARI symptoms/ signs meeting the ARI case definition as per Table 8 in Section 4.2.1.

8.2.7. Immunological correlates of protection

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

8.3. Safety assessments

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE. The investigator and any designees remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study.

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

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

8.3.1. Pre-vaccination procedures

8.3.1.1. Collection of demographic data

Prior to the study vaccination at Visit 1, record demographic data such as year of birth, and sex in the participant's eCRF.

8.3.1.2. Measure/record height and weight

Prior to the study vaccination at Visit 1, measure the participant's height and weight and record the values in the eCRF.

8.3.1.3. Medical history

Prior to the study vaccination at Visit 1, obtain the participant's medical history by interviewing the participant and/or review of the participant's medical records. Record any relevant pre-existing conditions, signs and/or symptoms present prior to the study vaccination in the eCRF.

A predefined list of comorbidities to be recorded will be available in the eCRF.

8.3.1.4. Vaccination history

Prior to the study vaccination at Visit 1, obtain the participant's vaccination history by interviewing the participant and/or review of the participant's vaccination records.

Any vaccine administered up to 1 year before the 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.

8.3.1.5. Smoking status and smoking exposure history

Prior to the study vaccination at Visit 1, the smoking status of study participants will be collected in the eCRF, differentiating tobacco use (cigarettes, cigars, cigarillos, pipes) 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.

8.3.1.6. Pre-vaccination body temperature

The body temperature of each participant needs to be measured prior to study vaccine administration and recorded in the eCRF. The route for measuring temperature can be oral or axillary. If the participant has fever (defined as temperature ≥37.3°C by axillary on the day of vaccination), the vaccination visit will be rescheduled.

8.3.1.7. Distribution of paper diary cards (Study participants in China only)

A paper diary card will be distributed to study participants in China at Visit 1 (day of vaccination) and will be used for recording solicited AEs on the day of vaccination and for 6 subsequent days (Days 1-7).

Another paper diary card will be used for recording unsolicited AEs and concomitant medications/products on the day of vaccination and for 29 subsequent days (Days 1-30) by study participants in China.

Refer to Section 10.3.5 for guidelines.

8.3.2. Procedures carried out at vaccination and non-vaccination visits

8.3.2.1. Physical examination

A physical examination should be performed at Visit 1 (Day 1) and at each ARI visit (Study participants in China only). Collected information needs to be recorded in the eCRF.

- If the investigator determines that the participant's health on the day of study intervention administration temporarily precludes dosing, the visit will be rescheduled. Refer to the Section 5.5 for the list of criteria for temporary delay of study intervention administration. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.
- Physical examination at each study visit after the study intervention administration will be performed only if the participant indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.

8.3.2.2. Body temperature during ARI episode (Study participants in China only)

The body temperature of the study participant in China should be measured at the ARI visit(s) and recorded in the eCRF. The route for measuring temperature can be oral or axillary.

8.3.2.3. Lung auscultation (Study participants in China only)

Lung auscultation should be performed at Visit 1 (Day 1) and at each ARI visit for study participants in China. Collected information needs to be recorded in the study participant's medical records.

Lung auscultation at Visit 2 (Day 31 post-Dose) and Visit 3 (Month 6) will be performed only if the study participant in China indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate.

8.3.2.4. Pulse oximetry (Study participants in China only)

Peripheral arterial oxygen saturation (SpO_2%) will be assessed using pulse oximetry at Visit 1 (Day 1) and at each ARI visit for study participants in China. Collected information needs to be recorded in the eCRF.

For the purpose of the study, the same validated oxygen saturation device will be provided to each study-site.

8.3.2.5. Vital signs

Resting vital signs should be checked at Visit 1 (Day 1) and at each ARI visit (Study participants in China only). 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.

8.3.3. Warnings and precautions to administration of study intervention

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

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

- Participant safety will be continuously monitored by the Medical Monitor, designated Safety Lead (or delegate), 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.
- The existing project's SRT will review blinded data on an ongoing basis during the entire study period.

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 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, surrogate, or the participant's legally authorized representative).

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.4.1. Time period and frequency for collecting AE, SAE, and AESIs (including PIMDs and AF)

All AEs and SAEs will be collected from the signing of the ICF until the time points specified in the SoA (Section 1.3).

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

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

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

Table 15 Collection and reporting of safety information

	Screening visit*	Vacc			6 months after vaccination for each participant	Study conclusion***
	Day (-28) to Day 1	D1	D7	D30		
Solicited administration site and systemic AEs (Study participants in China only)						
Unsolicited AEs † (Study participants in China only)						
All SAEs†						
All pIMDs						
SAEs related to study intervention†						
PIMDs related to study intervention						
SAEs related to study participation or concurrent GSK medication/vaccine**						
Fatal SAEs†						
AEs/SAEs leading to withdrawal from the study						
Intercurrent medical conditions						

Vacc: vaccination; D: Day; AE: adverse event; AESI: Adverse event of special interest; SAE: serious adverse event; pIMD: potential immune-mediated disease

Note: Visit 3 (Month 6) is considered at the study conclusion for overseas participants. Visit 3/Month 6 (or last ARI visit/ contact whichever is later) is considered as the study conclusion for participants in China. Refer to Table 1 and Table 3 for more details.

* Applicable for RSV OA Vaccine group (Overseas) study participants only.

** Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
***Study conclusion for participants in China is Visit 3 [Month 6] or last ARI visit/contact, whichever is later; and for study participants in Overseas is Visit 3 [Month 6].
† 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 (Study participants in China only) 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.
The shaded region in the table indicates time period of data collection.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined above.

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, SAEs and AESIs (including pIMDs and AF). Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE/SAE/AESI (including pIMDs with AF) occurrences.

8.4.3. Follow-up of AEs and SAEs

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

8.4.4. AESIs

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

8.4.4.1. Potential immune-mediated diseases

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

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the 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 16 List of potential immune-mediated diseases (pIMDs)

Blood disorders and coagulopathies	Cardio-pulmonary inflammatory disorders	Endocrine disorders
• Antiphospholipid syndrome • Autoimmune aplastic anemia • Autoimmune hemolytic anemia, including: – Warm antibody hemolytic anemia – Cold antibody hemolytic anemia • Autoimmune lymphoproliferative syndrome (ALPS) • Autoimmune neutropenia • Autoimmune pancytopenia • Autoimmune thrombocytopenia – Frequently used related terms include: “autoimmune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura (ITP)”, “idiopathic immune thrombocytopenia”, “primary immune thrombocytopenia”. • Evans syndrome • Pernicious anemia • Thrombosis with thrombocytopenia syndrome (TTS)	• Idiopathic Myocarditis/Pericarditis, including: – Autoimmune / Immune-mediated myocarditis – Autoimmune / Immune-mediated pericarditis – Giant cell myocarditis • Idiopathic pulmonary fibrosis, including: – Idiopathic interstitial pneumonia (Interstitial lung disease, Pulmonary fibrosis, Immune-mediated pneumonitis) – Pleuroparenchymal fibroelastosis (PPFE) • Pulmonary alveolar proteinosis (PAP) – Frequently used related terms include: “pulmonary alveolar lipoproteinosis”, “phospholipidosis”	• Addison’s disease • Autoimmune / Immune-mediated thyroiditis, including: – Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) – Atrophic thyroiditis – Silent thyroiditis – Thyrotoxicosis • Autoimmune diseases of the testis and ovary, including: – Autoimmune oophoritis – Autoimmune ovarian failure – Autoimmune orchitis • Autoimmune hyperlipidemia • Autoimmune hypophysitis • Diabetes mellitus type I • Graves’ or Basedow’s disease, including: – Marine Lenhart syndrome – Graves' ophthalmopathy,

• Thrombotic thrombocytopenic purpura – Also known as "Moschcowitz-syndrome" or "microangiopathic hemolytic anemia"		also known as thyroid eye disease (TED) or endocrine ophthalmopathy • Insulin autoimmune syndrome • Polyglandular autoimmune syndrome, including: – Polyglandular autoimmune syndrome type I, II and III
Eye disorders	**Gastrointestinal disorders**	**Hepatobiliary disorders**
• Ocular Autoimmune / Immune-mediated disorders, including: – Acute macular neuroretinopathy (also known as acute macular outer retinopathy) – Autoimmune/Immune-mediated retinopathy – Autoimmune/Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia – Cogan's syndrome: an oculo-audiovestibular disease – Ocular pemphigoid – Ulcerative keratitis – Vogt-Koyanagi-Harada disease	• Autoimmune / Immune-mediated pancreatitis • Celiac disease • Inflammatory Bowel disease, including: – Crohn's disease – Microscopic colitis – Terminal ileitis – Ulcerative colitis – Ulcerative proctitis	• Autoimmune cholangitis • Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis
Musculoskeletal and connective tissue disorders	**Neuroinflammatory/neuromuscular disorders**	**Renal disorders**
• Gout, including: – Gouty arthritis • Idiopathic inflammatory myopathies, including: – Dermatomyositis – Inclusion body myositis – Immune-mediated necrotizing myopathy – Polymyositis • Mixed connective tissue disorder • Polymyalgia rheumatica (PMR) • Psoriatic arthritis (PsA) • Relapsing polychondritis • Rheumatoid arthritis, including: – Rheumatoid arthritis associated conditions	• Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants, including: – Acute necrotising myelitis – Bickerstaff's brainstem encephalitis – Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) – Myelin oligodendrocyte glycoprotein antibody-associated disease – Neuromyelitis optica (also known as Devic's disease)	• Autoimmune/Immune-mediated glomerulonephritis, including: – IgA nephropathy – IgM nephropathy – C1q nephropathy – Fibrillary glomerulonephritis – Glomerulonephritis rapidly progressive – Membranoproliferative glomerulonephritis – Membranous glomerulonephritis – Mesangioproliferative glomerulonephritis

– Juvenile idiopathic arthritis – Palindromic rheumatism – Still's disease – Felty's syndrome • Sjogren's syndrome • Spondyloarthritis, including: – Ankylosing spondylitis – Juvenile spondyloarthritis – Keratoderma blenorrhagica – Psoriatic spondylitis – Reactive Arthritis – Undifferentiated spondyloarthritis • Systemic Lupus Erythematosus, including: – Lupus associated conditions (e.g., Cutaneous lupus erythematosus, Lupus nephritis, etc.) – Complications such as shrinking lung syndrome (SLS) • Systemic Scleroderma (Systemic Sclerosis), including: – Raynaud's syndrome – Systemic sclerosis with diffuse scleroderma – Systemic sclerosis with limited scleroderma (also known as CREST syndrome)	– Noninfective encephalitis/ encephalomyelitis / myelitis – Postimmunization encephalomyelitis • Guillain-Barré syndrome (GBS)*, including: – Variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN) • Idiopathic cranial nerve palsies/paresis and inflammations (neuritis), including: – Cranial nerve neuritis (e.g., Optic neuritis) – Idiopathic nerve palsies/paresis (e.g., Bell's palsy) – Melkersson-Rosenthal syndrome – Multiple cranial nerve palsies/paresis • Multiple Sclerosis (MS), including: – Clinically isolated syndrome (CIS) – Malignant MS (the Marburg type of MS) – Primary-progressive MS (PPMS) – Radiologically isolated syndrome (RIS) – Relapsing-remitting MS (RRMS) – Secondary-progressive MS (SPMS) – Uhthoff's phenomenon • Myasthenia gravis, including: – Ocular myasthenia – Lambert-Eaton myasthenic syndrome • Narcolepsy (with or without presence of unambiguous cataplexy) • Peripheral inflammatory demyelinating neuropathies and plexopathies, including – Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) – Antibody-mediated demyelinating neuropathy – Chronic idiopathic axonal polyneuropathy (CIAP) – Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants	– Tubulointerstitial nephritis and uveitis syndrome

	(e.g., multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) – Multifocal motor neuropathy (MMN) • Transverse myelitis (TM), including: – Acute partial transverse myelitis (APTM) – Acute complete transverse myelitis (ACTM)	
Skin and subcutaneous tissue disorders	**Vasculitis**	**Other (including multisystemic)**
• Alopecia areata • Autoimmune / Immune-mediated blistering dermatoses, including: – Bullous Dermatitis – Bullous Pemphigoid – Dermatitis herpetiformis – Epidermolysis bullosa acquisita (EBA) – Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease – Pemphigus • Erythema multiforme • Erythema nodosum • Lichen planus, including: – Liquen planopilaris • Localised Scleroderma (Morphoea) – Eosinophilic fasciitis (also called Shulman syndrome) • Psoriasis • Pyoderma gangrenosum • Reactive granulomatous dermatitis, including: – Interstitial granulomatous dermatitis – Palisaded neutrophilic granulomatous dermatitis • Stevens-Johnson Syndrome (SJS), including: – Toxic Epidermal Necrolysis (TEN) – SJS-TEN overlap • Sweet's syndrome, including: – Acute febrile neutrophilic dermatosis • Vitiligo	• Large vessels vasculitis*, including: – Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) – Giant cell arteritis (also called temporal arteritis) – Takayasu's arteritis • Medium sized and/or small vessels vasculitis*, including: – Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) – Behcet's syndrome – Buerger's disease (thromboangiitis obliterans) – Churg–Strauss syndrome (allergic granulomatous angiitis) – Erythema induratum (also known as nodular vasculitis) – Henoch-Schonlein purpura (also known as IgA vasculitis) – Microscopic polyangiitis – Necrotizing vasculitis – Polyarteritis nodosa – Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) – Granulomatosis with polyangiitis	• Anti-synthetase syndrome • Capillary leak syndrome – Frequently used related terms include: "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome" • Goodpasture syndrome – Frequently used related terms include: "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)" • Immune-mediated enhancement of disease, including: – Vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE) • Immunoglobulin G4 related disease

		• Langerhans' cell histiocytosis • Multisystem inflammatory syndromes, including: – Kawasaki's disease – Multisystem inflammatory syndrome in adults (MIS-A) – Multisystem inflammatory syndrome in children (MIS-C) • Overlap syndrome • Raynaud's phenomenon • Sarcoidosis, including: – Loefgren syndrome • Susac's syndrome

8.4.4.2. Atrial fibrillation

AEs of AF are considered as AESI in this study.

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

When there is enough evidence to make the above diagnosis, the AE must be reported as AESI. Symptoms, signs or conditions which might (or might not) represent the 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. The collection of AF will be performed following the AE/SAE reporting periods. The reporting of non-serious AF (Study participants in China only) 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.

8.4.5. Regulatory reporting requirements for SAEs/AESI (including pIMDs and AF)

- Prompt notification by the investigator to the sponsor of an SAE and/or AESI (including pIMDs and AF) 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 and/or AESIs (including pIMDs and AF), the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.5.6.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Table 17 Timeframes for submitting SAE and other events reports to GSK

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic 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
pIMDs	24 hours**‡	electronic AEs Report	24 hours*	electronic AEs Report

AE: Adverse event; AF: Atrial fibrillation; pIMD: potential immune-mediated disease; SAE: serious adverse event
*Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD.
‡Paper AEs Report will be dated and signed by the investigator (or designee). For each SAE/pIMD, the investigator(s) must document in the medical notes that they have reviewed the SAE/pIMD and have provided an assessment of causality.
†Only AF meeting SAE definition will be reported in electronic Expedited AE Report and in the specific AF follow-up questionnaire. Non-serious AF will be reported in the non-serious AE eCRF screen and in the AF follow-up questionnaire.

8.4.6. Contact information for reporting SAEs and AESIs (including pIMDs and AF)

Table 18 Contact information for reporting SAEs and AESIs (including pIMDs and AF)

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

8.4.7. 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 keep the participant card in his/her possession at all times throughout the study. In an emergency, this card serves to inform the responsible attending physician/caregiver that

the participant is in a clinical study and that relevant information may be obtained by contacting the investigator.

8.4.8. 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 10.4.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 10.4 of the protocol.

8.4.8.1. 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 10.4.

8.4.8.2. 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.

8.4.8.3. 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.

8.4.8.4. 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. Frailty status assessment

To characterize the study population and determine if frailty may influence the safety or immune response following administration of the study vaccine, the participants' frailty status will be assessed at study entry (refer to Definition of Terms for the definition of frailty). Data should be recorded in the eCRF.

The frailty status will be determined using the Gait speed test (frailty instructions will be provided in a separate reference guide).

8.6. Pharmacokinetics

PK is not evaluated in this study.

8.7. Pharmacodynamics

PD is not evaluated in this study.

8.8. Genetics

Genetics are not evaluated in this study.

8.9. Biomarkers

Biomarkers are not evaluated in this study.

8.10. Immunogenicity assessments

Immunogenicity is described in Section 8.2.

8.11. Health economics or medical resource utilization and health economics

Not applicable for this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

Statistical hypotheses provided in Table 19 are associated to the confirmatory co-primary NI objectives. Each hypothesis will be tested at 2.5% (1-sided), and no multiplicity adjustment is needed.

Table 19 Study null hypothesis

Null hypothesis	Description
H1	The GMT ratio for RSV-A neutralization titers (RSV OA group [Overseas] / RSV OA group [China]) is > 1.5 at 1 month post RSVPreF3 OA vaccine administration.
H2	The SRR difference for RSV-A neutralization titers (RSV OA group [Overseas] - RSV OA group [China]) is > 10% at 1 month post RSVPreF3 OA vaccine administration.
H3	The GMT ratio for RSV-B neutralization titers (RSV OA group [Overseas] / RSV OA group [China]) is > 1.5 at 1 month post RSVPreF3 OA vaccine administration.
H4	The SRR difference for RSV-B neutralization titers (RSV OA group [Overseas] - RSV OA group [China]) is > 10% at 1 month post RSVPreF3 OA vaccine administration.

GMT=Geometric mean titer; OA=Older adults; RSV=Respiratory syncytial virus; SRR=Seroresponse rate.

9.2. Analysis sets

Analysis sets are presented in Table 20.

Table 20 Analysis sets

Analysis set	Description
Screened Set	All participants who were screened for eligibility.
Enrolled Set	All participants who entered the study (who were randomized or received study intervention or underwent a post-screening study procedure). NOTE: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed to reach the target enrolment) are excluded from the Enrolled Set as they did not enter the study.
Exposed Set	All participants who received the study intervention. Analysis per group is based on the administered intervention.
Per-Protocol Set*	All eligible participants who received the study intervention as per protocol, had immunogenicity results pre- and post-dose, complied with blood draw intervals, without intercurrent conditions that may interfere with immunogenicity and without prohibited concomitant medication/vaccination. Analysis per group is based on the administered intervention.

* Contribution of participants to Per-Protocol Set will be defined by timepoint.

9.2.1. Criteria for elimination from analysis

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

Participants may be eliminated from the Per-Protocol Set 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

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

9.3.1. Primary endpoints/estimands analysis

Considering the sampling timepoint at 1 month post-study intervention administration, the 2-sided 95% CIs for group GMT ratios (RSV OA group [Overseas] / RSV OA group [China]) will be derived from an ANCOVA model on log_{10}-transformed titers for each neutralization titers. The model will include the group and the baseline log_{10}-transformed titer as covariate.

The SRR is defined as the proportion of participants having at least a 4-fold increase in neutralizing titers (1 month post-study intervention administration over pre-study intervention administration ≥4). The 2-sided 95% CIs for group SRR difference (RSV RSV OA group [Overseas] - OA group [China]) will be derived using the method of Miettinen and Nurminen [Miettinen, 1985].

Missing data will not be imputed.

NI for co-primary objectives will be claimed to be successful if the upper limit of the 2-sided 95% CI for the GMT ratio will be ≤1.5 and the upper limit of the 2-sided 95% CI for the SRR difference will be ≤ 10% for both RSV-A and B.

The primary analysis set will be the PPS.

9.4. Interim analyses

9.4.1. Sequence of analyses

The analyses will be performed stepwise:

- **Day 31 (PCA)**: The first analysis will be performed when immunogenicity and reactogenicity data up to Visit 2 (Day 31) are available. This analysis will be considered as final for those data. Safety data up to database lock point will also be included into the analysis.

  The analysis will be performed by study statistician who will be unblinded to the details of the treatment assignments at the time of the Day 31 analysis. Refer to Section 6.4 for details of blinding and unblinding procedures.

- **Month 6 Safety Analysis**: An optional analysis may be conducted when safety data up to Month 6 are available.
- **End of Study Analysis:** The final analysis will be performed when all data for the secondary endpoints of descriptive immunogenicity at Month 6, ARI surveillance and safety up to study conclusion are available.

9.4.2. Statistical considerations for interim analysis

Not applicable.

9.5. Sample size determination

The target sample size for the study is approximately 2600 participants: i.e. 1800 participants in China [2:1 randomization allocation between RSV OA group (China) and Placebo group (China)], 800 participants in RSV OA group (Overseas).

The sample size in the groups receiving the investigational vaccine is driven by need to meet local regulatory requirements and the statistical power to prove the primary NI objectives.

Based on a sensitivity analysis for the study power (Table 21), the sample size is able to provide ≥ 90% power to demonstrate the primary NI objectives in RSV OA group (China) compared to the RSV OA group (Overseas) for all the scenarios presented, assuming an attrition rate of 10%:

- The Power of the NI testing for the GMT is calculated by SAS 9.4 using the two-sample t-test for non-inferiority assuming equal variance.
- The Power of the NI testing for the SRR is calculated by SAS 9.4 using the non-inferiority tests for the difference between two proportions applying the method of Miettinen and Nurminen.

Table 21 Sensitivity analysis for the power of co-primary NI testing

	Statistical Assumptions				Individual Powers				Overall Power
Hypothesis	**H1**	**H2**	**H3**	**H4**	**H1**	**H2**	**H3**	**H4**	
Endpoint	**GMR***	**SRR****	**GMR***	**SRR****	**GMR**	**SRR**	**GMR**	**SRR**	
Scenario 1	1.06	80.3%, 82.3%	1.10	76.7%, 73.4%	100%	100%	100%	90.5%	90.5%
Scenario 2	1.11	80.3%, 83.2%	1.14	76.7%, 75.0%	100%	100%	100%	98.2%	98.2%
Scenario 3	1.17	80.3%, 84.5%	1.18	76.7%, 77.0%	99.9%	100%	99.8%	99.9%	99.6%
Scenario 4	1.17	81.7%, 83.2%	1.19	77.4%, 75.0%	99.9%	100%	99.6%	96.5%	96.0%

H1, H2, H3, H4 = Null hypothesis 1, 2, 3 and 4 respectively.

* GMR is the geometric mean titer ratio of RSV OA group (Overseas) / RSV OA group (China). Its individual level standard deviation of log10 titers for RSV neutralization is assumed as 0.45.

** The values are the assumed seroresponse rate in the RSV OA group (Overseas) and RSV OA group (China), respectively.
SRR = Seroresponse rate.
The assumptions are based on the data from RSV OA=ADJ-004 study.

Participants who withdraw from the study will not be replaced.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

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

10.1.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate

financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants 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 local regulations, ICH guidelines, 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.

10.1.4. Recruitment strategy

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

- Approximately 40% of participants 60-69 YOA, approximately 30% of participants 70-79 YOA and approximately 10% of participants ≥ 80 YOA. The remaining 20% can be distributed freely across the 3 age categories.
- Approximately 40% of participants from each sex; the remaining 20% can be distributed freely between the 2 sexes.

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 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 data will be used as described in the informed consent.

- The participant must be informed that medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

10.1.6. Committees structure

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country. This includes IRBs/IECs for review and approval of the protocol and subsequent amendments, ICF and any other documentation.

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 contributes to the continual assessment of incoming new efficacy and blinded safety information.

10.1.7. Dissemination of Clinical Study Data

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

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

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the quality plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan and/or contracts.
- 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 15 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.

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 source data acknowledgment or monitoring guidelines.
- 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.

10.1.10. Study and site start and closure

Start of study and first act of recruitment

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

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any

contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication policy

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

10.2. Appendix 2: Clinical laboratory tests

10.2.1. Laboratory assays for immune response

RSV A/B neutralization assay

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

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

10.2.2. Laboratory assays for molecular biology

RT-PCR able to discriminate RSV A and RSV B subtypes

Briefly, RSV A and RSV B RNAs extracted from the nasal/throat swabs are detected in a duplex RT-PCR format using specific amplification primers and fluorescent probes designed in the RSV N gene, encoding the RSV nucleocapsid protein. The process

involves nucleic acids extraction, conversion of RNA to complementary deoxyribonucleic acid by reverse transcription and detection by real-time PCR reaction using a calibration curve.

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). • "Lack of efficacy" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
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:

a. Results in death

b. 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.

c. 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.

d. 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.

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 diary. The following administration site events will be solicited: • Pain at administration site • Erythema at administration site • Swelling at administration site The following systemic events will be solicited: • Fever • Headache • Myalgia (muscle pain) • Arthralgia (joint pain) • Fatigue (tiredness)

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 AESIs (including pIMDs and AF)

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.

A Diary will be used in this study to capture solicited administration site or systemic events. The study participant in China should be trained on how and when to complete the Diary.

Anyone who measures administration site or systemic events and who will record the event in the Diary should be trained on using the Diary. This training must be documented in the participant's source record.

For each solicited and unsolicited AE the study participant in China experiences, the participant will be asked if they received medical attention (defined as unscheduled visit to or from medical personnel for any reason, including emergency room visits). This information will be recorded in the participant's diary and in the participant's eCRF as part of normal AE reporting (for solicited and unsolicited AEs). Medical attention received for SAEs/AESIs will have to be reported using the normal AE reporting process in the eCRF.

If the collection of solicited AEs was not possible for any reasons via the Diary and solicited AEs were reported to the investigator by the study participant in China, 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 (including pIMDs and AF) will have to be reported using the normal AE reporting process in the eCRF.

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

All AEs that occur during 30 days (for participants in China) following administration of the dose of study intervention (Day 1 to Day 30) must 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.

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

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

10.3.5.2. Assessment of intensity

The investigator will make an assessment of intensity for each AE, AESI (including pIMDs and AF) 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 22 Intensity scales for solicited events in participants in China

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 at administration site		Greatest surface diameter in mm
Swelling at administration site		Greatest surface diameter in mm
Temperature*		Temperature in °C
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

Event	Intensity grade	Parameter
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

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

Intensity grade	Erythema/Swelling	Fever
0	≤20 mm	<37.3°C
1	>20 - ≤50 mm	≥37.3°C - <38.0°C
2	>50 - ≤100 mm	≥38.0°C - <38.5°C
3	>100 mm	≥38.5°C

*Fever is defined by axillary route as per Chinese guidelines [Grading Criteria for Adverse Events in Clinical Trials of Preventive Vaccines issued by NMPA in Dec 2019].

10.3.5.3. Assessment of causality

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

10.3.5.4. Assessment of outcomes

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

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

10.3.5.5. Follow-up of AEs, SAEs, AESIs (including pIMDs and AF), 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.
- 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 postmortem findings including histopathology.
- 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 (including pIMDs and AF) 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 end of the study or until the participant is lost to follow-up.

Follow-up during the study

AEs/AESIs (including pIMDs and AF) documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until end of study period.

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.

10.3.5.6. Updating of SAE and AESI (including pIMDs and AF) information after removal of write access to the participant's eCRF

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

10.3.5.7. Reporting of SAEs and AESIs (including pIMDs and AF)

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 8.4.6.

SAE Reporting to GSK via Paper Data Collection Tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the GSK/medical monitor.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.4.6.

10.4. Appendix 4: 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.

10.4.1. 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.

10.4.2. 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).

10.4.3. 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.

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

10.4.4.1. 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.

10.4.4.2. Assessment of intensity

Refer to Section 10.3.5.2.

10.4.4.3. Assessment of causality

Refer to Section 10.3.5.3.

10.4.4.4. 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.

10.4.5. 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 8.4.6.

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 8.4.6.

10.4.6. 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 8.4.6.

10.4.7. 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 8.4.6 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.

10.5. Appendix 5: Country-specific requirements

10.5.1. China

Testing, analysis and destruction of Human Genetic Resource (HGR) Materials

Units list for HGRs testing and analysis and sample destruction.

Units for HGRs testing and analysis	Units for sample destruction
Investigator Sites PPD Laboratories (Suzhou) Co., Ltd.	Investigator Sites PPD Laboratories (Suzhou) Co., Ltd. Zhangjiagang Huarui Hazardous Wastes Treating Center Co., Ltd.

All above units are located in mainland China.

10.5.2. Japan

Regulatory and ethical considerations

The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27 March 1997)" and Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices.

The statement *"I agree to assume responsibility for the proper conduct of the study at this site."* On the Investigator Protocol Agreement Page means the investigator's responsibility as defined by Japanese GCP.

GSK Japan will submit the CTN to the regulatory authorities in accordance with Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Device before conclusion of any contract for the conduct of the study with study sites.

Study administrative structure

Sponsor Information and List of Medical Institutions and Investigators are included in Exhibit 1.

10.5.3. Republic of Korea

Exclusion criteria for enrollment of study participant

As per local Regulation on Approval for Enforcement Regulation on the Safety of Pharmaceuticals, etc., Article 24 paragraph 2, a study participant cannot be enrolled in a trial if he or she has "participated as a subject in a clinical trial targeting healthy people within the last 6 months."

Therefore, in order to comply with this local requirement, investigators from Republic of Korea should carefully check, before enrolling each participant in the study, that they have not participated in any other clinical study targeting healthy people within the last 6 months prior to enrolment/first study vaccination.

10.5.4. Countries in the EU

Statement for EU submission

Chinese participants may be enrolled one year later than overseas participants. Due to local requirements for sample import, it would take approximately one year for the serum samples transferred from overseas countries to China Lab for neutralization testing. For that reason, data from China arm and Lab might not be available for statistical analysis in due time to make it possible to submit a summary of the study results within one year of LSLV in Europe. The summary of results and a summary of laypersons will be submitted as soon as available.

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