Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals SA
Rue de l'Institut, 89
1330 Rixensart, Belgium

Primary Study vaccine	GlaxoSmithKline Biologicals SA (GSK)'s investigational respiratory syncytial virus (RSV) vaccine BIO RSV OA=ADJ (GSK3844766A)
Other Study vaccine	Placebo: Saline solution
eTrack study number and abbreviated title	212494 (RSV OA=ADJ-006)
EudraCT number	2020-000753-28
Date of protocol	Final: 16 October 2020
Date of protocol amendment	Amendment 1 Final: 25 February 2021 Amendment 2 Final: 6 October 2021 Amendment 3 Final: 24 January 2022 Amendment 4 Final: 23 March 2023 ***Amendment 5 Final: 12 July 2023***
Title *(Amended, 12 July 2023)*	A Phase 3, randomized, placebo-controlled, observer blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above.
Short title	Efficacy study of GSK's investigational respiratory syncytial virus (RSV) vaccine in adults aged 60 years and above.

Based on GSK Biologicals' Protocol WS v17.0

Protocol Amendment *5* Sponsor Signatory Approval

eTrack study number and Abbreviated Title	212494 (RSV OA=ADJ-006)
EudraCT number	2020-000753-28
Date of protocol amendment	Amendment ***5*** Final***: 12 July 2023***
Title (***Amended, 12 July 2023***)	A Phase 3, randomized, placebo-controlled, observer blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above.
Sponsor signatory	Marie Van Der Wielen***, MD*** Clinical Project Lead RSV Older Adults (***Amended, 12 July 2023***)
Signature	_____
Date	_____

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

Protocol Amendment *5* Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals SA.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study vaccine and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site.
- To ensure that any individual or party to whom I have delegated trial-related duties and functions conducted at the trial site are qualified to perform those trial-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 written informed consent of the participant.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representatives of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the trial.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational vaccine, and more generally about his/her financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of 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 other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	212494 (RSV OA=ADJ-006)
EudraCT number	2020-000753-28
Date of protocol amendment	Amendment ***5*** Final***: 12 July 2023***
Title *(Amended, 12 July 2023)*	A Phase 3, randomized, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above.
Investigator name	_____
Signature	_____
Date	_____
PPD PPD **name, function and title**	_____
Signature	_____
Date	_____
GSK Japan study representative name, function and title	_____
Signature	_____
Date	_____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Central Back-up Study Contact for Reporting SAEs: refer to the protocol section 8.3.4.

Study Contact for Reporting SAEs: refer to the local study contact information document.

5. GSK Biologicals' Helpdesk for Emergency Unblinding

Refer to the protocol section 6.3.5.1.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document history

Document	Date
Amendment 5	12 July 2023
Amendment 4	23 March 2023
Amendment 3	24 January 2022
Amendment 2	6 October 2021
Amendment 1	25 February 2021
Original Protocol	16 October 2020

Amendment 5:

This amendment is considered substantial based on the criteria defined in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because of significant changes in the conduct or management of the study.

Overall rationale for the current Amendment:

The purpose of this amendment is to remove Dose 3 administration before the start of Season 3 for participants in the NH and to add a blood sample at Visit 5NH for all participants who are not in the reactogenicity and immunogenicity subset.

The results of VE Analysis 3 evaluating efficacy and safety of RSVPreF3 OA investigational vaccine up to the end of Season 2 in the NH, showed that a single dose of the RSVPreF3 OA investigational vaccine was efficacious against RSV-confirmed LRTD and severe LRTD over 2 RSV seasons. The VE against RSV-confirmed LRTD was 67.18% [97.5% CI: 48.19, 80.04]. The VE against severe LRTD was 78.83% (95% CI: 52.59, 91.96).

The study also evaluated efficacy following an annual revaccination schedule. Over 2 seasons, the VE in participants who received a second dose of the vaccine before Season 2 was similar to the VE in participants who had received a single dose of vaccine prior to Season 1 with VE of 67.12% (97.5% CI: 48.09, 80.00) against RSV-confirmed LRTD. These data suggest that a revaccination administered approximately 12 months after the first dose does not confer additional benefit for the overall population. The optimal timing for revaccination still needs to be determined.

Safety and reactogenicity data post-Dose 2 were consistent with previous results from the Phase 3 program. Based on available reactogenicity and safety data up to the end of Season 2 in the NH (DLP 31 March 2023), with a median follow-up time from Dose 1 up to DLP of approximately 18.2 months, and from Dose 2 up to DLP of approximately 6.7 months, the RSVPreF3 OA investigational vaccine showed a clinically acceptable safety profile in adults ≥ 60 YOA. The reactogenicity of the RSVPreF3 OA investigational vaccine was similar following each dose, with most of the solicited events being mild to moderate and of short duration. No safety concerns were identified with currently available data.

Based on these observations, the study design was modified to remove the next planned dose of the study intervention (Dose 3 pre-Season 3) in the NH. The clinical development program will continue to evaluate long-term follow-up and the optimal timing for revaccination.

To evaluate further the correlation between humoral immune response and protection, an additional blood sample has been added at Visit 5NH for all participants who are not in the reactogenicity and immunogenicity subset.

This amendment does not impact participants enrolled in the SH as they have completed the 2 doses of study intervention as per study design.

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

Other updates are described in the table below:

List of main changes in the protocol and their rationale

Section # and title	Description of change	Brief rationale
Title page; sponsor approval page; investigator agreement page 3. Objectives and endpoints 7.1 Discontinuation of study intervention 9.4.4.4 Quality of life	'Annual revaccination doses' has been changed to 'Annual revaccination' and 'Annual revaccinations' has been changed to 'Annual revaccination'.	As Dose 2 pre-Season 2 administered 12 months post-Dose 1 did not confer additional benefit in prevention of RSV-confirmed LRTD, the study design was modified to remove the next planned dose of the study vaccine (Dose 3 pre-Season 3). These sections were thus updated to reflect this change.
1.1 Synopsis 2.1 Study rationale 2.2 Background 4.2.2 Rationale for the use of Placebo	Clinical development status of GSK's RSVPreF3 OA investigational vaccine has been updated. Marketing authorization approval of the study vaccine has been added.	As GSK's RSVPreF3 OA investigational vaccine is now approved for use, the clinical development status of the study vaccine was modified from 'developing' to 'developed' and the market authorization approval details have been added.
1.3 Schedule of activities (Table 1, Table 2, Table 4 and Table 5)	For Table 1, table title has been revised to indicate that activities listed in this table is applicable for participants in the NH who have their Visit 5NH before the approval of the current Protocol Amendment 5. A new table has been added for the schedule of activities for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 (Table 2). Intervals between study visits/contact for participants in the NH have been modified. Corrections have been made in the table footnotes to align with the changes made in the tables. Section has been updated to reflect that a blood sample will be taken at Visit 5NH from all participants in the NH who have their Visit 5NH after the approval of the current Protocol Amendment 5. Option for use of paper questionnaire for atrial fibrillation has been removed. Corrections in the footnotes were made to algin with the changes made in the table.	To align with the changes made to the study design with respect to removal of Dose 3 (pre-Season 3) and study procedures related to Dose 3 administration. Blood samples collection from all participants in the NH at Visit 5NH (pre-Season 3) was added to allow for further assessment of correlation between humoral immune response and protection. As only electronic questionnaires will be used for follow-up of atrial fibrillation, the option for paper questionnaire was removed.
2.3 Benefit/Risk assessment 2.3.2 Benefit assessment	Updated to clarify the current status of VE assessment and clinical benefit provided to participants.	Since initial protocol approval, VE data has become available at VE Analysis 3. This section was thus updated to reflect this information.

Section # and title	Description of change	Brief rationale
3 Objectives and endpoints	The secondary confirmatory objectives have been modified to indicate that efficacy would be assessed for only 1 annual revaccination before Season 2. The term 'pre-Dose 3' has been removed from the secondary and tertiary immunogenicity endpoints.	To align with the changes made to the study design with respect to removal of Dose 3 (pre-Season 3) and study procedures related to Dose 3 administration.
3 Objectives and endpoints	Tertiary endpoint pertaining to assessment of correlate of protection has been modified in indicate that RSVPreF3 IgG-binding antibody concentration will also be assessed at pre-Season 3 for all participants in the NH.	To allow for further assessment of correlation between humoral immune response and protection.
4 Study design 4.1 Overall study design (Figure 1)	Study design has been updated to clarify that at Visit 5NH (pre-Season 3) participants who will have their Visit 5NH before the approval of Protocol Amendment 5 will receive the study intervention as planned according to their group allocation. Participants having their Visit 5NH after approval of the current Protocol Amendment 5 will not receive any study intervention at pre-Season 3 visit (Visit 5NH). Dose 3 at Visit 5NH (pre-Season 3), Visit 6NH and Contact 5 have been removed from the study design figure.	To align with the changes made to the study design with respect to removal of Dose 3 (pre-Season 3) and study procedures related to Dose 3 administration.
4.1 Overall study design 8.1.3.2 Biological samples for immunogenicity assessment 8.1.5 Immunological read-outs 8.1.7 Immunological correlates of protection 9.4.5.4.1 Correlate of protection	This section have been updated to reflect that a blood sample will be collected from all participants in the NH at Visit 5NH (pre-Season 3). Volume of blood sample to be collected from participants in the NH has been added.	To allow for further assessment of correlation between humoral immune response and protection.
4.2 Scientific rationale for the study design	Updated to include the rationale for removing Dose 3 administration from the study design.	To support the changes made to the study design with respect to removal of Dose 3 and study procedures related to Dose 3 administration.
6.1 Study intervention administered 6.3.2 Randomization to study intervention 6.3.4 Allocation of participants to assay subsets 6.5 Concomitant therapy 7.1.2 Contraindications to subsequent vaccine administration	Updated to reflect that for participants in the NH who have their Visit 5NH after the approval of the current Protocol Amendment 5, administration of Dose 3 at Visit 5NH (pre-Season 3) as well as all study procedures related to Dose 3 administration have been cancelled.	As Dose 2 administered 12 months post-Dose 1 did not confer additional benefit in prevention of RSV-confirmed LRTD, the study design was modified to remove the next planned dose of the study vaccine (Dose 3 pre-Season 3).

Section # and title	Description of change	Brief rationale
8.2.1.7 Distribution of paper diary cards 8.2.2.3 Lung auscultation 10.3.8 Recording and follow-up of AEs, SAEs, AESIs (including pIMDs and AF)		
8.1.1.5 Scheduled site staff contacts	Figure 2 and its corresponding footnote has been updated to correct typographical errors. Visit 5SH was erroneously indicated as Visit 4SH both in the Figure and footnote and Visit 7NH was erroneously indicated as Visit 6NH.	To correct typographical error.
8.3.1 Time period and frequency for collecting AE, SAE and other safety information	Safety information related to Dose 3 administration, collected at Day 1 - 4, Day 30 and Month 6 post-Dose 3 have been removed for participants in NH who have their Visit 5NH after the approval of the current Protocol Amendment 5 and will not receive any study intervention at pre-Season 3 visit (Visit 5NH).	To align with changes in the study design related to removal of Dose 3 (pre-Season 3).
9.1.2 Secondary objectives 9.2.2 Secondary objectives 9.4.4.1 Efficacy 9.4.5.1 Efficacy	The secondary confirmatory objectives, endpoints, and analyses have been modified to indicate that efficacy would be assessed for only 1 annual revaccination before Season 2. The term 'pre-Dose 3' has been removed from the secondary and tertiary immunogenicity endpoints. A note has been added to clarify that participants who received Dose 3 of the study vaccine will not be included in the evaluation of VE of the annual revaccination over 3 season. The expected total number of RSV LRTD cases and the power for each analysis provided in Table 28 have been updated. The expected number of RSV-confirmed LRTD cases for the evaluation of VE of the annual revaccination for Season A3NH provided in Table 30 have been updated.	This section has been updated to align with the changes made in the secondary confirmatory objectives.
9.3 Populations for analyses	The following note has been added: Exposed Set Dose 2 and Exposed Set Dose 3 including all participants who received the 2nd and the 3rd dose, respectively, will also be used to report analysis on post-dose 2/3 data.	To account for data collected from participants in the NH who will have their Visit 5NH before the approval of the Protocol Amendment 5 and will receive Dose 3 of the study interventions at pre-Season 3 visit (Visit 5NH).

Section # and title	Description of change	Brief rationale
	A note has been added to clarify that participants who received Dose 3 of the study vaccine will not be included in the evaluation of VE of the annual revaccination over 3 season.	In addition, the section has been updated to align with the changes made in the secondary confirmatory objectives.
9.5.1 Sequence of analyses	Formatting error in the numbering of analyses steps has been corrected.	To correct typographical error.
10.5.1 List of Abbreviations	Updated to change mg to µg.	To correct typographical error.

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1. PROTOCOL SUMMARY

1.1. Synopsis (Amended, 12 July 2023)

Rationale:

GlaxoSmithKline Biologicals SA (GSK) ***has developed a new RSV PreFusion protein F3 Older Adult (***RSVPreF3 OA***) vaccine*** against RSV-associated (subtypes A and B) disease in adults ≥ 60 years of age (YOA).

The purpose of this study is to demonstrate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of reverse-transcriptase polymerase chain reaction (RT-PCR)-confirmed lower respiratory tract disease (LRTD) caused by RSV A and/or B in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA vaccine and following annual revaccination doses. The vaccine cross-protection against RT-PCR-confirmed LRTD caused by human metapneumovirus (hMPV) will also be evaluated. In addition, the safety and immunogenicity of the vaccine will be assessed after each dose.

Surveillance for acute respiratory illness (ARI) will be carried out during the entire study via spontaneous reporting by the study participant (starting on the first vaccination day [Visit 1]) and via scheduled site staff contacts (as of Visit 2 onwards).

Based on the first results obtained in the Phase 1/2 dose formulation selection study for the RSVPreF3 OA investigational vaccine (RSV OA=ADJ-002), RSVPreF3 recombinant antigen 120 µg adjuvanted with $AS01_E$ as a single dose was selected for further evaluation in the Phase 3 program.

Objectives and endpoints:

Refer to Table 8 in Section 3 for an overview of the study objectives and endpoints.

1.2. Schema

Refer to Figure 1 for an overview of the study design.

1.3. Schedule of activities (Amended, 12 July 2023)

For participants who will have the Visit 5NH (pre-Season 3 visit) taking place BEFORE the approval of this Protocol Amendment 5, the study procedures should be performed according to the previously approved protocol amendment version. Refer to Table 1 for details.

For participants who will have the Visit 5NH (pre-Season 3 visit) taking place AFTER the approval of this Protocol Amendment 5, the study procedures should be performed according to the current Protocol Amendment 5: Dose 3 administration should be cancelled as well as other procedures related to Dose 3 administration. Visit 6NH and Contact 5 should be cancelled for these participants. Blood sample should be collected for all participants at Visit 5NH. Refer to Table 2 for details.

Timeframe for Visit 5NH are defined in Table 5.

Table 1 Schedule of activities for participants in Northern hemisphere that have their Visit 5NH BEFORE approval of this Protocol amendment 5 (Amended, 12 July 2023)

Type of contact for NH[1]	**V1**	**V2**	**C1[2]**	**C2**	**V3**	**V4**	**C3[2]**	**C4**	**V5NH**	**V6NH**	**C5[2]**	**V7NH**	**Notes for more information and details**
Timepoint	**Day 1 Dose 1**	**Day 31 Post-D1**	**Month 6 Post-D1**	**End S1**	**Pre S2 Dose 2**	**Day 31 Post-D2**	**Month 6 Post-D2**	**End S2**	**Pre S3 Dose 3**	**Day 31 Post-D3**	**Month 6 Post-D3**	**End S3**	
Study participant informed consent	●[3]												See Section 10.1.3
Study participant informed consent for annual revaccinations[4]					●								
Distribution of participant card	○												See Section 8.3.6
Check inclusion/exclusion criteria	●												See Sections 5.1 and 5.2
Check with participant if he/she will appoint a caregiver and distribute information letter(s) to caregiver, when applicable	○	○			○	○			○	○			See Sections 5.3 and 10.1.3
Baseline and demography assessments													
Collect demographic data	●												See Section 8.2.1.1
Measure/record height and weight	●												See Section 8.2.1.2
Record medical history	●												See Section 8.2.1.3
Record history of vaccine administration[5]	●												See Section 8.2.1.4
Physical examination/Vital signs	●	○[6]			●	○[6]			●	○[6]		○[6]	See Section 8.2.2
Lung auscultation	○	○[6]			○	○[6]			○	○[6]		○[6]	See Section 8.2.2.3
Record oxygen saturation	●				●				●				See Section 8.2.2.4
Record smoking status and smoking exposure history (including electronic smoking devices)	●												See Section 8.2.1.5. Refer to Section 10.5.2 for definitions of current and former smoker.
Clinical specimens for laboratory assays													
Blood sampling in all participants (~20 mL)	●[7]	●											See Section 8.1.3.2
Blood sampling in subset (~20 mL)[8]					●[7]				●[7]				See Section 8.1.3.2

Type of contact for NH[1]	V1	V2	C1[2]	C2	V3	V4	C3[2]	C4	V5NH	V6NH	C5[2]	V7NH	Notes for more information and details
Timepoint	**Day 1 Dose 1**	**Day 31 Post-D1**	**Month 6 Post-D1**	**End S1**	**Pre S2 Dose 2**	**Day 31 Post-D2**	**Month 6 Post-D2**	**End S2**	**Pre S3 Dose 3**	**Day 31 Post-D3**	**Month 6 Post-D3**	**End S3**	
Vaccine(s)													
Check criteria for temporary delay for enrollment and/or vaccination	○				○				○				See Section 7.1.1
Check contraindications to vaccination					○				○				See Section 7.1.2
Study group and intervention number allocation	○				○				○				See Sections 6.3.2 and 6.3.3
Record pre-vaccination body temperature	●				●				●				The route for measuring temperature can be oral, axillary or tympanic (see Section 8.2.1.6).
Vaccine administration (including 30-minute post-vaccination observation)	●				●				●				See Section 6.1
Safety assessments													
Distribute paper diary cards[9]	○				○				○				See Section 8.2.1.7
Return of paper diary cards		○				○				○			See Section 10.3.8
Record solicited administration site and systemic events (Days 1-4) in the reactogenicity subset	●	●			●	●			●	●			See Section 10.3.8
Record unsolicited AEs (Days 1-30) in all participants[11]	●	●			●	●			●	●			See Section 10.3.8
Record concomitant medications/vaccinations	●	●	●	●	●	●	●	●	●	●	●	●	See Table 15 for specific collection period and Section 6.5
Record intercurrent medical conditions	●	●	●	●	●	●	●	●	●	●	●	●	See Section 9.3.1.1
Record all SAEs and pIMDs[11]	●	●	●		●	●	●		●	●	●		See Section 10.3.8
Record fatal SAEs, SAEs related to study vaccination, COVID-19 cases and pIMDs related to study vaccination[11]	●	●	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8
Record AEs/SAEs leading to withdrawal from the study	●	●	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8

Type of contact for NH[1]	V1	V2	C1[2]	C2	V3	V4	C3[2]	C4	V5NH	V6NH	C5[2]	V7NH	Notes for more information and details
Timepoint	**Day 1 Dose 1**	**Day 31 Post-D1**	**Month 6 Post-D1**	**End S1**	**Pre S2 Dose 2**	**Day 31 Post-D2**	**Month 6 Post-D2**	**End S2**	**Pre S3 Dose 3**	**Day 31 Post-D3**	**Month 6 Post-D3**	**End S3**	
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine[10]	●	●	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8
ARI surveillance													
Instruct/remind participants of ARI surveillance	○	○	○	○	○	○	○	○	○	○	○		See Section 8.1.1
Nasal self-swab training with the study participant		○											See Section 8.1.1.1.1
Distribute material for nasal self-swab collection (including instructions)		○			○				○				See Section 8.1.1
Frailty status													
Assess frailty status with Gait Speed test	●												See Section 8.4
HR-QoL questionnaires													
Distribute the daily health questionnaires for participants to complete at home in case of ARI		○			○				○				See Section 8.10.1
Completion of daily health questionnaires by the participant		●											See Section 8.10.1
Completion of EQ-5D and SF-12 questionnaires by the participant	●				●				●				See Section 8.10.1
Study conclusion for NH												●	See Section 4.4

Note: The double-line borders indicate the analyses, which will be performed on data that are as clean as possible: VE Analysis 2 at the end of Season 1 in NH, Safety analysis when all safety data up to 6 months post-Dose 1 will be available for all participants in NH and SH, VE Analysis 3 after at least 2 seasons in NH and 1 season in SH, and VE Analysis ***6*** after 3 seasons in NH and 2 seasons in SH (end of study). VE Analysis 1 will be case-driven. ***Additional analyses, not indicated in this table, will be performed as detailed in*** Section 9.5.1.

Note: If following the sample size re-assessment an additional cohort needs to be enrolled before the next season in NH (see Section 9.2.3), the participants enrolled in this cohort will follow the same schedule of activities as indicated in this table.

ARI: acute respiratory illness; C: Contact; D: Dose; EQ-5D: EuroQol 5-dimension health questionnaire; HR-QoL: health-related quality of life; pIMDs: potential immune-mediated diseases; S: Season; SAE: serious adverse event; SF-12: Short Form 12-item health survey; Pre-S1: pre-Season 1; Pre-S2: pre-Season 2; Pre-S3: pre-Season 3***;*** V: Visit

● 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. Study visits should preferably be done on site or in the LTCF. If deemed necessary, study visits can be done at home. 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, or via a visit for LTCF participants. 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. Contacts 1, 3 and 5 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months after each vaccination for each participant. These contacts can be combined with another contact or visit.
3. Freely given and written informed consent must be obtained from each study participant prior to participation in the study. The participant's informed consent may be obtained prior to Visit 1. ***In addition, participants should sign the ICF addendum for revaccination (Protocol Amendment 3) at Visit 3.***
4. In case the participant does not agree to continue the study for the annual revaccination, the study conclusion page of the eCRF should be completed.
5. Any vaccination administered up to 1 year before administration of the first study vaccine dose should be recorded in the eCRF. Administration of *Shingrix* at any timepoint (even if longer than 1 year before the first study vaccination) should be recorded in the eCRF.
6. If deemed necessary by the investigator.
7. The blood samples at Visits 1, 3 and 5NH should be taken prior to vaccine administration.
8. These blood samples should only be taken from participants in the reactogenicity and immunogenicity subset.
9. A paper diary will be distributed to all study participants on each vaccination day (at Visits 1, 3 and 5NH). All participants will record unsolicited AEs and concomitant medications/products on the day of each vaccination and for 29 subsequent days (Days 1-30). In addition, participants in the reactogenicity subset will be asked to record solicited events on the day of each vaccination and for 3 subsequent days (Days 1-4).
10. SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to administration of the first study vaccine dose) up to study end.
11. 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) in eCRF. The collection of AF will be performed following the AE/SAE reporting periods. For AF that were reported before the implementation of ***the*** Protocol Amendment 4, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

Table 2 ***Schedule of activities for participants in Northern hemisphere that have their Visit 5NH AFTER the approval of this Protocol Amendment 5 (Amended, 12 July 2023)***

Type of contact for NH[1]	V1	V2	C1[2]	C2	V3	V4	C3[2]	C4	V5NH	V6NH[11]	C5[11]	V7NH	Notes for more information and details
Timepoint	**Day 1 Dose 1**	**Day 31 Post-D1**	**Month 6 Post-D1**	**End S1**	**Pre S2 Dose 2**	**Day 31 Post-D2**	**Month 6 Post-D2**	**End S2**	**Pre S3 Dose 3**	**Day 31 Post-D3**	**Month 6 Post-D3**	**End S3**	
Study participant informed consent	●[3]												See Section 10.1.3
Study participant informed consent for annual revaccination					●								
Study participant informed consent addendum for Protocol Amendment 5									●				
Distribution of participant card	○												See Section 8.3.6
Check inclusion/exclusion criteria	●												See Sections 5.1 and 5.2
Check with participant if he/she will appoint a caregiver and distribute information letter(s) to caregiver, when applicable	○	○			○	○			○				See Sections 5.3 and 10.1.3
Baseline and demography assessments													
Collect demographic data	●												See Section 8.2.1.1
Measure/record height and weight	●												See Section 8.2.1.2
Record medical history	●												See Section 8.2.1.3
Record history of vaccine administration[4]	●												See Section 8.2.1.4
Physical examination/Vital signs	●	○[5]			●	○[5]			●			○[5]	See Section 8.2.2
Lung auscultation	○	○[5]			○	○[5]			○			○[5]	See Section 8.2.2.3
Record oxygen saturation	●				●				●				See Section 8.2.2.4
Record smoking status and smoking exposure history (including electronic smoking devices)	●												See Section 8.2.1.5. Refer to Section 10.5.2 for definitions of current and former smoker.

Type of contact for NH[1]	V1	V2	C1[2]	C2	V3	V4	C3[2]	C4	V5NH	V6NH[11]	C5[11]	V7NH	Notes for more information and details
Timepoint	**Day 1 Dose 1**	**Day 31 Post-D1**	**Month 6 Post-D1**	**End S1**	**Pre S2 Dose 2**	**Day 31 Post-D2**	**Month 6 Post-D2**	**End S2**	**Pre S3 Dose 3**	**Day 31 Post-D3**	**Month 6 Post-D3**	**End S3**	
Clinical specimens for laboratory assays													
Blood sampling in all participants (~20 mL)	●[6]	●							●[12]				See Section 8.1.3.2
Blood sampling in subset (~20 mL)[7]					●[6]								See Section 8.1.3.2
Vaccine(s)													
Check criteria for temporary delay for enrollment and/or vaccination	○				○								See Section 7.1.1
Check contraindications to vaccination					○								See Section 7.1.2
Study group and intervention number allocation	○				○								See Sections 6.3.2 and 6.3.3
Record pre-vaccination body temperature	●				●								The route for measuring temperature can be oral, axillary or tympanic (see Section 8.2.1.6).
Vaccine administration (including 30-minute post-vaccination observation)	●				●								See Section 6.1
Safety assessments													
Distribute paper diary cards[8]	○				○								See Section 8.2.1.7
Return of paper diary cards		○				○							See Section 10.3.8
Record solicited administration site and systemic events (Days 1-4) in the reactogenicity subset	●	●			●	●							See Section 10.3.8
Record unsolicited AEs (Days 1-30) in all participants[10]	●	●			●	●							See Section 10.3.8
Record concomitant medications/vaccinations	●	●	●	●	●	●	●	●	●			●	See Table 15 for specific collection period and Section 6.5
Record intercurrent medical conditions	●	●	●	●	●	●	●	●	●			●	See Section 9.3.1.1
Record all SAEs and pIMDs[10]	●	●	●		●	●	●						See Section 10.3.8

Type of contact for NH[1]	V1	V2	C1[2]	C2	V3	V4	C3[2]	C4	V5NH	V6NH[11]	C5[11]	V7NH	Notes for more information and details
Timepoint	**Day 1 Dose 1**	**Day 31 Post-D1**	**Month 6 Post-D1**	**End S1**	**Pre S2 Dose 2**	**Day 31 Post-D2**	**Month 6 Post-D2**	**End S2**	**Pre S3 Dose 3**	**Day 31 Post-D3**	**Month 6 Post-D3**	**End S3**	
Record fatal SAEs, SAEs related to study vaccination, COVID-19 cases and pIMDs related to study vaccination[10]	●	●	●	●	●	●	●	●	●			●	See Section 10.3.8
Record AEs/SAEs leading to withdrawal from the study	●	●	●	●	●	●	●	●	●			●	See Section 10.3.8
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine[9]	●	●	●	●	●	●	●	●	●			●	See Section 10.3.8
ARI surveillance													
Instruct/remind participants of ARI surveillance	○	○	○	○	○	○	○	○	○				See Section 8.1.1
Nasal self-swab training with the study participant		○											See Section 8.1.1.1.1
Distribute material for nasal self-swab collection (including instructions)		○			○				○				See Section 8.1.1
Frailty status													
Assess frailty status with Gait Speed test	●												See Section 8.4
HR-QoL questionnaires													
Distribute the daily health questionnaires for participants to complete at home in case of ARI		○			○				○				See Section 8.10.1
Completion of daily health questionnaires by the participant		●											See Section 8.10.1
Completion of EQ-5D and SF-12 questionnaires by the participant	●				●				●				See Section 8.10.1
Study conclusion for NH												●	See Section 4.4

Note: The double-line borders indicate the analyses, which will be performed on data that are as clean as possible: VE Analysis 2 at the end of Season 1 in NH, Safety analysis when all safety data up to 6 months post-Dose 1 will be available for all participants in NH and SH, VE Analysis 3 after at least 2 seasons in NH and 1 season in SH, and VE Analysis ***6*** after

3 seasons in NH and 2 seasons in SH (end of study). VE Analysis 1 will be case-driven. ***Additional analyses, not indicated in this table, will be performed as detailed in*** Section 9.5.1.

Note: If following the sample size re-assessment an additional cohort needs to be enrolled before the next season in NH (see Section 9.2.3), the participants enrolled in this cohort will follow the same schedule of activities as indicated in this table.

ARI: acute respiratory illness; C: Contact; D: Dose; EQ-5D: EuroQol 5-dimension health questionnaire; HR-QoL: health-related quality of life; pIMDs: potential immune-mediated diseases; S: Season; SAE: serious adverse event; SF-12: Short Form 12-item health survey; Pre-S1: pre-Season 1; Pre-S2: pre-Season 2; Pre-S3: pre-Season 3; V: Visit.

● 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. Study visits should preferably be done on site or in the LTCF. If deemed necessary, study visits can be done at home. 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, or via a visit for LTCF participants. 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. Contacts 1 and 3 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months after each vaccination for each participant. These contacts can be combined with another contact or visit.
3. Freely given and written informed consent must be obtained from each study participant prior to participation in the study. The participant's informed consent may be obtained prior to Visit 1. ***In addition, participants should sign the ICF addendum for revaccination (Protocol Amendment 3) at Visit 3 and ICF addendum for Protocol Amendment 5 at Visit 5NH.***
4. Any vaccination administered up to 1 year before administration of the first study vaccine dose should be recorded in the eCRF. Administration of Shingrix at any timepoint (even if longer than 1 year before the first study vaccination) should be recorded in the eCRF.
5. If deemed necessary by the investigator.
6. The blood samples at Visits 1 and 3 should be taken prior to vaccine administration.
7. The blood samples at Visit 3 should only be taken from participants in the reactogenicity and immunogenicity subset.
8. A paper diary will be distributed to all study participants on each vaccination day (at Visits 1 ***and*** 3). All participants will record unsolicited AEs and concomitant medications/products on the day of each vaccination and for 29 subsequent days (Days 1-30). In addition, participants in the reactogenicity subset will be asked to record solicited events on the day of each vaccination and for 3 subsequent days (Days 1-4).
9. SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to administration of the first study vaccine dose) up to study end.
10. 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) in eCRF. The collection of AF will be performed following the AE/SAE reporting periods. For AF that were reported before the implementation of the Protocol Amendment 4, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.
11. ***Visit 6NH and Contact 5 are not applicable for participants that did not receive the Dose 3 but are not removed from the schedule of activities table as these timepoints still appear in the eCRFs.***
12. ***At Visit 5NH, a blood sample of 20 mL should be taken from all participants including the participants of the immunogenicity and reactogenicity subset.***

Table 3 Schedule of activities for all participants in Southern hemisphere (Amended, 12 July 2023)

Type of contact for SH[1]	V1	V2	V2b[2]	C1[3]	C2	V3	V4	C3[3]	C4	V5SH	Notes for more information and details
Timepoint	**Day 1 Dose 1**	**Day 31 Post-D1**	**Pre S1**	**Month 6 Post-D1**	**End S1**	**Pre S2 Dose 2**	**Day 31 Post-D2**	**Month 6 Post-D2**	**End S2**	**End of study**	
Study participant informed consent	●[4]										See Section 10.1.3
Study participant informed consent for annual revaccination[5]						●					
Distribution of participant card	○										See Section 8.3.6
Check inclusion/exclusion criteria	●										See Sections 5.1 and 5.2
Check with participant if he/she will appoint a caregiver and distribute caregiver information letter(s), when applicable	○		○			○	○				See Sections 5.3 and 10.1.3
Baseline and demography assessments											
Collect demographic data	●										See Section 8.2.1.1
Measure/record height and weight	●										See Section 8.2.1.2
Record medical history	●										See Section 8.2.1.3
Record history of vaccine administration[5]	●										See Section 8.2.1.4
Physical examination/Vital signs	●	○[7]	●			●	○[7]			○[7]	See Section 8.2.2
Lung auscultation	○	○[7]	○			○	○[7]			○[7]	See Section 8.2.2.3
Record oxygen saturation	●		●			●					See Section 8.2.2.4
Record smoking status and smoking exposure history (including electronic smoking devices)	●										See Section 8.2.1.5. Refer to Section 10.5.2 for definitions of current and former smoker.
Clinical specimens for laboratory assays											
Blood sampling in all participants (~20 mL)	●[8]	●									See Section 8.1.3.2
Blood sampling in subset (~20 mL)[9]						●[8]					See Section 8.1.3.2
Vaccine(s)											
Check criteria for temporary delay for enrollment and/or vaccination	○					○					See Section 7.1.1
Check contraindications to vaccination						○					See Section 7.1.2

Type of contact for SH[1]	V1	V2	V2b[2]	C1[3]	C2	V3	V4	C3[3]	C4	V5SH	Notes for more information and details
Timepoint	**Day 1 Dose 1**	**Day 31 Post-D1**	**Pre S1**	**Month 6 Post-D1**	**End S1**	**Pre S2 Dose 2**	**Day 31 Post-D2**	**Month 6 Post-D2**	**End S2**	**End of study**	
Study group and intervention number allocation	○					○					See Sections 6.3.2 and 6.3.3
Record pre-vaccination body temperature	●					●					The route for measuring temperature can be oral, axillary or tympanic (see Section 8.2.1.6).
Vaccine administration (including 30-minute post-vaccination observation)	●					●					See Section 6.1
Safety assessments											
Distribute paper diary cards[10]	○					○					See Section 8.2.1.7
Return of paper diary cards		○					○				See Section 10.3.8
Record solicited administration site and systemic events (Days 1-4) in the reactogenicity subset	●	●				●	●				See Section 10.3.8
Record unsolicited AEs (Days 1-30) in all participants[12]	●	●				●	●				See Section 10.3.8
Record concomitant medications/vaccinations	●	●	●	●	●	●	●	●	●	●	See Table 15 for specific collection period and Section 6.5
Record intercurrent medical conditions	●	●	●	●	●	●	●	●	●	●	See Section 9.3.1.1
Record all SAEs and pIMDs[12]	●	●	●	●		●	●	●			See Section 10.3.8
Record fatal SAEs, SAEs related to study vaccination, COVID-19 cases and pIMDs related to study vaccination[12]	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8
Record AEs/SAEs leading to withdrawal from the study	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine[11]	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8

Type of contact for SH[1]	V1	V2	V2b[2]	C1[3]	C2	V3	V4	C3[3]	C4	V5SH	Notes for more information and details
Timepoint	**Day 1 Dose 1**	**Day 31 Post-D1**	**Pre S1**	**Month 6 Post-D1**	**End S1**	**Pre S2 Dose 2**	**Day 31 Post-D2**	**Month 6 Post-D2**	**End S2**	**End of study**	
ARI surveillance											
Instruct/remind participants of ARI surveillance	○	○	○	○	○	○	○	○	○		See Section 8.1.1
Nasal self-swab training with the study participant		○									See Section 8.1.1.1.1
Distribute material for nasal self-swab collection (including instructions)		○	○			○					See Section 8.1.1
Frailty status											
Assess frailty status with Gait Speed test	●										See Section 8.4
HR-QoL questionnaires											
Distribute the daily health questionnaires for participants to complete at home in case of ARI		○				○					See Section 8.10.1
Completion of daily health questionnaires by the participant		●									See Section 8.10.1
Completion of EQ-5D and SF-12 questionnaires by the participant	●					●					See Section 8.10.1
Study conclusion for SH										●	See Section 4.4

Note: The double-line borders indicate the analyses, which will be performed on data that are as clean as possible: Safety analysis when all safety data up to 6 months post-Dose 1 will be available for all participants in NH and SH, VE Analysis 3 after at least 2 seasons in NH and 1 season in SH and VE Analysis 4 after 3 seasons in NH and 2 seasons in SH (end of study). VE Analysis 1 will be case-driven and VE Analysis 2 will be performed at the end of Season 1 in NH. Refer to Section 9.5.1 for details.

ARI: acute respiratory illness; C: Contact; D: Dose; EQ-5D: EuroQol 5-dimension health questionnaire HR-QoL: health-related quality of life; pIMDs: potential immune-mediated diseases; S: Season; SAE: serious adverse event; SF-12: Short Form 12-item health survey; Pre-S1: pre-Season 1; Pre-S2: pre-Season 2; V: Visit

● 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. Study visits should preferably be done on site or in the LTCF. If deemed necessary, study visits can be done at home. 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, or via a visit for LTCF participants. 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. Visit 2b in SH (Pre-Season 1 visit) should be performed at the earliest 3 months before the start of Season 1 in SH. This Visit 2b should not be performed for participants that have their Visit 2 planned within 3 months before the start of Season 1. For all participants in SH that have their Visit 2 more than 3 months before the start of Season 1, Visit 2b should be planned as a stand-alone visit. Refer to Table 6 for details of the interval allowed for study visits.

3. Contacts 1 and 3 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months after each vaccination for each participant. These contacts can be combined with another contact or visit.
4. Freely given and written informed consent must be obtained from each study participant prior to participation in the study. The participant's informed consent may be obtained prior to Visit 1.
5. In case the participant does not agree to continue the study for the annual revaccination, the study conclusion page of the eCRF should be completed.
6. Any vaccination administered up to 1 year before administration of the first study vaccine dose should be recorded in the eCRF. Administration of *Shingrix* at any timepoint (even if longer than 1 year before the first study vaccination) should be recorded in the eCRF.
7. If deemed necessary by the investigator.
8. The blood samples at Visits 1 and 3 should be taken prior to vaccine administration.
9. These blood samples should only be taken from participants in the reactogenicity and immunogenicity subset.
10. A paper diary will be distributed to all study participants on each vaccination day (at Visits 1 and 3). All participants will record unsolicited AEs and concomitant medications/products on the day of each vaccination and for 29 subsequent days (Days 1-30). In addition, participants in the reactogenicity subset will be asked to record solicited events on the day of each vaccination and for 3 subsequent days (Days 1-4).
11. SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to administration of the first study vaccine dose) up to study end.
12. 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) in eCRF. The collection of AF will be performed following the AE/SAE reporting periods. For AF that were reported before the implementation of ***the*** Protocol Amendment 4, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

Table 4 Schedule of activities for ARI surveillance (Amended, 12 July 2023)

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]	Notes for more information and details
ARI surveillance							
Instruct/remind participants of ARI surveillance procedures	○						See Section 8.1.1.4
Record contact dates	●	●					See Section 8.1.1
Schedule the ARI visit	○[5]	○					See Section 8.1.1.6.1
Distribution of new material for nasal self-swab collection (including instructions)[6]			○				See Section 8.1.1.6
Record date of nasal self-swab collection[6]			●				See Section 8.1.1.6
Nasal and throat swab sampling by the site staff			●				See Section 8.1.1.1.1
Record ARI information	●[5]	●	●	●	●	●	See Section 8.1.1.6
HR-QoL questionnaires							
Completion of EQ-5D and SF-12 questionnaires by the participant			●				See Section 8.10.1
Distribution of daily health questionnaires (to be completed in case of another ARI)[6]			○				See Section 8.10.1
Completion of daily health questionnaires by the participant[6,7]	○[5]	○	○	○			See Section 8.10.1
Remind participant to complete the daily health questionnaires[6]	○[5]	○	○	○			See Section 8.10.1
Check completion of the daily health questionnaires[6]			○	○			See Section 8.1.1.6.1
Remind participant to return the daily health questionnaires[6]				○			See Section 8.10.1
Enter daily health questionnaires data in eCRF[6]					●		See Section 8.10.1
HCRU							
Record HCRU			●	●	●	●	See Section 8.10.2
Safety assessments							
Physical examination/Vital signs			●				See Section 8.2.2
Lung auscultation			●				See Section 8.2.2.3
Record oxygen saturation			●				See Section 8.2.2.4
Record medications taken to treat ARI (prescribed/self-treatment) or an ARI-related complication			●	●	●	●	See Table 15 for specific collection period and Section 6.5

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]	Notes for more information and details
Record intercurrent medical conditions	●		●	●	●	●	See Section 9.3.1.1
Recording of all SAEs and pIMDs up to 6 months post-vaccination[9]	●		●	●	●	●	See Section 10.3.8
Recording of fatal SAEs, SAEs related to study vaccination, COVID-19 cases and pIMDs related to study vaccination[9]	●		●	●	●	●	See Section 10.3.8
Recording of AEs/SAEs leading to withdrawal from the study	●		●	●	●	●	See Section 10.3.8
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[8]	●		●	●	●	●	See Section 10.3.8

ARI: acute respiratory illness; EQ-5D; EuroQol 5-dimension health questionnaire; HCRU: healthcare resource utilization; HR-QoL: health-related quality of life; pIMDs: potential immune-mediated diseases; SAE: serious adverse event; SF-12: Short Form 12-item health survey; FU: follow-up

● 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 seasons and every month during the inter-season periods. 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, or via a visit for LTCF participants. 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 or in the LTCF. 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 or visit to the LTCF.
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 or visit to the LTCF.
5. If an ARI is reported during a scheduled surveillance contact, then all the procedures expected at the “participant call” should be performed.
6. Not applicable for ARI reported before Visit 2 (Day 31).
7. The daily health questionnaires should be completed from the participant’s call (Day 2) until the end of the ARI episode or for maximum 14 consecutive days (i.e., from Day 2 until Day 15 at the latest).
8. SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to administration of the first study vaccine dose) up to study end.
9. 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) in eCRF. The collection of AF will be performed following the AE/SAE reporting periods. For AF that were reported before the implementation of ***the*** Protocol Amendment 4, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

Table 5 Intervals between study visits/contacts for all participants in Northern hemisphere (Amended, 12 July 2023)

Interval[3]	Length of interval	Allowed interval
Visit 1 → Visit 2	30 days	28-42 days[1]
Visit 1 → Contact 1	180 days	180-210 days[2]
Contact 2 (End of Season 1)	Between 1 and 31 May Study Year 2	
Visit 3 (Pre-Season 2/Dose 2)	Between 1 August and 30 September Study Year 2[4]	
Visit 3 → Visit 4	30 days	28-42 days[1]
Visit 3 → Contact 3	180 days	180-210 days[2]
Contact 4 (End of Season 2)	Between 1 and 31 May Study Year 3	
Visit 5NH (Pre-Season 3)	Between 1 August and 30 September Study Year 3[4,5]	
Visit 5NH → Visit 6NH[6]	30 days	28-42 days[1]
Visit 5NH → Contact 5[6]	180 days	180-210 days[2]
Visit 7NH (End of Season 3)	Between 1 and 31 May Study Year 4	

1. If Visits 2, 4 or 6NH occur within 28 or 29 days after the vaccination visit, the site staff should ensure that unsolicited AEs are reported up to 30 days post-vaccination.
2. Contacts 1, 3 and 5 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months after each vaccination for each participant. These contacts can be combined with another contact or visit.
3. If following the sample size re-assessment an additional cohort needs to be enrolled before the next season in NH (see Section 9.2.3), similar intervals will apply up to the end of the third season for those participants. Study Year 1 corresponds to the year in which the enrollment started for the cohort.
4. In exceptional cases, the revaccination dose can be given before 30 October.
5. ***For participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5, in exceptional cases Visit 5NH can be organized before 30 October.***
6. ***Visit 6NH and Contact 5 are not applicable for participants who will have their Visit 5NH after the approval of the current Protocol Amendment 5 and did not receive study intervention (Dose 3) at pre-Season 3 visit (Visit 5NH).***

Table 6 Intervals between study visits/contacts for all participants in Southern hemisphere

Interval	Length of interval	Allowed interval
Visit 1 → Visit 2	30 days	28-42 days[1]
Visit 2b (Pre-Season 1)[2]	Between 1 December Study Year 1 and 28 February Study Year 2	
Visit 1 → Contact 1	180 days	180-210 days[3]
Contact 2 (End of Season 1)	Between 1 and 31 October Study Year 2	
Visit 3 (Pre-Season 2/Dose 2)	Between 1 January and 28 February Study Year 3[4]	
Visit 3 → Visit 4	30 days	28-42 days[1]
Visit 3 → Contact 3	180 days	180-210 days[3]
Contact 4 (End of Season 2)	Between 1 and 31 October Study Year 3	
Visit 5SH	Between 1 and 31 May Study Year 4	

1. If Visits 2 or 4 occur within 28 or 29 days after the vaccination visit, the site staff should ensure that unsolicited AEs are reported up to 30 days post-vaccination.
2. Visit 2b in SH (Pre-Season 1 visit) should be performed at the earliest 3 months before the start of Season 1 in SH. This Visit 2b should not be performed for participants that have their Visit 2 planned within 3 months before the start of Season 1. For all participants in SH that have their Visit 2 more than 3 months before the start of Season 1, Visit 2b should be planned as a stand-alone visit.
3. Contacts 1 and 3 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months after each vaccination for each participant. These contacts can be combined with another contact or visit.
4. In exceptional cases, the revaccination dose can be given before 31 March.

Table 7 Intervals between study visits/contacts for ARI surveillance

Interval	Length of interval	Allowed interval
Between each surveillance contact (planned or spontaneous report) during the RSV seasons[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, 5]
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, 6]
Between each additional follow-up contact[7]	At 14 days from last FU contact	±3 days

1. Refer to Section 8.1.1.1 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 seasons 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 pre-defined 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 10 in Section 4.2.1).
5. In special circumstances (for example in case of suspected COVID-19 infection and pending COVID-19 test result, or self-quarantine) and if it is not possible to perform the ARI visit within 6 days after ARI onset (i.e., within Day 3 to Day 7), then the interval for this visit may be extended up to maximum 14 days after ARI onset (i.e., until Day 15).
6. 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 or visit to the LTCF.
7. Only applicable for participants with ARI/complications(s) lasting beyond the ARI closure contact.

2. INTRODUCTION

2.1. Study rationale (Amended, 12 July 2023)

GSK ***has developed a new*** RSVPreF3 OA ***vaccine*** against RSV-associated (subtypes A and B) disease in adults ≥ 60 YOA.

The purpose of the current study is to demonstrate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RT-PCR-confirmed LRTD caused by RSV A and/or B in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA vaccine and following annual revaccination. The vaccine cross-protection against RT-PCR-confirmed LRTD caused by human metapneumovirus (hMPV) will also be evaluated. In addition, the safety and immunogenicity of the vaccine will be assessed after each dose.

The rationale for the study design is presented in Section 4.2.

2.2. Background (Amended, 12 July 2023)

RSV is a ribonucleic acid (RNA) virus of which 2 antigenically distinct subtypes exist, referred to as RSV A and RSV B [Borchers, 2013]. RSV is a highly contagious human pathogen that causes respiratory tract infections in people of all ages. In temperate climates throughout the world, RSV predictably causes fall-winter epidemics. In (sub) tropical regions, viral activity is more endemic, and outbreaks are less temporally focused.

As the global population ages, the morbidity and mortality of respiratory infections appear to be steadily increasing in the older adult population [Lee, 2013; Binder, 2017]. Based on epidemiological data collected prospectively in 2008-2010 in 14 countries worldwide (including North America, Europe and East Asia), the average percentage of documented RSV infections in older adults (≥ 65 years) with influenza-like illness is 7.4%, with values between 0% and 17.1% across countries [Falsey, 2014]. In 2015, an estimated 1.5 million episodes of RSV-related acute respiratory illness occurred in older adults in industrialized countries; approximately 14.5% of these episodes involved a hospital admission [Nam, 2019]. Further information on RSV incidence and disease burden can be found in the Investigator's Brochure (IB).

Previous infection with RSV does not prevent subsequent infections. Therefore, re-infection with RSV occurs throughout an individual's lifetime and is common in all age groups [Simoes, 1999; Krilov, 2011]. Generally, these re-infections go undiagnosed because they usually manifest as common acute upper respiratory tract infections. However, in more vulnerable individuals (e.g., immunocompromised persons or older adults), re-infections can also lead to severe disease [Graham, 2011].

hMPV is an RNA pneumovirus related to RSV, sharing similar genomic/structural organizations and associated clinical manifestations [ICTV, 2019]. Similar to RSV, hMPV is a highly contagious human pathogen causing upper and lower respiratory tract infections in people of all ages. In older adults, clinical manifestations can be asymptomatic or ranging from mild upper respiratory tract infections to severe pneumonia [Walsh, 2008]. Older adults aged 65 years or above are at increased risk of severe hMPV disease and hospitalization [Falsey, 2003; Walsh, 2008; Widmer, 2012].

Rates of intensive care unit admissions, mechanical ventilation, length of hospital or intensive care unit stay were similar for hMPV, RSV and influenza infected adults [Haas, 2013; Walsh, 2008; Widmer, 2012].

At the time of initiation of this study, no vaccine nor other prophylactic treatment was available against RSV or hMPV in older adults. Since then, GSK's RSVPreF3 OA investigational vaccine was first approved for use in an adults ≥ 60 YOA in the US on 3 May 2023, followed by the European Union on 6 June 2023.

The RSVPreF3 OA investigational vaccine was administered for the first time to adults 60–80 YOA according to a 0, 2-month intramuscular vaccination schedule in another clinical study (RSV OA=ADJ-002). The vaccine formulation and schedule used in the present study, i.e., RSVPreF3 recombinant antigen, 120 µg adjuvanted with $AS01_E$ as a single dose, was selected based on safety and immunogenicity data from the RSV OA=ADJ-002 study. In addition, the Phase 1 study RSV OA=ADJ-003 has been conducted in Japan to evaluate the safety, reactogenicity and immunogenicity of the RSVPreF3 OA investigational vaccine (RSVPreF3 recombinant antigen, 120 µg adjuvanted with $AS01_B$) in 40 healthy ethnic Japanese adults 60-80 YOA. No safety concerns were identified so far.

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

In this study, up to 12 500 participants will be exposed to at least one dose of the RSVPreF3 OA investigational vaccine, whereas up to 12 500 participants will receive a placebo (refer to Section 9.2 for more details on the number of participants to be enrolled).

2.3.1. Risk assessment

Information about the reasonably expected adverse events (AEs) and the known and expected benefits and potential risks (potential syncope, hypersensitivity) of the RSVPreF3 OA investigational vaccine or the adjuvant system (potential immune-mediated diseases [pIMDs]) can be found in the IB and the Development Safety Update Report (DSUR).

Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at injection site, erythema and swelling.

In addition to potential risks related to the vaccine, there may be risks related to the blood sampling planned in the study:

- Pain and bruising may occur at the site where blood is drawn; as a mitigation strategy, a topical analgesic may be applied to the site where blood will be taken.
- Syncope (fainting) can occur following or even before any blood draw as a psychogenic response to the needle insertion.

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

2.3.2. Benefit assessment (Amended, 12 July 2023)

At the start of this study, the efficacy of the RSVPreF3 OA investigational vaccine was not demonstrated yet. Hence it was unknown if the participants receiving the RSVPreF3 OA investigational vaccine ***would*** benefit from this vaccination. ***Since then, the efficacy of RSVPreF3 OA investigational vaccine was demonstrated and the study primary confirmatory objective was met. One dose of RSVPreF3 OA investigational vaccine has shown a favorable benefit/risk profile. The vaccine was approved for use in an adults ≥ 60 YOA in the US on 3 May 2023, followed by the European Union on 6 June 2023.***

The VE Analysis 3 data showed that revaccination administered approximately 12 months after Dose 1 did not confer additional benefit in prevention of RSV-confirmed LRTD for the overall population of adults ≥ 60 YOA, while the second dose of vaccine has a clinically acceptable safety profile. The clinical development program will continue to evaluate longer term follow-up and the optimal timing for potential revaccination.

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 AND ENDPOINTS

Table 8 Study objectives and endpoints (Amended, 12 July 2023)

Objectives	Endpoints
Primary	
To demonstrate the efficacy of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD during the first season in adults ≥ 60 YOA. *Criterion: The lower limit (LL) of the 2-sided confidence interval (CI) for vaccine efficacy (VE) is above 20%.*	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*.
Secondary	
Secondary – Efficacy	
Secondary confirmatory	
To demonstrate the efficacy of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA over several seasons. Criterion: The lower limit (LL) of the 2-sided confidence interval (CI) for vaccine efficacy (VE) is above 20%.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*.
To demonstrate the efficacy of a single dose of the RSVPreF3 OA investigational vaccine followed by ***1*** annual revaccination ***before Season 2*** in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA over several seasons. Criterion: The LL of the 2-sided CI for VE is above 20%.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*.
To demonstrate the efficacy of a single dose and ***1*** annual revaccination ***before Season 2*** of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 YOA over 3 seasons. Criterion: The LL of the 2-sided CI for VE is above 0%.	First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition*, for RSV subtype A and RSV subtype B separately.
Other secondary descriptive	
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition*, for RSV subtype A and RSV subtype B separately.

Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine up to the end of Season 1.	First occurrence of RT-PCR-confirmed hMPV-associated LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by age category, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, in the following age categories: ≥ 65 YOA, ≥ 70 YOA and ≥ 80 YOA.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by season in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by season.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by year in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by year.
To evaluate the evolution of efficacy of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA over time.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA by baseline comorbidities, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD according to the case definitions*, by baseline comorbidities.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by baseline frailty status in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by baseline frailty status.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of severe RSV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated severe LRTD, according to the case definitions*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*.

Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of any ARI and any LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of ARI or LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of hospitalization due to respiratory diseases in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	• Occurrence of hospitalization due to respiratory diseases or due to a complication related to respiratory diseases during the RSV seasons† and during the entire follow-up. • Occurrence of hospitalization due to RSV-confirmed respiratory diseases or due to a complication related to RSV-confirmed respiratory diseases during the RSV seasons† and during the entire follow-up.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of complications related to RSV-confirmed ARI and any ARI in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Occurrence of complication related to RSV-confirmed ARI or related to any ARI during the RSV seasons†, according to the case definition* and during the entire follow-up.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on lower respiratory tract symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Maximum FLU-PRO Chest score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on ARI total symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Estimated Least Squares mean FLU-PRO total score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on health utility score in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Estimated Least Squares mean EQ-5D utility score at the ARI visit for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on physical functioning in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Estimated Least Squares mean SF-12 Physical Functioning score at the ARI visit for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To describe RSV-confirmed ARI cases and RSV-confirmed LRTD cases in the RSVPreF3 and Placebo groups.	Descriptors of RT-PCR-confirmed RSV A and/or B ARI and LRTD cases, including duration of episodes, reported symptoms/signs and respiratory tract infection severity.
Secondary – Immunogenicity	
To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine.	In a subset of participants, at pre-Dose 1 (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (pre-Season 2) and pre-Season 3: • RSVPreF3 IgG-binding antibody concentrations.

Objectives	Endpoints
	• Neutralizing titers against RSV A. • Neutralizing titers against RSV B.
Secondary – Safety	
To evaluate the reactogenicity of the RSVPreF3 OA investigational vaccine.	In a subset of participants, occurrence, intensity and duration of solicited administration site and systemic events with an onset during the 4-day follow-up period after each vaccination (i.e., the day of vaccination and 3 subsequent days).
To evaluate the safety of the RSVPreF3 OA investigational vaccine.	In all participants: • Occurrence of unsolicited AEs with an onset during the 30-day follow-up period after each vaccination (i.e., the day of vaccination and 29 subsequent days). • Occurrence of all serious adverse events (SAEs) from the day of vaccination up to 6 months after each vaccination. • Occurrence of all pIMDs from the day of vaccination up to 6 months after each vaccination. • Occurrence of SAEs related to study vaccination from Day 1 up to study end. • Occurrence of pIMDs related to study vaccination from Day 1 up to study end. • Occurrence of any fatal SAEs from Day 1 up to study end.
Tertiary	
Tertiary – Efficacy	
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV and/or hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV and/or hMPV-associated LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination up to the end of Season 2 and Season 3.	First occurrence of RT-PCR-confirmed hMPV-associated LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of severe hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed hMPV-associated severe LRTD, according to the case definitions*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI for each RSV subtype (A and B) separately in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV-associated ARI, according to the case definition*, for RSV subtype A and RSV subtype B separately.

Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI by age category, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*, in the following age categories: ≥ 65 YOA, ≥ 70 YOA and ≥ 80 YOA.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI by season, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*, by season.
To evaluate the evolution of efficacy of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI over time.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI in adults ≥ 60 YOA by baseline comorbidities, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definitions*, by baseline comorbidities.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of all-cause mortality during the RSV seasons† in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Occurrence of any death during the RSV seasons†.
To estimate the proportion of participants with > 1 case of ARI or LRTD by season and participants reporting respiratory diseases in consecutive seasons, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Number of participants with > 1 case of ARI, LRTD, RT-PCR-confirmed RSV A and/or B-associated ARI and RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definitions* by season and in consecutive seasons.
To estimate the proportion of co-infections with other viral pathogens for RSV-confirmed or hMPV-confirmed ARI cases, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Number of participants with other viral pathogens (detected by RT-PCR) co-existing with RSV or hMPV among RT-PCR-confirmed RSV or RT-PCR-confirmed hMPV ARI episodes.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on upper respiratory tract symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the Placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	Maximum FLU-PRO upper respiratory symptom score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To assess the impact of the RSVPreF3 OA investigational vaccine on healthcare resource utilization (HCRU) for participants with RSV-confirmed ARI and any ARI, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	• Hospitalization rate during the ARI episode for participants with RT-PCR-confirmed RSV A and/or B-associated ARI and any ARI, according to the case definitions*. • Antibiotic use during the ARI episode for participants with RT-PCR-confirmed RSV A and/or B-associated ARI and any ARI, according to the case definitions*.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on patient-reported severity of respiratory symptoms in participants with RSV-confirmed LRTD in the RSVPreF3 groups compared to the Placebo	Maximum patient global impression of severity (PGI-S) score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated LRTD.

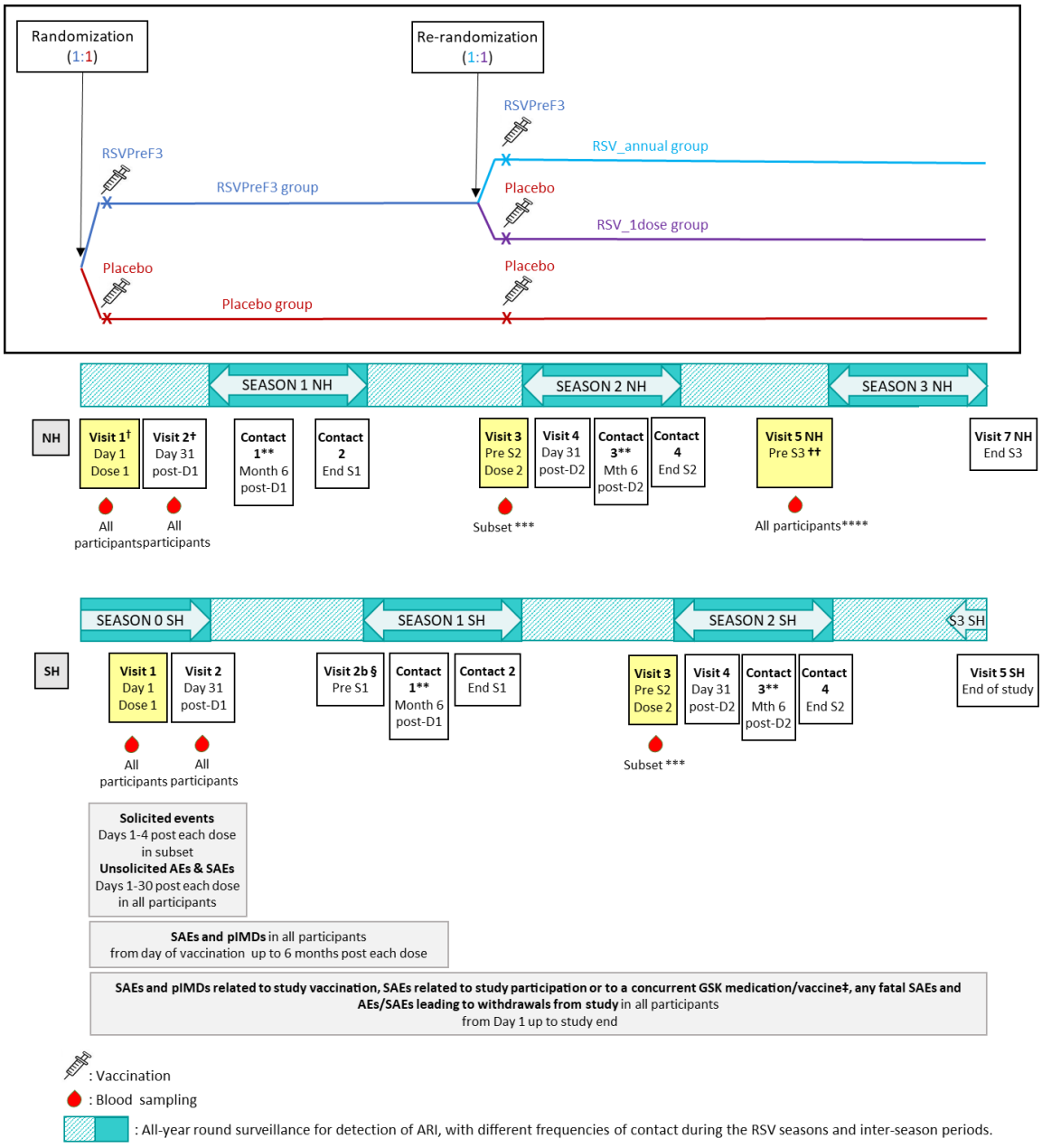
Objectives	Endpoints
group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination.	
Tertiary - Immunogenicity and Safety	
To assess the correlation of the humoral immune response to the RSVPreF3 OA investigational vaccine at 30 days post-Dose 1 with protection against RSV disease.	RSVPreF3 IgG-binding antibody concentrations at pre-Dose 1 (Day 1), 30 days post-Dose 1 (Day 31) ***and pre-Season 3**** in all participants with RSV disease compared to a subset of controls.‡
To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine by baseline frailty status.	In a subset of participants, at pre-Dose 1 (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (pre-Season 2) and pre-Season 3: • RSVPreF3 IgG-binding antibody concentrations classified by baseline frailty score. • Neutralizing titers against RSV A classified by baseline frailty score. • Neutralizing titers against RSV B classified by baseline frailty score.
To further characterize immune responses to the RSVPreF3 OA investigational vaccine and/or the pathogens under study.	Any further exploratory immunology to investigate RSV and/or hMPV-related immune responses.
To evaluate the reactogenicity of the RSVPreF3 OA investigational vaccine by baseline frailty status.	In a subset of participants, occurrence, intensity and duration of solicited administration site and systemic events with an onset during the 4-day follow-up period after the first vaccination (i.e., the day of vaccination and 3 subsequent days) classified by baseline frailty score.

* Case definitions are described in Section 4.2.1.
† The RSV seasons defined for this study are from 1 October to 30 April in NH and from 1 March to 30 September in SH.
‡ Additional testing such as but not limited to neutralization assay(s) and systems serology testing might be performed on the same subset of participants to investigate a correlate of protection.
***** ***Blood sample at pre-Season 3 is applicable for all participants in the NH who have their Visit 5NH after the approval of the current Protocol Amendment 5.***

4. STUDY DESIGN

4.1. Overall design (Amended, 12 July 2023)

Figure 1 Study design overview for (Amended, 12 July 2023)



Note: For simplicity, the randomization in this figure is presented as 1:1 between the RSVPreF3 OA vaccine and the placebo group. Participants will be randomized with a ratio of 1:1:1:3 to 1 of 4 study groups (RSVPreF3 Lot 1/2/3 versus Placebo) for Part 1 of the study and a ratio of 1:1 to 1 of 2 study groups (RSVPreF3 Lot 4 versus Placebo) for Part 2 before Season 1 (refer to the experimental design below and Section 6.3.2 for details).
Note: If following the sample size re-assessment an additional cohort needs to be enrolled before the next season in NH (see Section 9.2.3), the participants enrolled in this cohort will follow the same study design as indicated in this figure.

RSV_annual: RSVPreF3 OA annual revaccinations group
RSV_1dose: RSVPreF3 OA single vaccination group
AE: adverse event; ARI: acute respiratory illness; NH: Northern hemisphere; SH: Southern hemisphere; pIMD: potential immune-mediated disease; RSV: respiratory syncytial virus; SAE: serious adverse event
* Dose 3 only applies to participants in NH.
† Depending on the time of enrollment, Visit 1 and Visit 2 in NH can take place during Season 1.
** Contacts 1 ***and*** 3 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months after each vaccination for each participant. These contacts can be combined with another contact or visit.
§ Visit 2b in SH (Pre-Season 1 visit) should be performed at the earliest 3 months before the start of Season 1 in SH. This Visit 2b should not be performed for participants that have their Visit 2 planned within 3 months before the start of Season 1. For all participants in SH that have their Visit 2 more than 3 months before the start of Season 1, Visit 2b should be planned as a stand-alone visit.
*** Blood samples should only be taken from participants in the reactogenicity and immunogenicity subset in Part 1.‡
All SAEs related to study participation, or a GSK concomitant medication/vaccine are to be recorded from the time the participant consents to participate in the study. All other SAEs are to be reported after the first study vaccine administration.
†† ***Some participants in the NH may have Visit 5NH before the approval of the current Protocol Amendment 5. These participants should receive Dose 3 pre-Season 3 and all subsequent study procedures should be performed as planned in Protocol Amendment 4. Please refer to the Table 1 for the details of the procedures to be performed in participants that have their Visit 5NH before the approval of this amendment.***
**** ***For participants in the NH who have their Visit 5NH before the approval of the current Protocol Amendment 5, a blood sample should be taken only if the participant is in the reactogenicity and immunogenicity subset. Please refer to the Table 1 for the details of the procedures to be performed in participants that have their Visit 5NH before the approval of this amendment.***

- **Type of study**: self-contained.
- **Experimental design**: Phase 3, randomized, observer-blind, placebo-controlled multi-country study with 2 parts (see Figure 1):
  - Part 1 with 4 parallel groups randomized with a ratio of 1:1:1:3 (RSVPreF3 Lot 1/2/3 versus Placebo) before Season 1.
  - Part 2 with 2 parallel groups randomized with a ratio of 1:1 (RSVPreF3 Lot 4 versus Placebo) before Season 1, which will be initiated when the vaccine lots for Part 1 are no longer available at the study sites.

  Each of the 4 RSVPreF3 groups in both parts will be randomized before Season 2 into 2 sub-groups (RSV_annual group and RSV_1dose group) with a 1:1 ratio. The RSV_annual group will receive an additional dose of RSVPreF3 OA vaccine before each subsequent season while the RSV_1dose group will receive 1 dose of placebo at the same timepoints. To maintain the study blind, participants who were initially randomized to the Placebo group will also receive additional doses of placebo at the same timepoints.

  At the time of pre-Season 3 (Visit 5NH), participants in the NH who will have their Visit 5NH before approval of the current Protocol Amendment 5, will receive the study intervention as planned according to their group allocation. Participants having their Visit 5NH after approval of the current Protocol Amendment 5 will not receive any study intervention at pre-Season 3 visit (Visit 5NH).
- **Randomization for the additional cohort enrolled in NH after sample size re-assessment:** If following sample size re-assessment an additional cohort needs to be enrolled before the next season in NH (see Section 9.2.3), the participants in this additional cohort will be enrolled in 3 study groups (RSV_annual group, RSV_1dose

group and Placebo group) according to a 1:1:2 randomization ratio and will follow the same study design as indicated in Figure 1. They will have a blood sampling at Visit 1 and Visit 2 as for all study participants. There will be no subset for immunogenicity and reactogenicity for this cohort.

Note: Blood sample at Visit 5NH is not applicable for this cohort because it was never enrolled.

- **Duration of the study:**
  - Approximately 3 years per participant in NH (up to 3 consecutive RSV seasons).
  - Approximately 2.5 to 3 years per participant in SH (up to at least 2 consecutive RSV seasons).
- **Primary completion date:** Case-driven: Last contact point at which a data for primary VE Analysis 1 will be collected.
- **Control:** placebo saline solution.
- **Blinding:** observer-blind. Refer to Section 6.3.5 for details.
- **Data collection:** standardized electronic Case Report Form (eCRF). Solicited events and unsolicited AEs will be collected using a paper diary.
- **Study groups:** Refer to Figure 1 and Table 9 for an overview of the study groups.

Table 9 Study groups, intervention and blinding foreseen in the study (Amended, 12 July 2023)

Study groups	Number of participants*			Age	Intervention	Blinding	
	NH	SH	Total			Visit 1 → Visit 3 (Observer-blind)	Visit 3 → Visit 7NH/Visit 5SH (Observer-blind)
For Dose 1							
RSVPreF3_L1	Up to 11 500**	750-1 000**	Up to 12 500**	≥ 60 years	RSVPreF3 OA investigational vaccine L1	X	
RSVPreF3_L2					RSVPreF3 OA investigational vaccine L2	X	
RSVPreF3_L3					RSVPreF3 OA investigational vaccine L3	X	
RSVPreF3_L4					RSVPreF3 OA investigational vaccine L4***	X	
Placebo	Up to 11 500	750-1 000	Up to 12 500	≥ 60 years	Placebo	X	
For annual *revaccination*							
RSV_L1_annual	Up to 5 750	375-500	Up to 6 250	≥ 60 years	RSVPreF3 OA investigational vaccine		X
RSV_L2_annual							X
RSV_L3_annual							X
RSV_L4_annual							X
RSV_L1_1dose	Up to 5 750	375-500	Up to 6 250	≥ 60 years	Placebo		X
RSV_L2_1dose							X
RSV_L3_1dose							X
RSV_L4_1dose							X
Placebo	Up to 11 500	750-1 000	Up to 12 500	≥ 60 years	Placebo		X
Total	Up to 23 000	1 500-2 000	Up to 25 000				

NH: Northern hemisphere; SH: Southern hemisphere; L1: Lot 1; L2: Lot 2; L3: Lot 3; L4: Lot 4

* Numbers are approximate (see Section 9.2.1 for details on the sample size calculation).

** Participants enrolled in the RSVPreF3 groups will receive vaccine Lots 1, 2 or 3. When these lots are no longer available at the site, the site will switch to Lot 4. This is applicable in both SH and NH.

*** Re-supply lot for Part 2.

- **Vaccination schedule:** First dose of study vaccine (RSVPreF3 OA investigational vaccine or placebo) on Day 1 followed by annual revaccination of study vaccine (RSVPreF3 OA investigational vaccine or placebo) as follows:
  - Participants from the NH ***who will have their Visit 5NH before the approval of the current Protocol Amendment 5,*** will receive 2 additional doses, 1 before Season 2 and 1 before Season 3.
  - ***Participants from the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5, will not receive any study intervention at pre-Season 3 visit (Visit 5NH). These participants had received 1 additional dose before Season 2.***
  - Participants from the SH will receive 1 additional dose before Season 2.
- **Safety monitoring:** An IDMC, in addition to the existing GSK's Safety Review Team (SRT), will oversee the safety of the study participants and study conduct (refer to Section 8.2.3).
- **ARI surveillance:** Surveillance for ARI detection will be carried out during the entire study, via spontaneous reporting by the study participant (starting on the first vaccination day* [Visit 1]) and via scheduled site staff contacts (starting from Visit 2 onwards) with different frequencies of contact during the RSV seasons and the inter-season periods (refer to Section 8.1.1). Swab samples will be taken in all participants meeting pre-specified criteria for ARI case definition (refer to Section 4.2.1). Diagnosis and treatment of each ARI should be performed according to the local standard of care.

  * For detailed information on activities involved in ARI surveillance, refer to Table 4.

4.1.1. Overview of the recruitment plan

The aim is to enroll between at least 16 000 and up to 23 000 participants in the NH and between 1 500 to 2 000 participants in the SH with a randomization ratio of 1:1:1:3 for Part 1 of the study (RSVPreF3 Lot 1/2/3 versus Placebo) and a randomization ratio of 1:1 for Part 2 (RSVPreF3 Lot 4 versus Placebo) before Season 1. Refer to Section 9.2.1 for details on the sample size calculation.

The recruitment plan may be adapted based on the actual number of participants enrolled in each hemisphere or within each sex. In case a hemisphere or country would fall behind in participant recruitment (in a specific age group or overall), a redistribution of the enrollment target per hemisphere/country may be made to allow the other participating country(ies) to enroll additional participants in an effort to ensure full and timely enrollment of the overall targeted number of participants specified in this protocol.

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

4.1.2. Enrollment rules

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

- Approximately 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.

Participants from both community dwelling (CD) and long-term care facilities (LTCFs) may be enrolled.

Allocation of participants to the reactogenicity and immunogenicity subset:

Participants contributing to the reactogenicity and immunogenicity subset will be recruited from a selected number of countries and selected number of sites in Part 1. In the selected sites, the investigator will allocate the first participants in each age category to the reactogenicity and immunogenicity subset until the allocated target is reached.

4.2. Scientific rationale for study design (Amended, 12 July 2023)

The study is designed as a Phase 3, observer-blind, placebo-controlled study enrolling adults ≥ 60 YOA, who will be followed up for 3 consecutive RSV seasons in the NH and at least 2 consecutive RSV seasons in the SH. The study population will be representative of the global population beyond 60 YOA. Older adults living in the community (CD participants) and LTCFs residents (LTCF participants) with medically stable conditions may be enrolled. Please refer to Section 10.5.2 (Glossary of terms) for the definition of CD participants and LTCF.

There is uncertainty about the persistence of the immune response to the RSVPreF3 OA investigational vaccine administered as a single dose and the level of immune response that may be required for protection. In addition, older adults may require repeated dosing to maintain protection against the RSV disease over several seasons. This study has been designed to consider the possibility of a decline in the immune response and level of protection through the assessment of annual revaccination doses administered before the start of each season.

For that reason, the study will not only evaluate the efficacy, immunogenicity, safety and reactogenicity profile following a single dose vaccination regimen of the RSVPreF3 OA investigational vaccine in adults ≥60 YOA, but will also evaluate the efficacy, safety and reactogenicity of additional vaccine doses through annual revaccination. The RSV_1dose group will allow the evaluation of multi-year protection of a single dose of the RSVPreF3 OA vaccine and the RSV_annual group will allow the evaluation of VE of annual revaccination doses of the RSVPreF3 OA vaccine.

The results of VE Analysis 3 evaluating the efficacy and safety up to the end of Season 2 in the NH, showed that 1 dose of the RSVPreF3 OA vaccine is efficacious against RSV-LRTD and severe LRTD at least over 2 RSV seasons, and that a second dose of the study vaccine administered before Season 2 did not confer additional benefit in prevention of RSV-confirmed LRTD. Safety and reactogenicity data post-Dose 2 were consistent with previous results from the Phase 3 program.

Based on this observation, the study design was modified to remove the next annual revaccination dose of study vaccine (Dose 3 pre-Season 3) in the NH. The clinical development program will continue to evaluate long term follow-up and the optimal timing for revaccination.

4.2.1. Case definitions for evaluation of vaccine efficacy

All participants reporting at least 2 ARI symptoms/signs meeting the ARI case definition (see Table 10) 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/hMPV will be performed at GSK clinical laboratory or designated laboratory. Therefore, all participants 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, completion of QoL questionnaires, etc.).

Table 10 Case definitions for evaluation of vaccine efficacy

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[3] - New or increased crackles/ronchi[4] based on chest auscultation - Respiratory rate ≥ 20 respirations/min[4] - Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4] - Need for oxygen supplementation[4]	**Systemic symptoms and signs** - Fever[1]/feverishness[2] - Fatigue - Body aches - Headache - Decreased appetite
RT-PCR-confirmed RSV-ARI or hMPV-ARI[5]	An event meeting the case definition of ARI with at least one RSV-positive swab or at least one hMPV-positive swab detected by RT-PCR.[6]	

<table>
<tr><th>Endpoint</th><th>Case definition</th></tr>
<tr><td>LRTD</td><td>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[3]
- New or increased crackles/ronchi[4] based on chest auscultation
- Respiratory rate ≥ 20 respirations/min[4]
- Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]
- Need for oxygen supplementation[4]</td></tr>
<tr><td>RT-PCR-confirmed RSV-LRTD or hMPV-LRTD[5]</td><td>An event meeting the case definition of LRTD with at least one RSV-positive swab or at least one hMPV-positive swab detected by RT-PCR.[6]</td></tr>
<tr><td rowspan="2">RT-PCR-confirmed severe RSV LRTD or severe hMPV LRTD – Definition 1 “Clinical symptomology” [5]</td><td>Presence of a LRTD with at least one of the following criteria:
• at least 2 lower respiratory SIGNS
• an LRTD episode assessed as ‘severe’ by the investigator[7]
AND
• with at least one RSV-positive or hMPV-positive swab detected by RT-PCR</td></tr>
<tr><td>Lower respiratory signs
- New or increased wheezing[3]
- New or increased crackles/ronchi[4] based on chest auscultation
- Respiratory rate ≥ 20 respirations/min[4]
- Low or decreased oxygen saturation (= O_2 saturation <95% or ≤90 % if pre-season baseline is <95%)[4]
- Need for oxygen supplementation[4]</td></tr>
<tr><td>RT-PCR-confirmed severe RSV LRTD or severe hMPV LRTD – Definition 2 “Supportive therapy” [5]</td><td>Presence of a LRTD with at least one of the following criteria[8]:
• Need for oxygen supplementation[4]
• Need for positive airway pressure therapy (e.g., CPAP)
• Need for other types of mechanical ventilation
AND
• with at least one RSV-positive or hMPV-positive swab detected by RT-PCR</td></tr>
</table>

ARI: acute respiratory illness; LRTD: lower respiratory tract disease; RSV: respiratory syncytial virus
hMPV: human metapneumovirus; RT-PCR: reverse transcription polymerase chain reaction

1. Fever is defined as a temperature ≥ 38.0°C/100.4°F by any route.
2. Feverishness is defined as the feeling of having fever without objective measurement.
3. Reported by study participant or investigator.
4. Reported by investigator.
5. 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). In special circumstances (for example, in case of suspected COVID-19 infection and pending COVID-19 test result, or self-quarantine) and if it is not possible to perform the ARI visit within 6 days after ARI onset (i.e., within Day 3 to Day 7), then the interval for this visit and the site swab collection may be extended up to maximum 14 days after ARI onset (i.e., until Day 15).
6. Refer to Section 9.4.1.2 for details on the counting of cases that are positive for both RSV and hMPV.
7. The investigator will grade each ARI as mild, moderate or severe based on the grading scale presented in Table 16.
8. 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 (Amended, 12 July 2023)

As there ***was*** no licensed RSV vaccine available ***at the time of initiation of this study***, a placebo group (receiving saline solution) ***is*** used as control for the efficacy, safety/reactogenicity and immunogenicity assessments.

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. Please refer to Section 10.5.2 (Glossary of Terms) for the definition of observer-blind.

Further information on blinding and unblinding is provided in Section 6.3.5.

4.3. Justification for dose

Based on the results up to 1-month post-Dose 2 from study RSV OA=ADJ-002, a single dose regimen (0.5 mL) and the 120 µg RSVPreF3/AS01$_E$ formulation were selected for further evaluation in the Phase 3 clinical program. The RSV OA=ADJ-002 study was designed to assess the immunogenicity of a 2-dose AS01-adjuvanted or unadjuvanted vaccine administered according to a 0-, 2-month schedule with the aim to maximize the immune response against RSV and vaccine efficacy over several seasons. Based on the data from clinical development programs for AS01-adjuvanted protein antigen vaccines in OA, such as *Shingrix* and the chronic obstructive pulmonary disease (COPD) investigational vaccine, it was expected that immunological responses would reach higher levels 1-month post-Dose 2 as compared with 1-month post-Dose 1. However, the RSV OA=ADJ-002 results demonstrated that the second dose given 2 months after the first dose had no added value in terms of humoral and/or cellular immune responses. The humoral response, both in terms of RSV A neutralizing geometric mean titers (GMTs) and RSVPreF3-binding IgG geometric mean concentrations (GMCs), peaked 1 month after the first dose, and the second dose did not increase the level observed after first dose. For the rationale of the annual revaccinations, please refer to Section 4.2.

The results from study RSV OA=ADJ-002 demonstrated statistically significant superiority of the 120 µg formulations in terms of RSV A neutralizing titers over at least one of the 30 µg and 60 µg formulations with the same adjuvant content or unadjuvanted. An increase in the RSVPreF3-binding IgG GMCs and fold increase over baseline was also observed with increase in antigen dose from 30 µg to 120 µg. The data demonstrated an immunologic benefit of any AS01$_E$ or AS01$_B$ formulations over unadjuvanted formulations in terms of frequency of RSVPreF3-specific CD4+ T cells expressing at least 2 markers. Importantly, despite lower baseline observed in OA, the AS01-containing formulations induced CD4+ T cells frequencies at a close or similar level as in Young Adults, that is not observed with the unadjuvanted formulations.

There was no safety concern detected in unadjuvanted groups to be linked to the RSVPreF3 antigen assessed for the first time in OA. The acceptable safety/reactogenicity profile in all 120 µg groups, together with the immunological benefit demonstrated for the 120 µg antigen dose, supports the selection of a 120 µg based formulation. The

results also showed that all the AS01-adjuvanted formulations evaluated are considered to have a clinically acceptable safety profile. The AS01-adjuvanted formulation with the lowest reactogenicity profile, i.e., the $AS01_E$-based formulation, was selected. The immunological response observed after 1 vaccine dose of the $AS01_E$-based formulation is considered adequate for a RSVPreF3 OA candidate vaccine.

4.4. End of Study definition

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

End of Study (EoS): Release of the last testing results of samples collected at the last ARI visit. In these cases, EoS must be achieved no later than 8 months after Last Participant Last Visit (Visit 7NH/Visit 5SH).

5. STUDY POPULATION

5.1. Inclusion criteria for enrollment

Adherence to these criteria as specified in the protocol is essential. Inclusion criteria deviations are not allowed because they can jeopardize the scientific integrity or regulatory acceptability of the study or participant safety.

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

- Male or female participants ≥ 60 YOA at the time of first vaccination, who live in the community (CD participants) or in a LTCF (LTCF participants).

  Please refer to Section 10.5.2 (Glossary of Terms) for the definition of CD participants and LTCF.

- 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 and questionnaires, attend regular phone calls/study site visits, perform self-swabbing, ability to access and utilize a phone or other electronic communications).

  Note: In case of physical incapacity that would preclude the self-completion of the diary cards and/or questionnaires, 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 or in the LTCF). However, at no time, the site staff or caregiver will evaluate the participant's health status while answering diaries and/or questionnaires or make decisions on behalf of the participant. Refer to Section 10.5.2 for the definition of caregiver.

- Written or witnessed informed consent obtained from the participant prior to performance of any study specific procedure.

- Participants who are medically stable in the opinion of the investigator at the time of first 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.

5.2. Exclusion criteria for enrollment

Adherence to criteria specified in the protocol is essential. Exclusion criteria deviations are not allowed because they can potentially jeopardize the scientific integrity or regulatory acceptability of the study or safety of the participant.

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

5.2.1. Medical conditions

- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., current malignancy, human immunodeficiency virus) or immunosuppressive/cytotoxic therapy (e.g., medication used during cancer chemotherapy, organ transplantation, or to treat autoimmune disorders), based on medical history and physical examination (no laboratory testing required).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Hypersensitivity to latex.
- Serious or unstable chronic illness.
- Any history of dementia or any medical condition that moderately or severely impairs cognition.

  Note: If deemed necessary for clinical evaluation, the investigator can use tools such as Mini-Mental State Exam (MMSE), Mini-Cog or Montreal Cognitive Assessment (MoCA) to determine cognition levels of the participant.
- Recurrent or un-controlled 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 and questionnaires, attend regular phone calls/study site visits, perform self-swabbing).
- 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 3 years).
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.

5.2.2. Prior/Concomitant therapy

- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccine during the period beginning 30 days before the first study vaccine administration, or planned use during the study period.
- Planned or actual administration of a vaccine not foreseen by the study protocol in the period starting 30 days before each dose and ending 30 days after each dose of

study vaccine administration, with the exception of inactivated and subunit influenza vaccines which can be administered up to 14 days before or from 14 days after each study vaccination.

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

- Previous vaccination with an RSV vaccine.
- Administration of long-acting immune-modifying drugs or planned administration at any time during the study period (e.g., *infliximab*).
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 90 days before the first study vaccine administration or planned administration during the study period.
- Chronic administration (defined as more than 14 consecutive days in total) of immunosuppressants or other immune-modifying drugs during the period starting 90 days prior to the first study vaccine 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.

5.2.3. Prior/Concurrent clinical study experience

- Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or invasive medical device). Refer to Section 10.5.2 for the definition of invasive medical device.

5.2.4. Other exclusions

- History of chronic alcohol consumption and/or drug abuse as deemed by the investigator to render the potential participant unable/unlikely to provide accurate safety reports or comply with study procedures.
- Bedridden participants.
- Planned move during the study period that will prohibit participating in the study until study end. This includes:
  - Planned move during the study period to another LTCF that will prohibit participation in the study until study end.
  - Planned move from the community to a LTCF that will prohibit participation in the study until study end.
- Participation of any study personnel or their immediate dependants, family, or household members.

- Planned leave or holiday of 4 consecutive weeks or more during the RSV seasons* covered by the study, that would prohibit the reporting of ARI cases and attendance to ARI visit.

  *RSV seasons are from 1 October to 30 April in NH and from 1 March to 30 September in SH.

5.3. Caregiver support

Study participants may decide to assign a caregiver to help them fulfilling the study procedures. Please refer to Section 10.5.2 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 (for example in LTCF setting). 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 questionnaires and diaries, performing the nasal swab, transportation to and from the study site, etc. However, at no time, the caregiver should evaluate the participant's health status while answering diaries and/or questionnaires 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 (Visit 7NH/Visit 5SH), 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.

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

5.4. Screen failures

Not applicable.

6. STUDY INTERVENTION

A 'study intervention' is defined as a set of investigational or marketed product(s) or placebo intended to be administered to a participant during the study.

Refer to the SPM for additional details.

6.1. Study interventions administered (Amended, 12 July 2023)

After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be prepared and administered as shown in Table 11 for Dose 1 and Table 12 for the annual revaccination. Refer to Section 4.1 for the schedule of vaccine administration.

Note that the RSVPreF3 OA investigational vaccine must be reconstituted before administration. Refer to the SPM for instructions on study vaccine reconstitution.

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

For Dose 1:

The RSVPreF3 study groups will receive adjuvanted vaccine consisting of unique combinations of RSVPreF3 antigen lots, i.e., Lot 1, Lot 2, Lot 3 or Lot 4, and extemporaneously reconstituted with $AS01_E$ adjuvant lots, i.e., Lot A, Lot B, Lot C and Lot D. It will result in 4 unique combinations. Before Season 1 in Part 1, the first 3 unique combinations (Lot 1/Lot A, Lot 2/Lot B, Lot 3/Lot C) will be assigned randomly to the participants in the first 3 RSVPreF3 OA investigational vaccine lot groups. Before Season 1 in Part 2, the RSVPreF3 group will receive the 4^{th} unique combination (Lot 4/Lot D). Refer to Section 4.1 for details on the study design and Section 6.3.2 for details on the randomization.

For the annual revaccination:

The RSV_annual group will receive an additional dose of RSVPreF3 OA vaccine before each subsequent RSV season while the RSV_1dose and Placebo groups will receive 1 dose of placebo at the same timepoints*. Refer to Section 4.1 for details on the study design.

**** Participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 will not receive any study intervention at pre-Season 3 visit (Visit 5NH).***

Table 11 Study interventions administered for Dose 1

Study intervention name	RSVPreF3 OA interventional vaccine Lot 1	RSVPreF3 OA interventional vaccine Lot 2	RSVPreF3 OA interventional vaccine Lot 3	RSVPreF3 OA interventional vaccine Lot 4†	Placebo
Formulation	RSVPreF3 (120 µg) Lot 1	RSVPreF3 (120 µg) Lot 2	RSVPreF3 (120 µg) Lot 3	RSVPreF3 (120 µg) Lot 4	NaCl
	$AS01_E$ Lot A: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injections q.s. 0.5 mL	$AS01_E$ Lot B: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injections q.s. 0.5 mL	$AS01_E$ Lot C: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injections q.s. 0.5 mL	$AS01_E$ Lot D: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injections q.s. 0.5 mL	
Presentation	RSVPreF3: Vial; Powder for suspension for injection	RSVPreF3: Vial; Powder for suspension for injection	RSVPreF3: Vial; Powder for suspension for injection	RSVPreF3: Vial; Powder for suspension for injection	Syringe
	AS01E: Vial; Suspension for injection	AS01E: Vial; Suspension for injection	AS01E: Vial; Suspension for injection	AS01E: Vial; Suspension for injection	
Route of administration	IM	IM	IM	IM	IM
Administration site					
Location	Deltoid	Deltoid	Deltoid	Deltoid	Deltoid
Laterality**	Non-dominant	Non-dominant	Non-dominant	Non-dominant	Non-dominant
Number of doses to be administered for Dose 1	1	1	1	1	1
Volume to be administered***	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.7 mL****
Packaging, labeling and TM	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details	Refer to SPM for more details
Manufacturer	GSK	GSK	GSK	GSK	GSK

IM: Intramuscular; SPM: Study Procedures Manual

† Part 2 with the RSVPreF3 OA interventional vaccine Lot 4 will be initiated when the vaccine Lots 1/2/3 for Part 1 are no longer available at the study sites.

*QS-21: Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)

** The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.

*** Refer to the SPM for reconstitution guidance.

**** The volume of the saline pre-filled syringe may be between 0.6 mL and 0.8 mL. The full volume is to be injected.

Table 12 Study interventions administered for annual revaccination (Amended, 12 July 2023)

Study intervention name	RSVPreF3 OA interventional vaccine revaccination lot	Placebo
Formulation	RSVPreF3 (120 µg) revaccination lot	NaCl
	$AS01_E$ revaccination lot: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injections q.s. 0.5 mL	
Presentation	RSVPreF3: Vial; Powder for suspension for injection	Syringe
	AS01E: Vial; Suspension for injection	
Route of administration	IM	IM
Location	Deltoid	Deltoid
Laterality**	Non-dominant	Non-dominant
Number of doses to be administered for annual revaccination	RSV_annual group: 2 doses in NH† 1 dose in SH	RSV_1dose and Placebo groups: 2 doses in NH† 1 dose in SH
Volume to be administered***	0.5 mL	0.7 mL****
Packaging, labeling and TM	Refer to SPM for more details	Refer to SPM for more details
Manufacturer	GSK	GSK

IM: Intramuscular; SPM: Study Procedures Manual
*QS-21: Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
** The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.
*** Refer to the SPM for reconstitution guidance.
**** The volume of the saline pre-filled syringe may be between 0.6 mL and 0.8 mL. The full volume is to be injected.
† ***Participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5, will not receive any study intervention at pre-Season 3 visit (Visit 5NH).***

6.2. Preparation/Handling/Storage/Accountability

The study vaccine must be stored in a safe, locked place at the temperature specified on the vaccine label. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Only authorized study personnel should be allowed access to the study vaccine. Storage conditions will be assessed by a sponsor study contact during pre-study activities. Refer to the section on Study Supplies in the SPM for more details on storage and handling of the study vaccine.

6.3. Measures to minimize bias: randomization and blinding

6.3.1. Participant identification

Participant identification numbers will be assigned to the participants who have consented to participate in the study, according to the range of participant identification numbers allocated to each study center.

6.3.2. Randomization to study intervention (Amended, 12 July 2023)

For Dose 1, the randomization will be stratified by part:

- In Part 1, the study participants will be randomly assigned in a 1:1:1:3 ratio to 1 of the 4 study groups at Visit 1 (Day 1).
- In Part 2, the study participants will be randomly assigned in a 1:1 ratio to 1 of the 2 study groups at Visit 1 (Day 1). Part 2 will be initiated when the vaccine lots for Part 1 are no longer available at the study sites.

To allow GSK to take advantage of greater rates of recruitment in this multi-center study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

At Visit 3 (pre-Season 2), all participants who received 1 of the RSVPreF3 vaccine lots will be re-randomized in a 1:1 ratio into 2 sub-groups (RSV_annual group and RSV_1dose group) to receive annual revaccination (Dose 2 and Dose 3* in NH and Dose 2 in SH).

**** Participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 will not receive any study intervention at pre-Season 3 visit (Visit 5NH).***

The randomization of supplies within blocks will be performed at GSK, using MATerial EXcellence (MAtEx), a program developed for use in Statistical Analysis System (SAS) (Cary, NC, United States [US]) by GSK. Entire blocks will be shipped to the study centers/warehouse(s).

6.3.3. Intervention allocation to the participant

An automated internet-based system (Source data Base for Internet Randomization [SBIR]) will be used for randomization and for identification of intervention material. For Dose 1 in Part 1, the system's randomization algorithm will use a stratification by subset (participants included in reactogenicity/immunogenicity subset or not) and a minimization procedure accounting for center, age and region within each subset. For Dose 1 in Part 2, the system's randomization algorithm will use a minimization procedure accounting for center, age and region. Minimization factors will have equal weight in the minimization algorithm.

The intervention numbers will be allocated by component.

Upon providing the participant identification number and the participant's category for all minimization factors, the randomization system will determine the study group and will provide the intervention number to be used for the vaccination.

When all participants will be randomized for their Dose 1 in the SBIR system, a re-randomization will be run as follows:

- The randomization file related to Dose 1 will be extracted from SBIR.
- A re-randomization of the participants included in the RSVPreF3 groups will be prepared to identify which of those participants will be allocated to the RSV_annual groups or to the RSV_1dose groups in a 1:1 ratio.

  This re-randomization will be accounting for:

  – The different stratification and minimization factors used for the initial randomization: part (Part 1 or Part 2), subset (participants included in reactogenicity/immunogenicity subset or not), center, age and region;

  – The RSVPreF3 OA investigational vaccine lot allocated for Dose 1 (Lot 1, 2, 3 or 4).
- The updated randomization file including the allocation of participants to one of the 2 groups for each lot (RSV_annual group or RSV_1dose group) will be uploaded in SBIR.

The re-randomization file will be prepared by an unblinded independent statistician. It will not be accounting for any data collected in the eCRF, but only for data collected in SBIR for the allocation to the initial study group.

Upon providing the participant identification number, the randomization system will provide the intervention number to be used for the re-vaccination doses.

When SBIR is not available, please refer to the SBIR user guide or SPM for specific instructions.

Refer to the SPM for additional information relative to the intervention number allocation.

6.3.4. Allocation of participants to assay subsets

Evaluation of solicited events and the humoral immune response will be performed in a subset of participants, referred to as reactogenicity and immunogenicity subset. This subset will include approximately 1800 participants (corresponding to ~7% of the total study population) from the 3 RSVPreF3 OA investigational vaccine lot groups and placebo group (1:1:1:3 ratio) in Part 1, including participants from NH and SH, as indicated in Table 13.

Table 13 Number of participants in reactogenicity and immunogenicity subset (Amended, 12 July 2023)

For Dose 1					
	RSVPreF3_L1	**RSVPreF3_L2**	**RSVPreF3_L3**	**Placebo**	**Total**
NH	~270	~270	~270	~810	~1620
SH	~30	~30	~30	~90	~180
For Dose 2					
	RSV_annual group		**RSV_1dose group**	**Placebo**	**Total**
NH	~405		~405	~810	~1620
SH	~45		~45	~90	~180
For *immunogenicity pre-Season 3*					
	RSV_annual group		**RSV_1dose group**	**Placebo**	**Total**
NH	~405		~405	~810	~1620

NH: Northern hemisphere; SH: Southern hemisphere.

Participants contributing to the reactogenicity and immunogenicity subset will be recruited from a selected number of countries and selected number of sites. In the selected sites, the investigator will allocate the first participants in each age category to the reactogenicity and immunogenicity subset until the allocated target is reached.

At time of randomization for Dose 1, the subset will be entered in SBIR as stratification factor. A randomization blocking scheme (1:1:1:3 ratio) will be used to ensure that balance between interventions is maintained. The randomization algorithm will use a minimization procedure accounting for center, age and region within the subset. All minimization factors will have equal weight in the minimization algorithm.

6.3.5. Blinding and unblinding

Data will be collected in an observer-blind manner. 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, efficacy).

The unblinded study personnel are allowed to transcribe source data into the eCRF without interpretation or generation of data.

The laboratory in charge of the sample testing will be blinded to the intervention assignment. Codes will be used to link the participant and study (without any link to the intervention attributed to the participant) to each sample.

At different analyses, there will be a risk of individual unblinding. Given that summary safety results may unblind some specific participants (e.g., an AE occurring only in a single group), anyone having access to these analyses could become unblinded regarding that specific case. In order to maintain the whole team (Central, Local, Investigators) and participants blinded at the individual participant level, a firewall team will be set up. This firewall team will allow all analyses until the implementation of Protocol Amendment 4 to be performed and results reported to the relevant authorities while the study blind is maintained. In case no participant is reported in 1 group (e.g., a certain event being only reported in participants in the other study group), the blinding of results is managed by an

Independent External Statistician (IES). In this situation, exact results per group are not provided to the blinded team members and the investigators. The firewall team will review the results before they are distributed to the study team, to prevent these data potentially leading to unblinding at participant level of the study team. Further details of this approach can be found in the firewall charter.

For analyses planned as of the implementation of Protocol Amendment 4, GSK RSV OA team members will be unblinded at the individual participant level in order to support the regulatory activities and study results interpretation, with the exception of GSK RSV OA team members involved in clinical evaluation (i.e., personnel involved in data review and validation, ARI/LRTD case adjudication, laboratory testing), study participants, investigators and site personnel involved in the clinical evaluation of the participants, who will remain blinded at the individual participant level up to end of study. In case no participant is reported in 1 group (e.g., a certain event being only reported in participants in the other study group), exact results per group will not be provided to blinded team members and the investigators. The firewall team will no longer be active.

A participant may continue in the study if that participant's intervention assignment is unblinded (see Sections 6.3.5.1 and 6.3.5.2).

6.3.5.1. Emergency unblinding

Unblinding a participant's individual intervention number should occur ONLY in case of a medical emergency when knowledge of the intervention is essential for the clinical management or welfare of the participant.

The emergency unblinding process enables the investigator to have unrestricted, immediate and direct access to the participant's individual study intervention via SBIR.

As back-up process, the investigator has the option of contacting a GSK Helpdesk (refer to the Table 14) if he/she needs help performing the unblinding (i.e., he/she cannot access SBIR).

A non-investigator physician (e.g., physician from emergency room) or participant/caregiver member may also request emergency unblinding either via the investigator (preferred option) or via the GSK Helpdesk (back-up process). The patient/participant card lists contact information for both the investigator and GSK Helpdesk.

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

Table 14 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and e-mail Toll-free number: Australia: PPD Belgium: PPD Canada: PPD Estonia: PPD Finland: PPD Germany: PPD Italy: PPD Japan: PPD Mexico: PPD Russia: PPD South Africa: PPD South Korea: PPD Spain: PPD United Kingdom: PPD United States: PPD Phone (for all countries where the toll-free number is not available): PPD Fax: PPD E-mail: PPD

6.3.5.2. Emergency unblinding prior to regulatory reporting of SAEs

GSK policy (which incorporates ICH E2A guidance, the EU Clinical Trial Directive and US Federal Regulations) is to unblind the report of any unexpected SAE and which is attributable/suspected to be attributable to the study vaccine, prior to regulatory reporting. Vaccines Clinical Safety and Pharmacovigilance (VCSP) is responsible for unblinding the intervention assignment in accordance with the specified timeframes for expedited reporting of SAEs (refer to the Section 10.3.10.1).

In addition, GSK VCSP staff may unblind the intervention assignment for any participant with a Suspected Unexpected Serious Adverse Reaction (SUSAR) or a Serious Adverse Event that is fatal or life-threatening. If the SAE requires 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.

6.4. Study intervention compliance

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

6.5. Concomitant therapy (Amended, 12 July 2023)

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 each dose of study vaccine (Day 1 to Day 30 after each dose).
- 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 8.3.1 and 10.3.8. These must also be recorded on the Expedited Adverse Event report.
- For all AF AESIs (including serious and non-serious), concomitant drugs which could be associated with development or worsening of AF must be reported in the AF follow-up questionnaire.
- Any prophylactic medication (e.g., analgesics, antipyretics) administered on each study vaccination day (Day 1, pre-Season 2 and pre-Season 3*) in the absence of ANY symptom and in anticipation of a reaction to the vaccination.

  **** Not applicable for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 and will not receive any study intervention at pre-Season 3 visit (Visit 5NH).***
- 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.
- 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).

Refer to Table 15 for an overview of the timing for recording of concomitant medication during the study.

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

Table 15 Timing of collection of concomitant medication to be recorded (Amended, 12 July 2023)

	Dose 1 Day 1 post-D1	Day 30 post-D1	Dose 2 Day 1 post-D2	Day 30 post-D2	Dose 3* Day 1 post-D3	Day 30 post-D3	Study Conclusion
All concomitant medication, except vitamins and dietary supplements					***	***	
All concomitant vaccination							
All concomitant medication including vaccines/products which may explain/cause/be used to treat an SAE/pIMD/AF**							
Any prophylactic medication					***		
All concomitant medications taken for the treatment of an ARI or for an ARI-related complication							
Any investigational or non-registered product							
Chronic administration (defined as more than 14 consecutive days in total) of immunosuppressants or other immune-modifying drugs							
Administration of immunoglobulins and/or any blood products							
Administration of long-acting immune-modifying drugs							

AF: Atrial Fibrillation; D: Dose; ARI: acute respiratory illness; SAE: serious adverse event; pIMD: potential immune-mediated disease;
Note: The collection period for the concomitant medications to be recorded in eCRF is indicated in grey.
* Only applicable for participants in Northern hemisphere.
** 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.
****** Not applicable for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 and will not receive any study intervention at pre-Season 3 visit (Visit 5NH).***

6.6. Dose modification

Not applicable.

6.7. Intervention after the end of the study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention (Amended, 12 July 2023)

'Discontinuation' of study intervention means any participant who has not received all planned doses of vaccine. A participant who discontinued study intervention may, if deemed appropriate by the investigator, continue other study procedures (e.g., subsequent dose, efficacy, safety or immunogenicity) if planned in the study protocol.

The primary reason for premature discontinuation of the study intervention will be documented in the eCRF based on the following:

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

Refer to Section 7.1.2 for contraindications to subsequent vaccination. Refer to Section 10.5.2 (glossary of terms) for the definition of intervention.

Participants who do not consent for the annual revaccination will be considered withdrawals from the study.

7.1.1. Criteria for temporary delay for enrollment and/or vaccination

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

- Acute disease and/or fever at the time of vaccination. Fever is defined as a temperature ≥ 38.0°C/100.4°F by any route. The route for measuring temperature can be oral, axillary or tympanic.

- Participants with symptoms suggestive of active Coronavirus Disease 2019 (COVID-19) infection (e.g. fever, cough, etc.). The return to the site of the participant will follow the specific guidance from local public health and other competent authorities (e.g., free of symptoms, COVID-19 negative testing, etc.).
- Participants with known COVID-19 positive contacts within the past 14 days may be vaccinated at the discretion of the investigator at least 14 days after the exposure if the participant remains symptom free.
- Participants with a minor illness (such as mild diarrhea, 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: Postponement of study vaccine administration within given protocol timelines to allow respect of the 14 day-interval between flu vaccination and study vaccine administration.

Refer to Table 5 and Table 6 in Section 1.3 for the allowed time intervals in Northern and Southern hemispheres, respectively.

7.1.2. Contraindications to subsequent vaccine administration (Amended, 12 July 2023)

Participants must be evaluated to confirm that there are no contraindications for subsequent vaccination before administering each additional study vaccine dose.

Participants who meet any of the criteria listed below or criteria listed in Sections 5.2.1, 5.2.2 and 5.2.3 should not receive additional vaccinations. However, these participants should be encouraged to continue other study procedures at the discretion of the investigator (Section 10.3.8.2). The relevant criteria for discontinuing vaccination must be recorded in the eCRF.

- Participants who experience any SAE judged to be possibly or probably related to the study vaccine or non-study concomitant vaccines, including hypersensitivity reactions.
- Participants who develop any new condition which, in the opinion of the investigator, may pose additional risk to the participant if he/she continues to participate in the study.
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, exposes the participant to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgment prior to administering the next dose of the vaccine. Refer to Section 10.3.5.1 for the definition of pIMDs.

Note: This section is not applicable at pre-Season 3 visit for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 and will not receive any study intervention at pre-Season 3 visit (Visit 5NH).

7.2. Participant discontinuation/withdrawal from the study

A participant is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this participant from the date of withdrawal/last contact.

From an analysis perspective, a 'withdrawal' from the study refers to any participant who did not return for the concluding visit foreseen in the protocol. Investigators will attempt to contact those participants who do not return for scheduled visits or follow-up. All data and samples collected until the date of withdrawal/last contact of the participant will be used for the analysis.

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

- AEs requiring expedited reporting to GSK (refer to Section 10.3.10.1 for details)
- Unsolicited non-serious AE
- Solicited event
- Withdrawal by participant, not due to an AE*
- Migrated/moved from the study area
- Lost to follow-up
- Sponsor study termination
- Other (specify).

* If a participant is withdrawn from the study because he/she has withdrawn consent and provided the reason for its withdrawal, the investigator must document this reason in the eCRF.

Participants who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow participants who are withdrawn from the study as result of an SAE/AE until the event is resolved (see Section 10.3.8.2).

7.3. Lost to follow-up

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

Please refer to the SPM for a description of the actions to be taken before considering the participant as lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES (AMENDED, 12 JULY 2023)

Study procedures and their timings are summarized in Table 1 and ***Table 2*** for participants in NH, Table 3 for participants in SH and Table 4 for ARI surveillance (Section 1.3). The intervals between study visits are provided in Table 5, Table 6 and Table 7, respectively. Study visits should preferably be done on site or in the LTCF. If deemed necessary and not possible for study participant to come to site, study visits can be done at home.

Adherence to the protocol is required for study conduct.

Protocol waivers or exemptions are not allowed unless necessary for the management of an immediate safety concern.

Immediate safety concerns should be discussed with the sponsor as soon as they occur or when the study team is aware of them. The purpose of this communication is to determine if the participant(s) should discontinue the study intervention.

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

During special circumstances (e.g., COVID-19 pandemic), the specific guidance from local public health and other competent authorities regarding the protection of individuals' welfare must be applied. For the duration of such special circumstances, the following measures may be implemented for enrolled participants:

- Safety follow-up may be made by a telephone call, other means of virtual contact or home visit (from the site staff or from home care service system), if appropriate.
- Diary cards may be transmitted from and to the site by electronic or conventional mail or collected at the participant's residence.
- Visits for suspected ARI may take place in a different location* other than the study site or at participant's home. If this is not feasible, then the medical evaluation of ARI may take place virtually with documentation of ARI symptoms and other relevant ARI information by phone or other means of virtual live contact.
- Biological samples may be collected at a different location* other than the study site or at participant's home. Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- Throat and/or nasal swab samples collected at ARI visits may be taken by someone else than the site staff (for example, a swab sample may be taken by the participant or caregiver) with site staff supervision and guidance, if required by local regulations.

- If despite best efforts it is not possible to perform the ARI visit within the interval pre-defined in the protocol (see Table 7) (for example in case of suspected COVID-19 infection and pending COVID-19 test result, or self-quarantine), then the interval for this visit may be extended up to maximum 14 days after ARI onset (i.e., until Day 15, refer to Figure 3 for ARI flow). In any case, the participant should be encouraged to take the self-swab as per protocol (i.e., preferably within 48 hours after ARI onset but not later than 5 days after ARI onset) to maximize the chance to detect the virus.

[*] *It is the investigator's responsibility to identify an alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, such as adequate facilities to perform study procedures, appropriate training of the staff and documented delegation of responsibilities in this location. This alternate location should be covered by proper insurance for the conduct of study on participants by investigator and staff at a site other than the designated study site. Refer to EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 2, 27 March, 2020) for more details.*

Refer to the SPM for further details on decentralized clinical trial solutions.

Impact on the per protocol sets for efficacy and immunogenicity will be determined on a case by case basis.

8.1. Efficacy and immunogenicity assessments

8.1.1. Efficacy assessments

8.1.1.1. ARI surveillance period and methods

Surveillance for detection of ARI episodes will be carried out during the entire study, via spontaneous reporting by the study participant (starting on the day of first vaccination* [Visit 1]) and by scheduled site staff contacts (starting from Visit 2 onwards) with different frequencies of contact during the RSV seasons and the inter-season periods. Based on the observed RSV circulation during the season, the ARI surveillance and/or the DLP for analyses could be adapted for the ongoing and/or subsequent seasons. Refer to Figure 2 for details on ARI surveillance. ARI episodes will be captured via 2 complementary methods: 1) spontaneous reporting by the participant (see Section 8.1.1.4) scheduled site staff contacts (see Section 8.1.1.4).

* For detailed information on activities involved in ARI surveillance, refer to Table 4.

Swab samples will be taken in all participants meeting pre-specified criteria for ARI case definition (see Table 10 in Section 4.2.1). Diagnosis and treatment of each ARI should be performed according to the local standard of care.

8.1.1.1.1. Nasal self-swab training with the study participant

At Visit 2, the study participants 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 as of Visit 1, however no nasal self-swab will be requested from the participant for ARI episodes occurring before Visit 2.

8.1.1.2. 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 10 in Section 4.2.1). 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 first vaccination day (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.

8.1.1.3. ARI capture and follow-up

ARI episodes will be captured via 2 complementary methods: 1) spontaneous reporting by the participant 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.

8.1.1.4. Spontaneous reporting by the participant

Participants will be instructed to contact spontaneously the investigator/site staff promptly if they experience at least 2 ARI symptoms/signs (see Table 10 in Section 4.2.1). The surveillance for ARI will start on the first 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 2, participants will be invited to practice nasal self-swab collection (refer to Section 8.1.1.1.1). Note that no nasal self-swab will be requested from the participant for ARI episodes occurring before Visit 2.

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

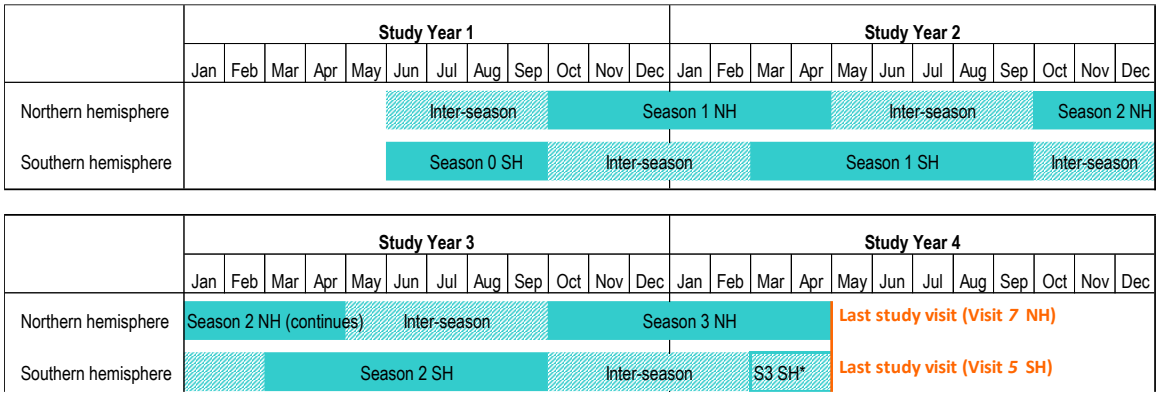
8.1.1.5. Scheduled site staff contacts (Amended, 12 July 2023)

As of Visit 2 onwards, the site staff will contact the participants regularly during the entire study to check if they have experienced any respiratory symptoms meeting the ARI case definition (see Table 10 in Section 4.2.1). These contacts will be performed:

- every 2 weeks during the RSV seasons,
- every month during the inter-season periods.

The RSV seasons defined for this study are from 1 October to 30 April in NH and from 1 March to 30 September in SH.

Figure 2 ARI surveillance in Northern and Southern hemispheres (Amended, 12 July 2023)



NH: Northern hemisphere; SH: Southern hemisphere.
In some SH countries, recruitment might start during an RSV Season (Season 0).
Surveillance for ARI will be carried out during the entire study, via spontaneous reporting by the study participant (starting on the day of first vaccination [Visit 1]) and by scheduled site staff contacts (starting from Visit 2 onwards) with different frequencies of contact during the RSV seasons and the inter-season periods.
The site staff surveillance contacts will be performed: every 2 weeks during the RSV seasons (Solid blue) and every month during the inter-season periods (Shaded blue). The RSV seasons defined for this study are: from 1 October to 30 April in NH and from 1 March to 30 September in SH. Based on the observed RSV circulation during the season, the ARI surveillance and/or the DLP for analyses could be adapted for the ongoing and/or subsequent seasons.
Note: If following the sample size re-assessment an additional cohort needs to be enrolled before the next season in NH (see Section 9.2.3), similar ARI surveillance will apply up to the end of the third season for those participants.
Study Year 1 corresponds to the year in which the enrollment started for the cohort.
* The last study visit in SH (Visit ***5*** SH) will occur approximately 2 months after the start of Season 3 in SH; yet the site staff surveillance contacts will be performed monthly during these last months (i.e., continuation of the inter-season frequency of contacts).

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, or via a visit for LTCF participants. 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.

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

- Any symptoms/signs meeting the ARI case definition (see Table 10 in Section 4.2.1).
- 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, and AESIs (including pIMDs and AF) should be reported to GSK during specified follow-up periods as described in Section 10.3.8.
- Any COVID-19 infection (suspected, probable or confirmed).
- 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 8.1.1.6.2.

*Note: In this study AF will be collected as AESIs. See definition of AESI in Section 10.3.5.

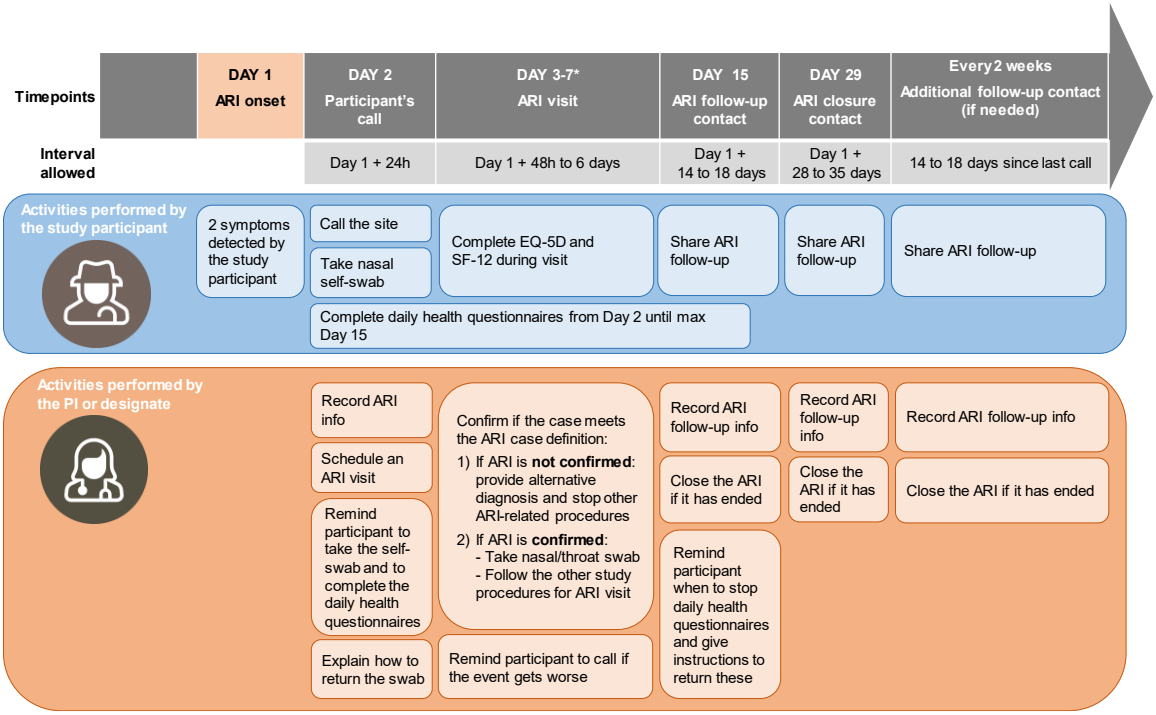
8.1.1.6. ARI procedures

8.1.1.6.1. Primary route to capture ARI episodes

Spontaneous reporting by the participant should be the main route to capture ARI episodes and the related procedures are described in Figure 3 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 10.3.8. If an ARI is a suspected, probable or confirmed COVID-19 case as per World Health Organization (WHO) case definitions, the COVID-19 specific eCRF page should be completed. Testing for detection of SARS-CoV-2 infections should be done according to local requirements and via local testing facilities.

Figure 3 ARI capture and follow-up



The ARI visit should preferably be done on site or in the LTCF. 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 or visit to the LTCF.
Nasal self-swab collection and completion of daily health questionnaires are not applicable for ARI episodes reported before Visit 2.
* In special circumstances (for example in case of suspected COVID-19 infection and pending COVID-19 test result, or self-quarantine) and if it is not possible to perform the ARI visit within 6 days after ARI onset (i.e., within Day 3 to Day 7), then the interval for this visit may be extended up to maximum 14 days after ARI onset (i.e., until Day 15). If the ARI visit takes place between Day 10 and Day 15, then the first follow-up contact may be skipped.

In case of at least 2 concomitant ARI symptoms/signs identified by the participant, the following visits and contacts will take place (refer to Table 7 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 (Note: this is not applicable for ARI episodes reported before Visit 2). 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.

- **Reminder to start completing the daily health questionnaires**: The questionnaires should be completed from the participant's call (Day 2) until the end of the ARI episode or for maximum 14 consecutive days (i.e., from Day 2 until Day 15 at the latest) (Note: this is not applicable for ARI episodes reported before Visit 2). Each study site should define upfront the most appropriate method(s) for collection of questionnaires completed by the participant (via mail, service courier, or other).

- **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.

  * Note: In special circumstances, (for example in case of suspected COVID-19 infection and pending COVID-19 test result, or self-quarantine) and if it is not possible to perform the ARI visit within 6 days after ARI onset (i.e., within Day 3 to Day 7), then the interval for ARI visit may be extended up to maximum 14 days after ARI onset (i.e., until Day 15). If the ARI visit occurs within 7 to 9 days after ARI onset (i.e., within Day 8 to Day 10), then the remaining follow-up contacts (i.e., Day 15 and Day 29) should be performed as described below. If the ARI visit occurs between 10 to 14 days after ARI onset (i.e., within Day 11 to Day 15), then the first follow-up contact (i.e., Day 15 contact) can be skipped; the next contact will be the Day 29 contact. In any case, the participant should be encouraged to take the self-swab as per protocol (i.e., preferably within 48 hours after ARI onset but not later than 5 days after ARI onset) to maximize the chance to detect the virus.
  ** Note: the nasal self-swab collection is not applicable for ARI episodes reported before Visit 2.

  During the ARI visit the following procedure should be performed (refer also to Table 4 in Section 1.3):

  - **Physical examination, body temperature and vital signs:** refer to Section 8.2.2.
  - **Pulse oximetry:** refer to Section 8.2.2.4.
  - **Confirmation of ARI:** The investigator or designee will confirm if the event meets the ARI case definition (see Table 10 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. The participant should

be instructed to stop completing the daily health questionnaires. Refer to the SPM for details on the handling of self-swab samples and the daily health questionnaires 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 4 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 Table 16.

  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 16 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 (Note: this is not applicable for ARI episodes reported before Visit 2).

– **Nasal and throat swab sampling:** For each ARI reported after the first 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 SPM.

  The swab samples will allow to assess the potential RSV and hMPV infections by RT-PCR at a sponsor or sponsor-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.

- **Collection of HCRU:** Each participant will be asked to answer questions on healthcare utilization since ARI onset until resolution of the episode. Refer to Section 8.10.2 for an overview of HCRU data to be recorded in the participant's eCRF.
- **HR-QoL questionnaires:** Participants will be asked to complete HR-QoL questionnaires (EQ-5D and SF-12) during the ARI visit. All HR-QoL questionnaires will be completed by the participant (or with the assistance of their caregiver in case of physical incapacity) in the presence of site staff.
- **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.
  The participant will also be reminded to complete the daily health questionnaires until the end of the ARI or for maximum 14 days (Note: this is not applicable for ARI episodes reported before Visit 2).
- **Recording of AEs, SAEs and other events of interest:** refer to Section 8.3.
- **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 and new daily health questionnaires to the study participant for the next ARI episode (Note: this is not applicable for ARI episodes reported before Visit 2).

- **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 or visit to the LTCF) approximately 14 days after ARI onset. If due to special circumstances (for example a suspected COVID-19 infection or pending COVID-19 test result, or self-quarantine), the ARI visit occurs between 10 to 14 days after ARI onset (i.e., within Day 11 to Day 15), then the first follow-up contact (i.e., Day 15 contact) can be skipped; the next contact will be the Day 29 contact.
  - **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 PCR diagnostic kit (if applicable) should be recorded in the eCRF.
  - **Daily health questionnaires:** The participant will be reminded to complete the daily health questionnaires until Day 15 at the latest in case the ARI is still ongoing. The participant should also be reminded when to stop completing the questionnaires and how the completed questionnaires should be returned to the site (Note: this is not applicable for ARI episodes reported before Visit 2).
  - **HCRU** should also be recorded.
  - **Recording of AEs, SAEs and other events of interest:** refer to Section 8.3.

- 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 seasons, or
  - within a maximum of 30 days if it's during the inter-season period.

8.1.1.6.2. 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 participant. 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 via the LTCF staff or hospital staff, for example.

If 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.

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 10.3.8. If an ARI is a suspected, probable or confirmed COVID-19 case as per WHO case definitions [WHO, 2020], the COVID-19 specific eCRF page should be completed.

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* and to complete the daily health questionnaires***. The site staff will organize an ARI visit within the per protocol window**. Refer to Section 8.1.1.6.3 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.
** Note: In special circumstances (for example in case of suspected COVID-19 infection and pending COVID-19 test result, or self-quarantine) and if it is not possible to perform the ARI visit within 6 days after ARI onset, then the interval for this visit may be extended up to maximum 14 days after ARI onset (i.e., until Day 15).

*** Note: If the ARI is reported more than 7 days after the ARI onset (i.e., on Day 8 or later), then the daily health questionnaires should not be completed for that ARI.

– 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 3 and Section 8.1.1.6.1.

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, the daily health questionnaires should not be completed 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 3 and Section 8.1.1.6.1.

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. The daily health questionnaires should not be completed, and no ARI visit should be organized.

8.1.1.6.3. Hospitalization during an ARI episode

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

Note that if the event also qualifies as an SAE**,** it should be reported to GSK during specified follow-up periods as described in Section 10.3.8. If an ARI is a suspected, probable or confirmed COVID-19 case as per WHO case definitions [WHO, 2020], the COVID-19 specific eCRF page should be completed.

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 4) and the daily health questionnaires should be completed.

  ** Note: In special circumstances (for example in case of suspected COVID-19 infection and pending COVID-19 test result, or self-quarantine) and if it is not possible to perform the ARI visit procedures within 6 days after ARI onset, then the interval for this visit may be extended up to maximum 14 days after ARI onset (i.e., until Day 15).*

- 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 3 and Section 8.1.1.6.1.

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 3 and Section 8.1.1.6.1.

8.1.2. Immunogenicity assessments

The immunogenicity of the vaccine will be evaluated by assessing the humoral immune response at different timepoints.

Serological assays for the characterization of the humoral immune response include ELISA for measurement of IgG antibodies binding to the RSVPreF3 protein and neutralization assay for determination of functional antibodies against RSV A and RSV B. RSVPreF3 IgG-binding ELISA and neutralization testing for RSV A and RSV B will be performed for participants included in the reactogenicity and immunogenicity subset. To evaluate the correlation between humoral immune response and protection, RSVPreF3 IgG-binding ELISA will also be tested on participants with RSV-confirmed disease and in a subset of control participants. A correlate of protection might also be investigated by testing the same subset by other relevant assays such as neutralization assay(s) and systems serology.

Additional assessments, including but not limited to ELISA or other relevant assays for hMPV serological testing, may be conducted.

8.1.3. Biological samples

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

Future findings may make it desirable to use the samples acquired in this study for future research not described in this protocol. Therefore, all participants in countries where this is allowed will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to prior IEC/IRB approval if required per local legislation.

Information on further investigations and their rationale can be obtained from GSK.

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

Collected samples will be stored for a maximum of 20 years. This storage period begins when the last participant performed the last study visit, unless local rules, regulations or guidelines require different timeframes or procedures, which would then be in line with participant consent. These extra requirements need to be communicated formally to, and discussed and agreed with GSK.

8.1.3.1. Biological samples for efficacy assessment

Swab samples will be taken in all participants meeting pre-specified criteria for case definition and evaluation of VE, according to the timing detailed in Section 8.1.1.6 (refer to Section 4.2.1) (see Table 17).

Table 17 Biological samples for efficacy assessment

Sample type	Timepoint	Subset name
Nasal self-swab specimen	Case-driven	All participants reporting at least 2 ARI symptoms/signs meeting the ARI case definition (see Table 10 in Section 4.2.1)
Nasal/throat swab specimen collected by qualified site staff	Case-driven (ARI visit)	All participants reporting at least 2 ARI symptoms/signs meeting the ARI case definition (see Table 10 in Section 4.2.1)

8.1.3.2. Biological samples for immunogenicity assessment (Amended, 12 July 2023)

A blood sample will be taken from all participants in both hemispheres at pre-Dose 1 (Day 1), 1-month post-Dose 1 (Day 31) ***and from all participants at Visit 5NH**** to allow the evaluation of a potential correlate of protection. In addition, the immune response to the RSVPreF3 OA investigational vaccine will be further evaluated at other timepoints in a subset of participants (see Table 18).

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

- ~60 mL (3 x 20 mL) for participants in the reactogenicity and immunogenicity subset from SH,
- ~80 mL (4 x 20 mL) for participants in the reactogenicity and immunogenicity subset from NH,
- ~40 mL (2 x 20 mL) for all other participants in SH.
- ***~60 mL (3 x 20 mL) for all other participants in NH****

****Applicable after the approval of the current Protocol Amendment 5.***

Table 18 Biological samples for immunogenicity assessment (Amended, 12 July 2023)

Sample type	Quantity	Unit	Timepoint	Subset name*
Blood for correlate of protection	~20	mL	Visit 1 (Day 1, pre-Dose 1) Visit 2 (Day 31, post-Dose 1)	All participants
	~20	***mL***	***Visit 5NH (Pre Season 3)***	***All participants******
Blood for antibody measurement	~20	mL	Visit 3 (Pre Season 2, pre-Dose 2) Visit 5NH (Pre Season 3)	Immunogenicity subset**

* Refer to Section 6.3.4 for subset description.
** Reactogenicity and immunogenicity subset (see Section 6.3.4).
****All participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 including participants in the immunogenicity subset.***

Note: After the approval of the current Protocol Amendment 5, participants from the immunogenicity subset will still provide only 1 blood sample at Visit 5NH. This sample will be used for both the assessment of humoral immune response and evaluation of correlate of protection.

8.1.4. Laboratory assays

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

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

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

8.1.4.1. Laboratory assays for efficacy assessment

For ARI cases identified during the efficacy surveillance, the potential RSV infections will be assessed by RT-PCR testing of swab samples (see Table 19). The multiplex PCR assay that will be used to assess the potential hMPV infections will also detect by default the potential infection to Adenovirus, Enterovirus and Parainfluenza viruses. Swab

samples that are positive for RSV and/or hMPV by RT-PCR will be further tested for additional respiratory viruses such as Influenza, Bocavirus, Coronavirus and Rhinovirus for detection of potential viral co-infections.

Further assessment of samples negative for RSV and negative for hMPV by RT-PCR may be performed with multiplex PCR if deemed necessary.

Additional viral/bacterial diagnosis or characterization testing on the swab samples may be done, if deemed necessary for accurate interpretation of the data and/or should such assays become available at the GSK laboratory or a laboratory designated by GSK.

Table 19 Laboratory assays for molecular biology (PCR tests)

System	Component	Method	Laboratory*
All nasal self-swab collected by the participant and nasal/throat swab specimen taken at ARI visit	Respiratory Syncytial Virus A RNA Respiratory Syncytial Virus B RNA	Quantitative RT-PCR	GSK**
All nasal self-swab collected by the participant and nasal/throat swab specimen taken at ARI visit	Human adenovirus (AdV) Human metapneumovirus (hMPV) Human enterovirus (HEV) Human parainfluenza virus including at least types 1, 2, 3 and 4 (PIV1, PIV2, PIV3 and PIV4)	Multiplex RT-PCR	GSK**
All nasal self-swab collected by the participant and nasal/throat swab specimen taken at ARI visit that are RSV A/B and/or hMPV positive by RT-PCR	Influenza A virus (Flu A) Influenza B virus (Flu B) Human respiratory syncytial virus A (RSV A) Human respiratory syncytial virus B (RSV B) Human Influenza A virus subtype H1 (Flu A-H1) Human Influenza A virus subtype H3 (Flu A-H3) Human Influenza A virus subtype H1pdm09 (Flu A-H1pdm09) Human bocavirus 1/2/3/4 (HBoV) Human rhinovirus A/B/C (HRV) Human coronavirus including at least 229E, NL63, OC43 and SARS-COV-2 species	Multiplex RT-PCR	GSK**

RT-PCR: reverse transcription polymerase chain reaction
* Refer to the list of clinical laboratories for details.
** GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. CLS may delegate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Sienna, Italy or to a contracted CRO.

8.1.4.2. Laboratory assays for immunogenicity assessment

Serological assays for the characterization of the humoral immune response include ELISA for measurement of IgG antibodies binding to the RSVPreF3 protein and neutralization assay for determination of functional capacity of serum to protect cells against RSV A and RSV B (see Table 20).

Table 20 Laboratory assays for humoral immune response (antibody determination)

System	Component	Method	Laboratory*
Serum	RSVPreF3-binding IgG antibody	ELISA	GSK**
Serum	Respiratory Syncytial Virus A antibody	Neutralization	GSK**
Serum	Respiratory Syncytial Virus B antibody	Neutralization	GSK**

ELISA: enzyme-linked immunosorbent assay; IgG: immunoglobulin G
* Refer to the list of clinical laboratories for details.
** GSK laboratory refers to the Clinical Laboratory Sciences (CLS) in Rixensart, Belgium; Wavre, Belgium. CLS may delegate testing to GSK Research laboratories in Rixensart, Belgium; Rockville, USA; Sienna, Italy or to a contracted CRO.

8.1.5. Immunological read-outs (Amended, 12 July 2023)

Table 21 Immunological read-outs (Amended, 12 July 2023)

Blood sampling time point		Subset tested	No. samples tested	Component	Components priority rank
Type of contact and time point	Sampling time point				
Visit 1 (Day 1)	Pre-Dose 1	Immunogenicity subset*	~1800	RSV A neutralizing antibody	1
				RSV B neutralizing antibody	2
				RSVPreF3-binding IgG antibody	3
		All participants with RSV disease + Subset of controls**	Case-driven**	RSVPreF3-binding IgG antibody	-
Visit 2 (Day 31)	30 days post-Dose 1	Immunogenicity subset*	~1800	RSV A neutralizing antibody	1
				RSV B neutralizing antibody	2
				RSVPreF3-binding IgG antibody	3
		All participants with RSV disease + Subset of controls**	Case-driven**	RSVPreF3-binding IgG antibody	-
Visit 3 (Pre S2)	Pre-Dose 2	Immunogenicity subset*	~1800	RSV A neutralizing antibody	1
				RSV B neutralizing antibody	2
				RSVPreF3-binding IgG antibody	3
Visit 5NH (Pre S3)	Pre-***Season 3***	Immunogenicity subset*	~1620	RSV A neutralizing antibody	1
				RSV B neutralizing antibody	2
				RSVPreF3-binding IgG antibody	3
		All participants with RSV disease + Subset of controls*	***Case-driven****	***RSVPreF3-binding IgG antibody***	-

RSV = respiratory syncytial virus; IgG = immunoglobulin G
* Reactogenicity and immunogenicity subset (see Section 6.3.4).
** A blood sample will be taken in all participants at Visit 1 and Visit 2 to allow the evaluation of a potential correlate of protection. RSVPreF3 ELISA will be tested on all participants with RSV-confirmed disease and in a subset of control participants. Additional testing such as but not limited to neutralization assay(s) and systems serology testing might be performed on the same subset of participants to investigate a correlate of protection. ***After approval of this Protocol Amendment 5, a blood sample will also be taken at Visit 5NH.***

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to priority ranking provided in Table 21.

8.1.6. Molecular biology read-outs

Table 22 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 participants with at least 2 ARI symptoms/signs*	Case-driven	RSV A/B RNA	1
				Human adenovirus (AdV) Human metapneumovirus (hMPV) Human enterovirus (HEV) Human parainfluenza virus including at least types 1, 2, 3 and 4 (PIV1, PIV2, PIV3 and PIV4)	2
		All RSV A/B or hMPV positive swab samples**	Case-driven	Respiratory virus panel	-
ARI visit (nasal and throat swabs)	Unscheduled	All participants with at least 2 ARI symptoms/signs*	Case-driven	RSV A/B RNA	1
				Human adenovirus (AdV) Human metapneumovirus (hMPV) Human enterovirus (HEV) Human parainfluenza virus including at least types 1, 2, 3 and 4 (PIV1, PIV2, PIV3 and PIV4)	2
		All RSV A/B or hMPV positive swab samples**	Case-driven	Respiratory virus panel	-

ARI: acute respiratory illness ; hMPV: human metapneumovirus; RSV: respiratory syncytial virus
* RSV A/B and hMPV RT-PCR will be performed on all specimen from participants with at least 2 ARI symptoms/signs meeting the ARI case definition as per Table 10 in Section 4.2.1.
** Respiratory virus panel (multiplex PCR) will be performed on all swabs RSV-A/B and/or hMPV positive by RT-PCR. Further assessment of RSV A/B and hMPV negative samples may be performed with multiplex PCR if deemed necessary.

8.1.7. Immunological correlates of protection (Amended, 12 July 2023)

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

This study will attempt to correlate humoral immune responses at Day 31 post-Dose 1 ***and at pre-Season 3 (Visit 5NH)*** with protection against RSV-confirmed disease (see Section 9.4.5.4.1). Additional testing such as but not limited to neutralization assay(s) and systems serology testing might be performed on a subset of participants with RSV-confirmed disease and in a subset of control participants.

8.2. Safety assessments

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.

8.2.1. Pre-vaccination procedures

8.2.1.1. Collection of demographic data

Prior to the first study vaccination at Visit 1, record demographic data such as year of birth, sex, race*, ethnicity*, geographical hemisphere location (Northern/Southern hemisphere) and type of residence (CD/LTCF) in the participant's eCRF.

*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.

8.2.1.2. Measure/record height and weight

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

8.2.1.3. Medical history

Prior to the first 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 first study vaccination in the eCRF.

A pre-defined list of comorbidities to be recorded will be available in the eCRF.

8.2.1.4. Vaccination history

Prior to the first 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 first 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 first study vaccine administration) should be recorded in the eCRF. The date of vaccinations should be collected and recorded in the eCRF.

8.2.1.5. Smoking status and smoking exposure history

Prior to the first study vaccination at Visit 1, the smoking status will be collected in the eCRF, differentiating tobacco use (cigarettes, cigars, cigarillos, pipes …) and use of electronic smoking devices (e-cigarettes). Refer to Section 10.5.2 for the definitions of current and former smoker.

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

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

8.2.1.6. Pre-vaccination body temperature

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

8.2.1.7. Distribution of paper diary cards (Amended, 12 July 2023)

A paper diary card will be distributed as follows:

- To all participants at Visit 1 (Day 1), Visit 3 (pre-Season 2) and Visit 5NH (pre-Season 3)***** to note down any unsolicited AE as well as any medication and vaccination taken in the 30-day period following vaccination.
- To participants in the reactogenicity and immunogenicity subset at Visit 1 (Day 1),Visit 3 (pre-Season 2) and Visit 5NH (pre-Season 3)***** to note down any solicited event, any unsolicited AE as well as any medication and vaccination taken in the 30-day period following vaccination.

****Not applicable for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5. Refer to Table 2 for details.***

Refer to Section 10.3.8 for guidelines.

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

8.2.2.1. Physical examination

A physical examination should be performed at Visit 1 (Day 1 pre-Dose 1), Visit 2b (pre-Season 1 in SH), Visit 3 (pre-Season 2) and Visit 5NH (pre-Season 3) and at each

ARI visit. Collected information needs to be recorded in the eCRF. If the investigator determines that the participant's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.

Physical examination at other study visits 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.

Treatment of any abnormality observed during physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

8.2.2.2. Body temperature during ARI episode

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

8.2.2.3. Lung auscultation (Amended, 12 July 2023)

Lung auscultation should be performed at Visit 1 (Day 1 pre-Dose 1), Visit 2b (pre-Season 1 in SH), Visit 3 (pre-Season 2), Visit 5NH (pre-Season 3) and at each ARI visit. Collected information needs to be recorded in the study participant's medical records.

Lung auscultation at Visit 2 (Day 31 post-Dose 1/pre-Season 1), Visit 4 (Day 31 post-Dose 2), Visit 6NH (Day 31 post-Dose 3)*, Visit 5SH (end of study) and Visit 7NH (end Season 3) 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.

**** Visit 6NH is not applicable for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5. Refer to Table 2 for details.***

8.2.2.4. Pulse oximetry

Peripheral arterial oxygen saturation (SpO_2%) will be assessed using pulse oximetry at Visit 1 (Day 1 pre-Dose 1), Visit 2b (pre-Season 1 in SH), Visit 3 (pre-Season 2), Visit 5NH (pre-Season 3) and at each ARI visit. 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.

8.2.2.5. Vital signs

Resting vital signs should be checked at Visit 1 (Day 1 pre-Dose 1), Visit 2b (pre-Season 1 in SH), Visit 3 (pre-Season 2) and Visit 5NH (pre-Season 3) and at each ARI visit.

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.

8.2.3. Safety monitoring

An IDMC will be appointed and operating under a charter to oversee the safety of participants and study conduct.

An IDMC is an independent group of experts established by GSK that advises GSK. The primary responsibilities of the IDMC are to (1) periodically review and evaluate the accumulated unblinded data with the RSVPreF3 OA investigational vaccine and (2) make recommendations to the sponsor (see also Section 9.6).

The IDMC includes experts in the field of geriatric medicine, internal medicine, epidemiology and biostatistics.

In addition to the IDMC, the existing project's SRT will review safety data on a regular basis as well. As of the implementation of Protocol Amendment 4, SRT will review unblinded safety data.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and other events of interest

8.3.1. Time period and frequency for collecting AE, SAE and other safety information (Amended, 12 July 2023)

An overview of the protocol-required reporting periods for AEs, SAEs, and AESIs (including pIMDs and AF) is given in Table 23.

Table 23 Timeframes for collecting and reporting of safety information (Amended, 12 July 2023)

	Pre-Vacc*	Dose 1				Dose 2				Dose 3#				Study conclusion
		Day 1 post-Dose 1	Day 4 post-Dose 1	Day 30 post-Dose 1	6 months post-Dose 1***	Day 1 post-Dose 2	Day 4 post-Dose 2	Day 30 post-Dose 2	6 months post-Dose 2***	Day 1 post-Dose 3#	Day 4 post-Dose 3#	Day 30 post-Dose 3#	6 months post-Dose 3***,#	
Solicited administration site and systemic events**										‡	‡			
Unsolicited AEs†										‡	‡	‡		
All SAEs†										‡	‡	‡	‡	
All pIMDs										‡	‡	‡	‡	
SAEs related to study vaccination†														
pIMDs related to study vaccination														

	Pre-Vacc*	Dose 1				Dose 2				Dose 3#				Study conclusion
		Day 1 post-Dose 1	Day 4 post-Dose 1	Day 30 post-Dose 1	6 months post-Dose 1***	Day 1 post-Dose 2	Day 4 post-Dose 2	Day 30 post-Dose 2	6 months post-Dose 2***	Day 1 post-Dose 3#	Day 4 post-Dose 3#	Day 30 post-Dose 3#	6 months post-Dose 3***,#	
SAEs related to study participation or concurrent GSK medication/vaccine														
Fatal SAEs†														
AEs/SAEs leading to withdrawal from the study														
Covid-19 cases														
Intercurrent medical conditions														

Vacc: vaccination; AE: adverse event; SAE: serious adverse event; pIMD: potential immune mediated disease
* Corresponds to day when informed consent is obtained (Day 1, prior to Dose 1).
** Only for participants in the reactogenicity and immunogenicity subset.
*** 6 months post-vaccination for each participant.
# ***Dose 3 is only applicable for participants in the NH who will have their Visit 5NH before the approval of the current Protocol Amendment 5.***
‡***For participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5, solicited, unsolicited AEs and all SAEs and pIMDs occurring after Visit 5NH will not be collected.***
† Atrial fibrillation (AF) will be considered as AESI in this study and will be additionally reported in the AF follow-up questionnaire in eCRF. The reporting of non-serious AF will be performed according to the unsolicited AE reporting period. The reporting of AF meeting the SAE definition will be performed according to the SAE reporting period. Fatal AF and

Serious AF judged as related to study vaccination will be performed according to the fatal SAE and related SAE reporting period, respectively. For AF that were reported before the implementation of ***the*** Protocol Amendment 4, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

The investigator or designee will record and immediately report all SAEs to the sponsor or designee via the Expedited AE Reporting Form. This reporting should, under no circumstances, occur later than 24 hours after the investigator becomes aware of an SAE, as indicated in Section 10.3.10. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting periods defined in Table 23. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs mentioned in Table 25.

8.3.2. Method of detecting AEs and SAEs and other events

Methods of detecting and recording AE/SAE/AESI (including pIMDs and AF) are detailed in Section 10.3.8. The assessment of AE/SAE intensity, causality and outcome are provided in the Section 10.3.9.

Open-ended and non-leading verbal questioning of the participants is the preferred method of acquiring information related to an AE/SAE/AESI (including pIMDs and AF).

8.3.3. Regulatory reporting requirements for SAEs and other events

Once an investigator (or designee) becomes aware that a study participant has experienced an SAE/AESI (including pIMDs and AF), he/she must report it to GSK using the required documentation, and within the timeframes, mentioned in Table 24. This is essential for meeting legal obligations and ethical responsibilities for participant safety and the safety of a study intervention under clinical investigation.

For SAEs/AESIs (including pIMDs and AF), the investigator will always provide an assessment of causality at the time of the initial report, as defined in Section 10.3.9.2.

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

The sponsor has a legal responsibility to notify local authorities and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements related to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Please refer to Section 10.3.10 for further details regarding the reporting of SAEs/AESIs (including pIMDs and AF).

Table 24 Timeframes for submitting serious adverse event and other events reports to GSK

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report
Serious AF†	24 hours*‡	electronic Expedited Adverse Events Report + AF follow-up questionnaire	24 hours*	electronic Expedited Adverse Events Report + AF follow-up questionnaire
pIMDs	24 hours**‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD.
‡ The investigator will be required to confirm review of the SAE/pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/pIMD.
†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 adverse event eCRF screen and in the AF follow-up questionnaire.

8.3.4. Contact information for reporting of SAEs, AESIs (including pIMDs and AF)

Table 25 Contact information for reporting of SAEs, AESIs (including pIMDs and AF)

Study contact for questions regarding SAEs/AESIs (including pIMDs and AF) Refer to the local study contact information document
Back-up study contact for reporting SAEs/AESIs (including pIMDs and AF) Available 24/24 hours and 7/7 days: **GSK Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: PPD or PPD E-mail address: PPD US sites only: Fax: PPD Canadian sites only: Fax: PPD

8.3.5. Treatment of adverse events

Any medication which may explain/cause/be used to treat an SAE/pIMD should be recorded in the Expedited Adverse Event Report of the participant's eCRF screen (refer to Section 10.3.10.1). For the AF, this information will be captured in the Expedited Adverse Events Report and in the AF follow-up questionnaire in eCRF.

8.3.6. 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. Frailty status assessment

To characterize the study population and determine if frailty may influence the safety, efficacy or immune response following administration of the study vaccine, the participants' frailty status will be assessed at study entry (refer to Section 10.5.2 for the definition of frailty). Data should be recorded in the eCRF.

The frailty status will be determined using the Gait speed test (refer to the SPM for details).

8.5. Treatment of overdose

Not applicable.

8.6. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.8. Genetics

Genetics are not evaluated in this study.

8.9. Biomarkers

Biomarkers for pharmacogenetics are not evaluated in this study.

8.10. Health outcomes

Economic outcome measures such as HCRU data associated with healthcare encounters, will be collected in the eCRF or another data collection method (participant questionnaires, etc.) by the investigator and study site personnel for participants reporting ARI cases. The statistical analyses must be adjusted for protocol-mandated procedures, tests, and encounters.

8.10.1. Completion of HR-QoL questionnaires

The EQ-5D and SF-12 questionnaires will be distributed and explained by the investigator or site staff and will be completed by all participants in the presence of site staff at Visit 1 (Day 1), Visit 3 (pre-Season 2) and Visit 5NH (pre-Season 3) and at the ARI visit for participants with ARI. Completeness of these questionnaires will be checked by the site staff in presence of the participant.

In addition, the daily paper health questionnaires will be distributed to all participants at Visit 2 (Day 31 post-Dose 1), Visit 3 (pre-Season 2) and Visit 5NH (pre-Season 3).

The daily health questionnaires include:

- The **Influenza patient-reported outcome** (FLU-PRO) questionnaire,
- The **Patient Global Impression of Severity** (PGI-S),
- The **Patient Global Impression of Change** (PGI-C).

The 3 questionnaires will be explained by the investigator or site staff and a first copy will be completed by all participants in the presence of site staff at Visit 2 as a baseline measurement. For each ARI episode, participants will be required to complete a copy of the health questionnaires at home daily starting from the day after the ARI onset until resolution of the episode or for a maximum of 14 days. (Note: completion of the daily health questionnaires is not applicable for ARI episodes reported before Visit 2).

Note:

- *In case of physical incapacity that would preclude the self-completion of the questionnaires, either site staff can assist the participant (for questionnaires completed during site visits) or the participant may designate a caregiver for transcribing responses to the questionnaire. However, at no time, the caregiver/site staff will evaluate the participant's health status, answer questionnaires or make decisions on behalf of the participant. Refer to Section 10.5.2 for definition of caregiver.*
- *In case the questionnaire was completed with the assistance of a caregiver/site staff, this should be recorded on the questionnaire.*

Please refer to the SPM for more information on the questionnaires, including data collection.

8.10.2. HCRU

For all participants reporting an ARI episode, scheduled and unscheduled healthcare use linked to the ARI will be recorded in the eCRF. This will include:

- Number of physician visits (General practitioner or specialist),
- Emergency department visits,
- Intensive care unit admissions,

- Hospitalizations,
- Treatment (including oxygen therapy, use of mechanical ventilation, medication [e.g., antibiotics]).

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

9.1.1. Primary objective

The primary objective of VE of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD during the first season in adults ≥ 60 years will be evaluated using a 1-sided test at alpha=2.5% level:

- *Criterion: VE will be demonstrated if the LL of the 2-sided 95% CIs is above 20%.*

VE Analysis 1:

The final analysis of the primary objective will be case-driven. It will be performed when at least 56 cases of RSV-confirmed LRTDs have been accrued in the primary cohort for efficacy.

This analysis will also include data from participants enrolled in SH available at that time.

If the number of cases triggering VE Analysis 1 (at least 56 cases) is not achieved at the end of Season 1 in NH, an optional interim analysis might be performed when at least 35 cases have been accrued (at the end of Season 1 in NH or later). In that case, an adjustment of the Type I error will be done in order to maintain the overall significance level at 2.5%. The Wang-Tsiatis approach which is an alpha spending method giving boundaries between O'Brien-Fleming and Pocock boundaries will be used [Wang, 1987] to determine the adjusted alpha levels for the interim ($\alpha 1$) and the final ($\alpha 2$) analyses. If the interim analysis is performed, then the final analysis will be performed when at least 60 cases are accrued in the primary cohort for efficacy or when all data associated to the primary objective are available.

Table 26 provides the 1-sided adjusted alpha levels obtained using the Wang-Tsiatis method with $\Delta = 0.3$, depending on the quantity of information accumulated at the time of interim analysis (using gsDesign package in R).

Table 26 One-sided alpha levels for interim and final analyses using Wang-Tsiatis method, according to information accumulated at interim analysis

	Interim			Final	
Information	α1	n1	Power	α2	n2
0.59	0.0108	35	54%	0.0193	59
0.65	0.0120	38	59%	0.0191	59
0.7	0.0130	41	66%	0.0191	59
0.75	0.0141	44	69%	0.0191	59
0.80	0.0153	47	77%	0.0193	58

Information=proportion of number of cases at interim analysis over those at final analysis
n1=number of cases at interim; n2=number of cases at final analysis
α1=1-sided alpha used for interim analysis; α2=1-sided alpha used for final analysis
Power calculated assuming a vaccine efficacy of 70%

9.1.2. Secondary objectives (Amended, 12 July 2023)

The confirmatory secondary objectives are the following:

- To demonstrate the efficacy of a single dose of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA over several seasons.

  Criterion: The LL of the 2-sided CI for VE is above 20%.

- To demonstrate the efficacy of a single dose of RSVPreF3 OA investigational vaccine followed by ***1*** annual revaccination ***before Season 2*** in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA over several seasons.

  Criterion: The LL of the 2-sided CI for VE is above 20%.

- To demonstrate the efficacy of a single dose and ***1*** annual revaccination ***before Season 2*** of RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 YOA over 3 seasons.

  Criterion: The LL of the 2-sided CI for VE is above 0%.

VE Analysis 2 after Season 1 in NH:

The confirmatory secondary objective assessing VE of a single dose of the RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 years after Season 1 in NH will be evaluated conditionally to the success of the primary objective (success indicated by the black arrows in Figure 4) using a 1-sided test at alpha=2.5% level.

VE Analysis 2 will be performed when participants in NH have been followed until the end of the first season in NH (30 April), i.e., when all ARI with onset visit and swabs collected until the end of the season (30 April) are adjudicated and RSV qRT-PCR results are available.

VE Analysis 2 will be performed if at least 1 additional RSV-confirmed ARI has been reported since VE Analysis 1 and if there are at least 2-3 weeks between the data lock point dates of the 2 analyses.

VE of a single dose over 2 and 3 seasons:

- The confirmatory secondary objective assessing VE of a single dose with RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 years after Season 2 in NH (S1+S2NH) will be evaluated conditionally to the success of the previous objective evaluating VE after Season 1 in NH (see Figure 4). A Bonferroni adjustment of alpha for multiplicity will be applied. Therefore, this analysis will be done using a 1-sided test at alpha=1.25% level.
- The confirmatory secondary objective assessing VE of a single dose with RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 years after Season 3 in NH (S1+S2+S3NH) will be evaluated conditionally to the success of the single dose objective after Season 2 (see Figure 4). This analysis will be done using a 1-sided test at alpha=1.25% level.
- The confirmatory secondary objective assessing VE of a single dose with RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 years after Season 3 in NH (S1+S2+S3NH) will be evaluated conditionally to the success of the RSV objective of single dose after Season 3. This analysis will be done using a 1-sided test at alpha=1.25% level.

  Analysis will be case-driven and will be performed if at least 61 cases are accrued for each subtype (RSV A and RSV B). The RSV A objective will be tested first, and if demonstrated, the RSV B objective will also be tested (see Figure 4).

VE of the *1* annual revaccination *given before Season 2* over 2 and 3 seasons:

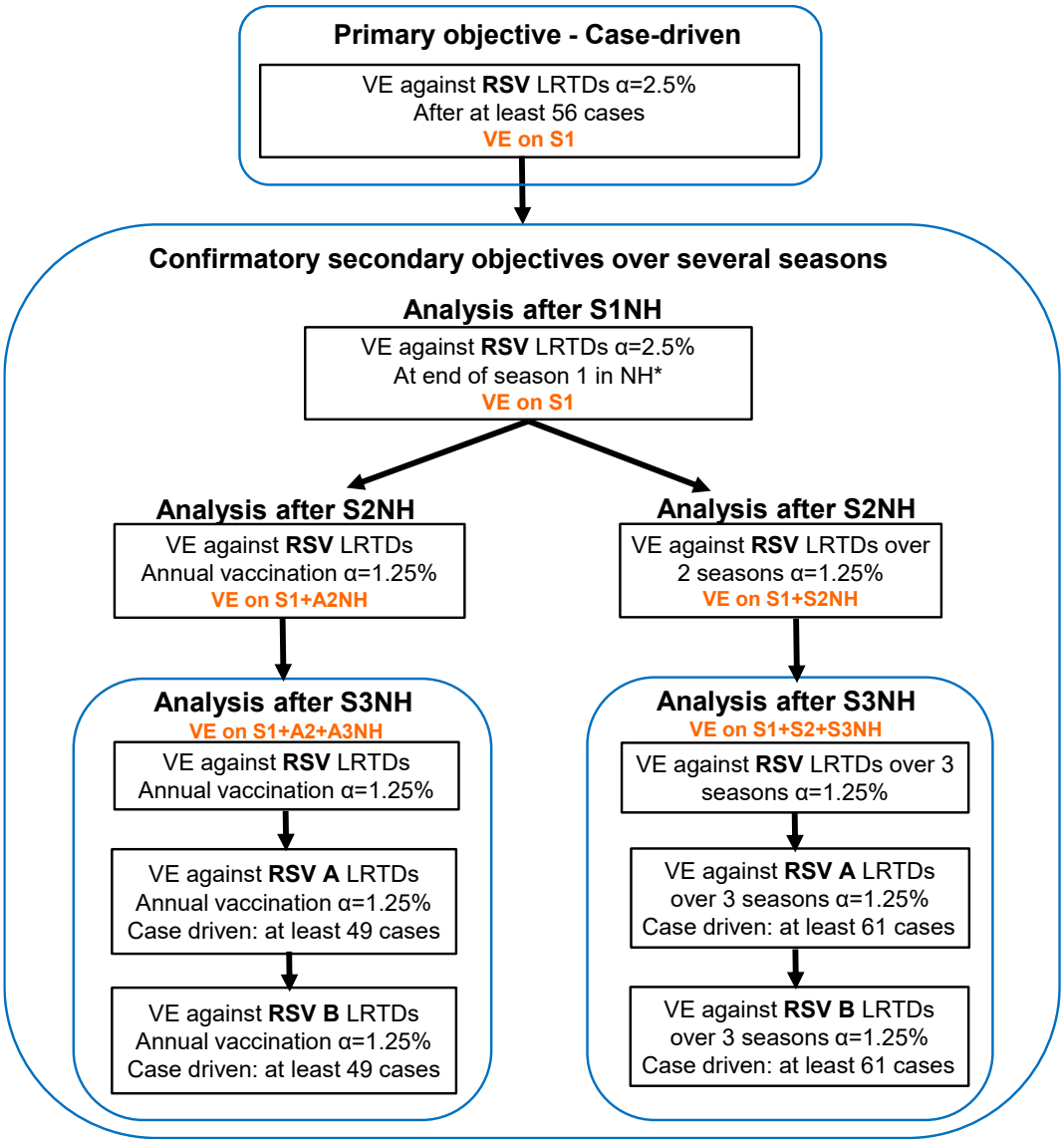
- The confirmatory secondary objective assessing VE of the annual revaccination ***given before Season 2*** with RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 years after Season 2 in NH (S1+A2NH) will be evaluated conditionally to the success of the previous objective evaluating VE after Season 1 in NH (see Figure 4). A Bonferroni adjustment of alpha for multiplicity will be applied. Therefore, this analysis will be done using a 1-sided test at alpha=1.25% level.
- The confirmatory secondary objective assessing VE of ***the*** annual revaccination ***given before Season 2*** with RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 years after Season 3 in NH (S1+A2+A3NH) will be evaluated conditionally to the success of the annual revaccination objective after Season 2 (see Figure 4). This analysis will be done using a 1-sided test at alpha=1.25% level.
- The confirmatory secondary objective assessing VE of ***the*** annual revaccination ***given before Season 2*** with RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 years after Season 3 in NH (S1+A2+A3NH) will be evaluated conditionally to the success of the RSV objective of annual revaccination after Season 3 (see Figure 4).

Analysis will be case-driven and will be performed if at least 49 cases are accrued for each subtype (RSV A and RSV B). The RSV A objective will be tested first, and if demonstrated, the RSV B objective will also be tested (see Figure 4).

Note that participants who received a third dose of RSVPreF3 OA investigational vaccine will not be included in the evaluation of annual revaccination over 3 seasons.

Figure 4 presents the sequence of analysis if at least 56 cases have been accrued before the end of Season 1 in NH.

Figure 4 Sequential evaluation of primary and confirmatory secondary objectives (Amended, 12 July 2023)



S1/S2/S3=Season 1/2/3 after a single dose
A2/A3 = Annual evaluation during Season 2/3 (after ***1*** revaccination ***given before Season 2***)

NH = Northern Hemisphere; Season 3 is only applicable in the NH
VE=Vaccine efficacy
* The end of S1NH analysis will be performed if at least 1 additional RSV-confirmed ARI has been reported since the analysis of the primary objective and if there are at least 2-3 weeks between the database cut-off dates of the 2 analyses.
Note: VE analysis by subtype will be case-driven and will be performed if at least 49/61 cases are accrued for each subtype, i.e., RSV A and RSV B.

All the objectives will be evaluated, but if one of them fails to be demonstrated, the remaining subsequent analysis will be performed as descriptive, and the Type I error may not be fully controlled.

If the 56 cases are not accrued before the end of the Season 1 in NH, an optional interim analysis might be performed when at least 35 cases are accrued (at the end of Season 1 in NH or later). In that case, the interim analysis will be tested using a 1-sided test at adjusted alpha level α1 and the final analysis will be performed when at least 60 cases are accrued (or when all data associated to the primary objective are available) using a 1-sided test at adjusted alpha level α2 (see Table 26).

If an interim analysis is performed, the adjusted alpha levels used for testing of the secondary confirmatory objectives will be evaluated by simulations and will be further described in the Statistical Analysis Plan (SAP).

9.2. Sample size determination

The study will enroll up to 25 000 participants, distributed as follows:

- Between at least 16 000 and up to 23 000 participants in the NH, and
- Between 1 500 and 2 000 participants in the SH.

Approximately 1 800 participants will be included in the reactogenicity and immunogenicity subset with 1 620 participants in NH and 180 participants in SH.

The sections below describe the assumptions and methodology used for the sample size calculation.

Withdrawals will not be replaced.

9.2.1. Primary objective: Vaccine efficacy

The overall Type I error is equal to 2.5% (1-sided alpha=0.025). The sample size has been calculated based on the number of cases needed to demonstrate a VE against RSV confirmed LRTD during the first season in NH, with the criterion of a LL of the 95% CIs >20%.

Hypothesis to show VE can be written as follows:

H_0: VE ≤ 20% versus Ha: VE >20%

And can also be translated using proportions:

$H_0 : p \geq p0 = 0.4444$ versus $Ha : p < p0$

Using a 1-sided exact binomial test (Pass 2019, Exact test for one proportion, 1-sided alpha=0.025), at least **56 cases of RSV-confirmed LRTDs** are needed in the primary cohort for efficacy to have at least 90% power to demonstrate a significant VE (LL of 95% CI > 20%), assuming a true VE of 70% (p=0.2308).

Therefore, assuming an attack rate of RSV-confirmed LRTD around 0.6% during the first season, and that approximately 10% of the vaccinated participants will be non-evaluable for the primary analysis of efficacy, a minimum of 16 000 participants has to be enrolled to reach the expected number of cases in NH.

However, due to the potential impact of COVID-19 pandemic measures on the RSV circulation and the difficulty to estimate the attack rate for the first season of the study, the sample size could be increased up to 23 000 participants in NH to mitigate the risk of a lower attack rate, as shown in Table 27.

Table 27 Total sample size to be enrolled in the NH to ensure at least 90% power to demonstrate the primary objective depending on attack rate, assuming a non-evaluable rate of 10%

Number of cases needed for Primary objective	Attack rate	Sample size
56 RSV-confirmed LRTD	0.6%	16 000
	0.55%	17 500
	0.5%	19 200
	0.45%	21 500
	0.42%	23 000
	0.4%	24 000

If an interim analysis is performed, the power to demonstrate the primary objective with at least 35 cases at interim is at least 54% (see Table 26). For the final analysis, at least 60 cases will be needed (at adjusted alpha level= α2, see Table 26), to have at least 90% power to demonstrate the primary objective.

9.2.2. Secondary objectives (Amended, 12 July 2023)

Table 28 provides the expected total number of RSV LRTD cases and the power for each analysis assuming:

- a minimum sample size of 16 000 participants in NH and of 1500 participants in SH,
- a maximum sample size of 23 000 participants in NH and of 2000 participants in SH,
- a non-evaluable rate of 10% for the efficacy analysis,
- a dropout rate of 20% between each season,
- an attack rate of 0.6% at each season for RSV-confirmed LRTDs,
- a VE against RSV-confirmed LRTDs of 70% over 1 season after ***Dose 1 (Season 1) and after 1 revaccination dose (Season 2), VE of 65% at Season 3.***

- a VE against RSV-confirmed LRTDs of 70/65/60% at Season 1/2/3 after a single dose, respectively.

Table 28 Power to demonstrate secondary confirmatory objectives (Amended, 12 July 2023)

Endpoint (success criterion)	Sample size	AR	Analysis	Expected number of cases	Power (1-sided alpha=1.25%)
RSV-confirmed LRTDs (LL>20%)	16000+1500	0.6%	S1+A2NH	101	97.7%
			S1+A2+A3NH	13***7***	99.***1***%
			S1+S2NH	102	95.8%
			S1+S2+S3NH	139	98.2%
	23000+2000	0.6%	S1+A2NH	144	99.8%
			S1+A2+A3NH	19***6***	≥99.9%
			S1+S2NH	146	99.5%
			S1+S2+S3NH	198	99.8%

S1/S2/S3 = Seasons 1/2/3***;*** A2/A3=Annual evaluation during Season 2/3 ***(after 1 revaccination given before Season 2)***; LL = lower limit
NH=North Hemisphere; AR=Attack rate; VE=vaccine efficacy
Power computed using Pass 2019, Exact test for one proportion, 1-sided alpha=0.0125

For the confirmatory secondary objective of VE against RSV-confirmed LRTD for each RSV subtype (A and B) separately after 3 seasons in NH, the analysis will be case-driven and will be performed if the trigger is reached for both RSV A and RSV B separately. The trigger has been computed to have 90% power to demonstrate each objective sequentially:

- For VE of a single dose: at least 61 cases are needed to have at least 90% power to demonstrate a significant VE (LL of 97.5% CI >0%);
- For VE of annual revaccination: at least 49 cases are needed to have at least 90% power to demonstrate a significant VE (LL of 97.5% CI >0%).

9.2.2.1. Expected number of RSV-confirmed LRTD cases (Amended, 12 July 2023)

As examples, Table 29 and Table 30 summarize the number of participants and number of RSV-confirmed LRTD cases expected after each season in each hemisphere for each schedule based on the assumptions used to compute the minimum sample size of 16 000 participants in the NH and 1500 participants in the SH.

Table 29 Expected number of RSV-confirmed LRTD cases for the evaluation of VE of the single dose

Season	N at start of season			Expected vaccine efficacy	Attack rate		Expected number of cases*
	RSVPreF3 group	RSV_1dose group	Placebo group		Placebo group	Vaccine group	
S1NH	8000	-	8000	70%	0.60%	0.18%	56
S1SH	750	-	750	70%	0.60%	0.18%	5
S2NH	-	3200	6400	65%	0.60%	0.21%	40
S2SH	-	300	600	65%	0.60%	0.21%	3
S3NH	-	2560	5120	60%	0.60%	0.24%	33

VE: Vaccine Efficacy
S1NH= End of Season 1 in Northern Hemisphere

S2NH= End of Season 2 in Northern Hemisphere for participants receiving a single dose
S3NH= End of Season 3 in Northern Hemisphere for participants receiving a single dose
S1SH= End of Season 1 in Southern Hemisphere
S2SH= End of Season 2 in Southern Hemisphere for participants receiving a single dose
* Considering a dropout rate between 2 seasons=20% and a non-evaluable rate=10%

Table 30 Expected number of RSV-confirmed LRTD cases for the evaluation of VE of the annual revaccination (Amended, 12 July 2023)

Season	N at start of season			Expected	Attack rate		Expected
	RSVPreF3 group	RSV_annual group	Placebo group	vaccine efficacy	Placebo group	Vaccine group	number of cases*
S1NH	8000	-	8000	70%	0.60%	0.18%	56
S1SH	750	-	750	70%	0.60%	0.18%	5
A2NH	-	3200	6400	70%	0.60%	0.18%	39
A2SH	-	300	600	70%	0.60%	0.18%	3
A3NH	-	2560	5120	***65***%	0.60%	0.18%	***32***

VE: vaccine efficacy
S1NH= End of Season 1 in the Northern Hemisphere
A2NH= End of Season 2 in the Northern Hemisphere for participants receiving a revaccination dose
A3NH= End of Season 3 in the Northern Hemisphere for participants receiving ***1*** revaccination dose ***before Season 2.***
S1SH= End of Season 1 in the Southern Hemisphere
A2SH= End of Season 2 in the Southern Hemisphere for participants receiving a revaccination dose
* Considering a dropout rate between 2 seasons=20% and a non-evaluable rate=10%

9.2.3. Sample size re-assessment

The number of RSV-confirmed LRTD cases for the primary objective will be monitored on an ongoing basis during Season 1. This will be performed in a blinded way by counting the total number of cases reported overall in the pooled RSV and Placebo groups.

If the total number of cases reported up to early April is low compared to the trigger for analysis (at least 56 cases), a second cohort (new participants) might be enrolled before the next season in NH, in order to continue the accrual of the cases at the next season (Season 1 of second cohort) and to increase the number of cases needed to demonstrate the primary objective.

At the time of evaluation, the following rule will be applied for the enrollment of the second cohort:

- If the total number of cases is greater than 50 cases or lower than 12 cases: No enrollment of second cohort. The monitoring will continue and VE Analysis 1 will be performed as described in Section 9.1.1.
- If the total number of cases is included in [12, 50 cases]: Enrollment of a second cohort. In that case, new participants in NH will be enrolled and vaccinated before the next season in NH. The monitoring will continue and VE Analysis 1 will be performed as described in Section 9.1.1.

  The study will be extended and will end when participants of the second cohort have been followed up to 3 consecutive RSV seasons.

According to feasibility of enrollment of this second cohort before the next season, it is estimated that a maximum number of 10 000 participants might be enrolled in the second cohort.

GSK can decide to cancel this re-enrollment if the final analysis (at least 56 cases) is performed at the end of Season 1 in NH or if the interim analysis is successful.

The participants in this second cohort will be randomized in 3 study groups: RSV_annual group, RSV_1dose group and Placebo group, according to a 1:1:2 randomization ratio, and they will follow the same study procedures as participants of the first cohort.

The system's randomization algorithm will use a minimization procedure accounting for center, age and region. Minimization factors will have equal weight in the minimization algorithm.

9.2.4. Reactogenicity subset

Solicited events information will be collected for a subset of participants using paper diaries. Approximately 1800 participants will be included in the reactogenicity subset from both NH and SH (see Table 13).

Table 31 presents the probability to observe at least one event, depending on the true AE rate, for 900 participants per group as well as for smaller subsets, as reactogenicity analysis might be done on several subgroups (e.g., by age category, region). A subset of 900 participants per group would provide a probability of 98.9% to observe at least one event with a true incidence rate of 0.5%.

Table 31 Probability (%) to observe at least one event depending on AE incidence

N in subset	Probability (%) to observe at least 1 event depending on AE incidence				
	0.1%	0.5%	1%	2%	3%
50	4.88	22.17	39.50	63.58	78.19
100	9.52	39.42	63.40	86.74	95.24
200	18.14	63.30	86.60	98.24	99.77
300	25.93	77.77	95.10	99.77	>99.9
400	32.98	86.53	98.20	>99.9	>99.9
500	39.36	91.84	>99%	>99.9	>99.9
700	50.36	97.01	>99%	>99.9	>99.9
900	59.36	98.90	>99%	>99.9	>99.9

9.3. Populations for analyses (Amended, 12 July 2023)

Table 32 Populations for analyses

Analysis set	Description
Enrolled set	Participants who agreed to participate in a clinical study after completion of the informed consent process*.
Exposed Set (ES)	All participants who received at least the first dose of the study intervention. The allocation in a group is done in function of the administered intervention.
Per Protocol Set for immunogenicity (PPSi)	All participants who received at least the first dose of the study intervention to which they were randomized, have post-vaccination immunogenicity data available, and did not meet protocol deviations that lead to exclusion.
Solicited Safety Set	All participants who received at least the first dose of the study intervention (Exposed Set) and have solicited safety data.

*All participants enrolled and included in the database will be part of the enrolled set.

Exposed Set Dose 2 and Exposed Set Dose 3 including all participants who received the 2nd and the 3rd dose, respectively, will also be used to report analysis on post-Dose 2/3 data.

In addition, the following populations will be defined for efficacy analyses (refer to Section 9.4.3 for detailed information on the analysis set):

- **Modified Exposed Set (mES):** the mES will be the primary population for efficacy analysis on RSV-confirmed cases. It will include all participants who received at least the first dose of the study intervention (ES) and who did not report an RSV-confirmed ARI prior to Day 15 after each vaccination. The allocation in a group is done in function of the administered intervention.

  mES will be defined by dose as follows:

  - mES: participants who received Dose 1 and who did not report RSV ARI within 15 days post-Dose 1,
  - mES Dose 2: participants who received Dose 2 and who did not report RSV ARI within 15 days post-Dose 2,
  - mES Dose 3: participants who received Dose 3 and who did not report RSV ARI within 15 days post-Dose 3.

  Note that participants who received a third dose of RSVPreF3 OA investigational vaccine will not be included in the primary evaluation of annual revaccination over 3 seasons. Details will be provided in the SAP.

- **Per Protocol set for efficacy (PPSe):** the PPSe will include all participants included in the mES who:

  – received at least the first dose of the study vaccine to which they were randomized,

  – did not have protocol deviations leading to exclusion.

The list of protocol deviations leading to exclusion from PPS will be defined in the SAP prior to study start.

In addition, the following populations will be defined for analyses of patient-reported outcomes (i.e., EQ-5D, SF-12 and daily health questionnaires):

- **mES RSV-confirmed ARI cases:** All participants in the mES-RSV who have an RT-PCR-confirmed RSV case.
- **mES RSV-confirmed LRTD cases:** All participants in the mES-RSV who have an RT-PCR-confirmed RSV-LRTD case.

9.3.1. Criteria for elimination from analysis

9.3.1.1. Intercurrent medical conditions and concomitant medications/products/vaccines that may lead to elimination of a participant from per protocol analyses

If the participant meets one of the criteria mentioned in Section 5.2.1 (medical conditions) or Section 5.2.2 (concomitant therapy), he/she may be eliminated from the PPSe and PPSi.

In addition, participants may be eliminated from the PPSi 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.

9.4. Statistical analyses

The SAP will be finalized prior to First Participant First Visit and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

For all statistical analyses described in this section, the 4 RSVPreF3 vaccine lots will be pooled and results will be presented for RSVPreF3 group, RSV_annual group or RSV_1dose group versus Placebo group.

9.4.1. General considerations

9.4.1.1. Demography

For a given participant and a given demographic variable, missing measurements will not be replaced.

9.4.1.2. Efficacy

All reported ARI cases will be reviewed by blinded, qualified GSK staff members to determine whether certain investigator-reported events meet the definition of efficacy endpoints (LRTD and severe LRTD), using pre-defined 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 for data obtained by methodologies which are not protocol-specified or for missing data, will be described in the adjudication charter.

For a given participant and a given efficacy measurement, missing or non-evaluable measurements will not be imputed for the primary analysis. The missing endpoint and censoring are supposed to occur independently, and the pattern of the missingness being either Completely At Random (MCAR) or Missing At Random (MAR) only.

The potential RSV or hMPV infections, including the potential infection to Adenovirus, Enterovirus and Parainfluenza viruses, will be assessed by RT-PCR testing of swab samples (see Table 19). Swab samples that are positive for RSV and/or hMPV by RT-PCR will be tested by a multiplex PCR (panel of viruses) for detection of potential viral co-infection.

A case that is positive by the quantitative RT-PCR for RSV A and/or RSV B will be counted as an RSV-confirmed case, whatever the result for RSVA/B tested by multiplex RT-PCR, for hMPV or other respiratory virus tested by multiplex RT-PCR (co-infection).

A case that is positive by multiplex RT-PCR for hMPV will be counted as a hMPV-confirmed case, whatever the result for RSV A/B or other respiratory virus (co-infection).

The events linked to primary and secondary efficacy outcomes will be identified and in case multiple events are observed for the same participant, only the first event will be considered for the primary analysis of all primary/secondary endpoints.

Therefore, for the primary analysis of the primary objective, the number of RSV-confirmed LRTD will be computed on the first occurrence of qRT-PCR-confirmed RSV A and/or RSV B associated LRTD, starting on Day 15 after the first vaccination for analysis on the mES-RSV and the PPSe.

For analysis on the ES, the analysis will include the first occurrence of the RSV-confirmed LRTD case reported after the first vaccination (starting from Visit 1).

9.4.1.3. Immunogenicity

- Any missing or non-evaluable immunogenicity measurement will not be replaced. The descriptive analysis performed for each assay at each time point will exclude participants with a missing or non-evaluable measurement.
- The geometric mean titers/concentrations (GMTs/GMCs) will be computed by taking the anti-logarithm of the arithmetic mean of the $\log_{10}$ transformed titers/concentrations.
- A seronegative participant will be defined as a participant whose antibody titer/concentration is below the cut-off value of the assay. A seropositive participant is a participant whose antibody titer/concentration is greater than or equal to the cut-off value of the assay.

- Antibody titers/concentrations below the assay cut-off will be given an arbitrary value of half the assay cut-off for the purpose of GMT/GMC calculation. Antibody titers/concentrations above the upper limit of quantification (ULOQ) of the assay will be given an arbitrary value of the ULOQ for the purpose of GMT/GMC calculation.
- The mean geometric increase (MGI) is defined as the geometric mean of the within participant ratios of the post-vaccination titer/concentration over the pre-vaccination titer/concentration.

9.4.1.4. Reactogenicity/Safety

- For a given participant and the analysis of solicited events within 4 days post-vaccination, missing or non-evaluable measurements will not be replaced. Therefore, the analysis of solicited events will include only vaccinated participants with documented solicited safety data (i.e., paper diary completed).
- For analysis of unsolicited AEs, SAEs, AESIs (including pIMDs and AF) and concomitant medications, all vaccinated participants will be considered. Participants who did not report an event or concomitant medication will be considered as participants without the event or the concomitant medication respectively.

9.4.1.5. Quality of life

- The FLU-PRO version 2.0 is a 32-item daily diary assessing influenza signs and symptoms across 6 body systems: Nose (4 items), Throat (3 items), Eyes (3 items), Chest/Respiratory (7 items, i.e., LRTI), Gastrointestinal (4 items), and Body/Systemic (11 items). Respondents are asked to rate each sign or symptom on a 5-point ordinal scale, with higher scores indicating a more frequent sign or symptom. For 27 of the items, the scale is as follows: 0 (“Not at all”), 1 (“A little bit”), 2 (“Somewhat”), 3 (“Quite a bit”), and 4 (“Very much”). For 2 items, severity is assessed in terms of numerical frequency, i.e., vomiting or diarrhea (0 times, 1 time, 2 times, 3 times, or 4 or more times); with the final 3 items; frequency of sneezing, coughing, and coughed up mucus or phlegm evaluated on a scale from 0 (“Never”) to 4 (“Always”). The FLU-PRO total score is computed as the mean score across all 32 items comprising the instrument. Total scores can range from 0 (symptom free) to 4 (very severe symptoms).

  In addition, a score assessing the symptoms associated with upper respiratory systems will be computed as the mean score across the 10 items that make up the Nose, Throat and Eyes domains.

  Six individual domain scores will also be computed, representing symptom severity in each of the assessed body areas: Nose, Throat, Eyes, Chest/Respiratory (i.e., LRTD), Gastrointestinal and Body/Systemic. Each domain score is calculated as the mean of all items comprising that domain, with scores ranging from 0 to 4.
- The PGI-S and the PGI-C are 2 patient-reported questions on the severity of symptoms and the change in symptoms, respectively. The PGI-S classifies the severity of symptoms into 5 categories (No symptoms, Mild, Moderate, Severe,

Very severe). The PGI-C classifies the change in symptoms from the previous day into 7 categories (Much better, Somewhat better, A little better, About the same, A little worse, Somewhat worse and Much worse).

- The EQ-5D health utility questionnaire, described through 5 dimensions scores (i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression) will be converted into generate health profiles, i.e., a respondent who responds 1 (no problem/no symptom) to all 5 items has a profile "11111" and similarly a participant who responds with the highest level of difficulty or symptom to all items has a profile "33333". These profiles are subsequently converted to a continuous single index utility score using a 1 to 1 matching.
- The SF-12 questionnaire is a multi-purpose health survey with 12 questions. The SF-12 covers 8 HR-QoL domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). From these domains, summary scores for the physical component and mental component are computed. Scale scores will be constructed following the summated ratings and standardized SF-12 scoring algorithms.

9.4.2. Demographics and participants disposition

Demographic characteristics (age at first vaccination in years, BMI, sex, race, ethnicity, geographical hemisphere location (Northern/Southern), type of residence (CD/LTCF), vital signs, comorbidities, frailty status and smoking status) will be summarized by group using descriptive statistics:

- Frequency tables will be generated for categorical variables such as race;
- Mean, median, standard deviation and range will be provided for continuous data as age.

The number of doses of the study vaccine administered will be tabulated by group.

The distribution of participants will be tabulated as a whole and per group, for each age category, for each country and for each subset.

The following age categories will be considered in the analysis: ≥65 years, ≥70 years, ≥80 years, 60-69 years, 70-79 years.

Withdrawal status will be summarized by group using descriptive statistics:

- The number of participants enrolled into the study as well as the number of participants excluded from PP analyses will be tabulated.
- The numbers of withdrawn participants will be tabulated according to the reason for withdrawal.

Participant disposition in the ES, mES and PPS (PPSi and PPSe) will be reported as a whole and per group, and for each age category.

9.4.3. Primary endpoint

The primary efficacy analysis will be performed on the mES-RSV. In addition, a second analysis will be performed on the PPSe and on the ES to complement the primary analysis.

The primary analysis of VE in terms of occurrence of RSV-confirmed LRTD will be evaluated using the conditional exact binomial method based on the Poisson model [Chan, 1998]. This method computes an exact CI around the rate ratio (ratio of the event rates in the vaccine versus control groups). The analysis will consider the exact inference on the relative risk, adjusted by age categories and regions, conditionally to the total number of cases observed and time at risk. VE is defined as 1 minus the relative risk.

For the primary analysis on the mES-RSV and the analysis on the PPSe, the time at risk will correspond to the period starting on Day 15 after the first vaccination up to the first occurrence of event or up to censoring.

For the analysis on the ES, the full period after the first vaccination up to the first occurrence of event or censoring will be considered for the time at risk.

During the surveillance period, all events related to the efficacy endpoints will be collected (see Section 8.1.1), but only the first event of RSV-confirmed LRTD will be considered for the primary analysis of efficacy endpoints.

For a given participant, the first occurrence of LRTD will be considered as a confirmed RSV positive case for primary efficacy analysis if:

- At least 1 sample is tested positive for RSV A and/or RSV B by GSK qRT-PCR, or
- At least 1 sample is tested positive for RSV A and/or B by an external PCR test (non-GSK), if a GSK qRT-PCR result is not available.

A sensitivity analysis of the primary efficacy endpoint will be performed considering the RSV cases confirmed by the GSK qRT-PCR only, i.e., excluding the ones identified by an external laboratory.

A second sensitivity analysis of the primary efficacy endpoint will be performed excluding RSV cases with respiratory co-infections (e.g., hMPV, SARS-CoV-2, FLU, etc.).

The methodology will be detailed in the SAP.

9.4.4. Secondary endpoints

9.4.4.1. Efficacy (Amended, 12 July 2023)

The primary analysis of secondary efficacy endpoints will be performed on the mES (see details in Section 9.3). In addition, for secondary confirmatory objectives, a second analysis will be performed on the PPSe and on the ES to complement the primary analysis.

The ES will be the primary population for secondary efficacy endpoints not related to RSV.

The same methodology as described for the primary endpoint (see Section 9.4.3) will be used to analyze the secondary efficacy endpoints described below. For the analysis over 2 or 3 seasons, the model will include season as covariate, in addition to age category and region. The first occurrence of the event meeting the case definition according to the endpoint will be considered for the primary analysis of those secondary efficacy endpoints.

Analysis of secondary efficacy endpoints will be performed at each VE analysis when applicable (see Section 9.5.1).

The following endpoints will be evaluated following a single dose of the RSVPreF3 OA investigational vaccine and following ***1*** annual revaccination dose ***given before Season 2***.

Note that participants who received a third dose of RSVPreF3 OA investigational vaccine will not be included in the primary evaluation of annual revaccination over 3 seasons. Secondary analysis of the annual revaccination on participants who received 3 doses of RSVPreF3 OA investigational vaccine might be performed depending on the number of participants who will receive the Dose 3. Details will be provided in the SAP.

Confirmatory objectives

- VE against RSV-confirmed LRTD over 3 seasons: VE will be evaluated at the end of Season 1 in NH, over 2 seasons at the end of Season 2 in NH and over 3 seasons at the end of Season 3 in NH.
- VE against RSV-confirmed LRTD by RSV subtype over 3 seasons: on RSV A and RSV B qRT-PCR-confirmed cases separately. This will be evaluated after the end of Season 3 in NH.

Other secondary objectives

- VE against RSV-confirmed LRTD by RSV subtype: on RSV-A and RSV-B qRT-PCR-confirmed cases separately.
- VE against hMPV-confirmed LRTD, up to the end of Season 1.
- VE against RSV-confirmed LRTD by age category: on participants ≥65 YOA, ≥70 YOA and ≥80 YOA at the time of first vaccination.

  VE will also be computed for participants in 60-69 YOA and 70-79 YOA.
- VE against RSV-confirmed LRTD by season:
  - VE during Season 1 in NH and SH, including first occurrence of cases reported during Season 1 from Day 15 after the first vaccination;
  - VE during Season 2 in NH and SH, including first occurrence of cases reported during Season 2 and excluding from the analysis participants who already reported an RSV-confirmed LRTD before the start of Season 2;

  - VE during Season 3 in NH and SH (partial Season 3 in SH), including first occurrence of cases reported during Season 3 and excluding from the analysis participants who already reported an RSV-confirmed LRTD before the start of Season 3.

  The time at risk for the analysis by season will be the period from the start of the corresponding season until the event, until the end of the season or until the last contact date for drop-out participants.

- VE against RSV-confirmed LRTD by year:
  - VE during the first year post-vaccination (Year 1) in NH and SH, including first occurrence of cases reported from Day 15 post-Dose 1 up to Dose 2 administration;
  - VE during the second year post-vaccination (Year 2) in NH and SH, including first occurrence of cases reported from Day 15 post-Dose 2 up to 12 months post-Dose 2 ***in NH and SH, or up to Dose 3 administration in NH***;
  - VE during the third year post-vaccination (Year 3) in NH and SH, including first occurrence of cases reported from ***12 months*** post-Dose ***2*** in NH up to study end.
- VE against RSV-confirmed LRTD by baseline comorbidities: using the Charlson Comorbidity Index and according to comorbidities of interest:
  - COPD,
  - Asthma,
  - Any chronic respiratory/pulmonary disease,
  - Diabetes mellitus Type 1 or Type 2,
  - Chronic heart failure,
  - Advanced liver or renal disease.
- VE against RSV-confirmed LRTD by baseline frailty status.
- VE against severe RSV-confirmed LRTD according to the case definition 1 and case definition 2;
- VE against RSV-confirmed ARI.
- VE against any ARI and any LRTD.
- Hospitalizations and complications:

  VE in the prevention of hospitalization and complications during RSV seasons and during the entire follow-up will be evaluated for:

  - Hospitalization due to respiratory diseases and due to complication related to respiratory diseases,
  - Hospitalization due to RSV-confirmed respiratory diseases and due to complication related to RSV-confirmed respiratory diseases,

  - Complications related to RSV-confirmed ARI,
  - Complications related to any ARI.

- VE over time: The evolution of VE of a single dose of the RSVPreF3 OA vaccine against RSV-confirmed LRTDs over time will be explored using the Cox proportional hazard regression model. The model assumes that the ratio between 2 hazards (vaccine versus placebo) does not depend on time. This assumption will be checked by a test based on the Schoenfeld residuals. In addition, the VE analysis will be performed by splitting participants in 2 groups according to the time of vaccination.

For all RSV-confirmed ARI and LRTD cases, descriptive statistics will also be computed to summarize the number of episodes reported, the duration of the RSV episodes, the occurrence of each reported symptoms and signs, including the need for oxygen supplementation, and the occurrence of cases according to severity (see Section 8.1.1.6.1 for severity assessment).

9.4.4.2. Immunogenicity

The primary analysis of immunogenicity will be performed on the PPSi for participants included in the immunogenicity and reactogenicity subset.

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

An immunogenicity analysis based on ES will include all vaccinated participants included in the reactogenicity and immunogenicity subset for whom immunogenicity data are available.

For each group, each immunological assay and at each time point that blood samples are collected, the following analysis will be tabulated:

- Percentage of participants with antibody titers/concentrations above pre-defined assay cut-offs and their 95% CIs;
- GMT/GMCs and their 95% CIs;
- Distribution of antibody titers/concentrations using reverse cumulative curves;
- MGI with 95% CI.

9.4.4.3. Safety

Reactogenicity analysis will be performed on the Solicited Safety set, for participants included in the immunogenicity and reactogenicity subset.

All other safety analyses will be performed on all participants included in the ES.

Reactogenicity analyses will include the following summaries by group:

- The number and percentage of participants with at least one administration site event (solicited and unsolicited), with at least one systemic event (solicited and unsolicited) and with any AE (solicited and unsolicited) with an onset during the 4 day or 30-day follow-up period after vaccination will be tabulated with exact 95% CI after each dose. The same computations will be done for Grade 3 AEs, for Grade 3 non-serious AEs and for AEs resulting in a medically attended visit.

  Those analyses will present all solicited and unsolicited AEs, including SAEs (unless otherwise specified) and will be performed on the ES.

- The number and percentage of participants reporting each individual solicited administration site or systemic event (any grade, Grade 3 and resulting in medically attended visit) with an onset during the 4-day follow-up period after vaccination will be tabulated with exact 95% CI after each dose.

- For fever, the number and percentage of participants reporting fever by half degree (°C) cumulative increments and fever resulting in medically attended visit with an onset during the 4-day follow-up period after vaccination will be tabulated after each dose. In addition, the prevalence of any and Grade 3 fever will be presented graphically over time after each dose.

- The number of days with solicited events reported with an onset during the 4-day follow-up period will be tabulated after each dose for each individual solicited event using descriptive statistics (mean, min, Q1, median, Q3, maximum).

Safety analyses will include the following summaries by group on the ES:

- The number and percentage of participants with any unsolicited AEs with an onset during the 30-day follow-up period with its exact 95% CI will be tabulated after each dose by group and by MedDRA Primary System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT). Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs and for unsolicited AEs resulting in a medically attended visit.

  The analyses of unsolicited AEs will include SAEs (unless otherwise specified).

- The verbatim reports of unsolicited AEs, including SAE, will be reviewed by a qualified person and the signs and symptoms will be coded according to the MedDRA Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate Preferred Term.

- The number and percentage of participants with at least one report of SAE classified by MedDRA Primary SOC, HLT and PT and reported from vaccination up to 6 months after vaccination will be tabulated after each dose with exact 95% CI. The same tabulation will be presented for pIMDs, fatal SAEs, causally related SAEs and causally related pIMDs.

- The number and percentage of participants with at least one report of causally related SAE classified by MedDRA Primary SOC, HLT and PT and reported during the entire study period will be tabulated after each dose from Day 1 up to study end with

exact 95% CI. The same tabulation will be presented for fatal SAEs and causally related pIMDs.

- SAEs/pIMDs will also be described in detail in a tabular listing.
- The number and percentage of participants starting a concomitant medication (any medication and any antipyretic) during the 4-day and the 30-day follow-up period after each dose will be tabulated with exact 95% CI.
- AEs/SAEs leading to study/intervention discontinuation from first vaccination up to study end will be tabulated.

9.4.4.4. Quality of life

All analysis of patient-reported outcomes (i.e., EQ-5D, SF-12 and the daily health questionnaires) for RSV-confirmed cases will be carried out on the mES RSV-confirmed ARI cohort or mES RSV-confirmed LRTD cohort, as appropriate. Data will be analyzed using descriptive statistics for the multi-item SF-12, EQ-5D and FLU-PRO scales for each study group at each time point.

Descriptive statistics of the EQ-5D, SF-12 and FLU-PRO scales completed pre-Seasons 1 and 2 will be presented for the mES.

For each confirmed case of RSV, the maximum score for FLU-PRO scale scores (e.g., Chest and upper respiratory) during the first RT-PCR-confirmed RSV episode during the first 7 days from the onset of ARI symptoms will be calculated. The maximum FLU-PRO scores (e.g., Chest and upper respiratory) during the first 7 days from the onset of ARI symptoms will be compared between study groups using a Wilcoxon non-parametric test.

Estimated Least Squares mean FLU-PRO total score during the first 7 days from the onset of RSV-ARI episode for participants with RT-PCR-confirmed RSV, will be analyzed using a repeated measures analysis of variance (ANOVA) model. The model will be fitted including terms for age category, region and study group by time interaction. The least squares mean (LSMEANS) estimates for time by study group and the difference in least squares means and associated P-values will be obtained from the ANOVA model. The PROC MIXED procedure in SAS will be used to carry out the ANOVA, with all terms fitted as fixed effects.

The study group difference in LSMEANS of the SF-12 physical functioning scores and EQ-5D utility score at the initial ARI visit will be estimated using repeated measures mixed effects model including the timepoints: pre-season, initial ARI visit, and pre-next-season visit. The model will include age categories and region as fixed effects.

The endpoints will be evaluated following a single dose of the RSVPreF3 OA investigational vaccine and following ***the*** annual revaccination dose.

9.4.5. Tertiary/exploratory endpoints

9.4.5.1. Efficacy (Amended, 12 July 2023)

The same methodology as described for the primary and secondary endpoints (see Sections 9.4.3 and 9.4.4.1, respectively) will be used to analyze the tertiary endpoints. The following endpoints will be evaluated following a single dose of the RSVPreF3 OA investigational vaccine and following ***the*** annual revaccination ***given before Season 2*** :

- VE against RSV and/or hMPV-confirmed LRTDs,
- VE against hMPV-confirmed LRTDs up to the end of Season 2 and Season 3,
- VE against severe hMPV-confirmed LRTDs according to the case definition 1 and case definition 2,

- VE against hMPV-confirmed ARI,
- VE against RSV-confirmed ARI by subtype, by age category and by season,
- VE against RSV-confirmed ARIs by baseline comorbidities: using the Charlson index and according to comorbidities of interest (as listed in Section 9.4.4.1),
- VE in the prevention of any death (all-cause mortality) during the RSV seasons.

The evolution of VE of a single dose of RSVPreF3 OA vaccine against RSV-confirmed ARI over time will be explored using the Cox proportional hazard regression model. The model assumes that the ratio between 2 hazards (vaccine versus placebo) does not depend on time. This assumption will be checked by a test based on the Schoenfeld residuals. In addition, the VE analysis will be performed by splitting participants in 2 groups according to the time of vaccination.

The number and percentage of participants who reported more than 1 case of the following event will be tabulated by group, by season and also in consecutive seasons: any ARI, any LRTD, RSV-confirmed ARI, RSV-confirmed LRTD (according to the case definitions).

The number and percentage of participants with other viral pathogens (detected by multiplex RT-PCR) co-existing with RSV or hMPV among RT-PCR-confirmed RSV or hMPV ARI episodes will be tabulated by group.

9.4.5.2. Analysis of HCRU

Descriptive analysis of HCRU will be performed for participants with RSV-confirmed ARI or with any ARI and will be reported by group:

- The number/percentage of participants who were hospitalized during the ARI episode or complication related to ARI,
- The number/percentage of participants who received antibiotics for the treatment of ARI or complication related to ARI.

For any other count variables that will be reported (e.g., any medication or any medical visit), the number and percentage of events/participants will be presented by group.

9.4.5.3. Quality of life

The maximum PGI-S score during the first 7 days from the onset of ARI symptoms for the first RT-PCR-confirmed RSV LRTD episode will be calculated. The maximum PGI-S score during the first 7 days from the onset of ARI symptoms will be compared between study groups using a Wilcoxon non-parametric test.

9.4.5.4. Immunogenicity

9.4.5.4.1. Correlate of protection (Amended, 12 July 2023)

An exploratory analysis will be implemented in attempt to correlate the humoral immune response to the RSVPreF3 OA investigational vaccine with protection against RSV-confirmed disease.

For that purpose, blood samples for humoral immune response will be collected from all participants at pre-Dose 1 (Day 1), 1-month post-Dose 1 (Day 31) ***and at Visit 5NH**** and may be tested for correlate of protection analysis in all participants with RSV-confirmed disease and in a subset of control participants.

There are 2 main strategies to define a subset of control: case-cohort and nested case control. For the same number of participants, both methods provide similar results. However, the case-cohort strategy has the advantage to be more flexible in terms of data exploration and modelling [Borgan, 2000].

Statistical analysis will be done in several steps:

1. Identification of Correlate of Risk: identify immunological response that correlates with the endpoint used to measure VE.
2. Validation of Correlate of Protection, which is a correlate of risk that is validated to predict a certain level of protection from the targeted endpoint.
3. Evaluation of a cut-off for protection: identify a "protective threshold" or humoral immune response level that distinguishes protected and unprotected individuals.

Further details on the methodology to assess the correlate of protection will be given in a separate SAP.

**** The blood sample at Visit 5NH is applicable after approval of the current Protocol Amendment 5.***

9.4.5.4.2. Within groups analysis

The immunogenicity analysis will also be performed by age category (≥ 65 YOA, ≥ 70 YOA, ≥ 80 YOA, 60-69 YOA, 70-79 YOA), by hemisphere (NH and SH), by region and by baseline frailty status.

9.4.5.5. Safety

The reactogenicity and safety analysis will also be performed by age category ≥ 65 YOA, ≥ 70 YOA, ≥ 80 YOA, 60-69 YOA, 70-79 YOA), by hemisphere (NH and SH) and by region.

The analysis of reactogenicity (solicited administration site and systemic events) will also be performed by baseline frailty status.

9.5. Interim analyses

The optional interim analysis is described in the below sequence of analyses.

9.5.1. Sequence of analyses (Amended, 12 July 2023)

This section is presenting the timing for each analysis. More information on the statistical link between the confirmatory objectives can be found in Section 9.1 (Figure 4).

Analyses to evaluate objectives and endpoints will be performed in several steps:

1. VE Analysis 1 – Season 1 (Primary Objective):

The final analysis of the primary objective will be case-driven. It will be performed when at least 56 cases of RSV-confirmed LRTDs have been accrued in the primary cohort for efficacy.

An optional interim analysis might be performed if the number of cases triggering VE Analysis 1 (at least 56 cases) is not achieved at the end of Season 1 in NH. This interim analysis will be performed if at least 35 cases have been accrued (at the end of Season 1 in NH or later). In that case, an adjustment of the Type I error will be done in order to maintain the overall significance level at 2.5%. The Wang-Tsiatis approach which is an alpha spending method giving boundaries between O'Brien-Fleming and Pocock boundaries will be used [Wang, 1987] to determine the adjusted alpha levels for the interim ($\alpha 1$) and the final ($\alpha 2$) analyses. The final analysis will be performed when at least 60 cases are accrued or when all data associated to the primary objective are available.

All data related to efficacy, safety and immunogenicity objectives available at that time will also be analyzed.

2. VE Analysis 2 – End of Season 1 in NH:

A second VE analysis will be performed when participants in NH have been followed until the end of the first season in NH (30 April).

All analysis generated at VE Analysis 1 will be performed at VE Analysis 2 in order to have an end of Season 1 analysis, if at least 1 additional RSV-confirmed ARI has been reported since VE Analysis 1 and if there are at least 2-3 weeks between the database cut-off dates of the 2 analyses.

If data related to endpoints not available at VE Analysis 1 become available at end of Season 1, the analysis might be performed at VE Analysis 2.

All data related to efficacy and immunogenicity objectives available at that time will also be analyzed.

3. Safety analysis:

An analysis of safety will be performed when all safety data up to 6 months post-Dose 1 will be available for all participants in NH and SH.

4. VE Analysis 3: end of Season 2 in NH

A fourth analysis will be performed to evaluate the efficacy, safety and immunogenicity objectives over 2 seasons, when all participants in NH have been followed until the end of second season (S2) in NH.

All the analyses described above will be performed on data as complete and as clean as possible, by an unblinded IES. The unblinded analyses will be shared with an unblinded committee independent from the project (firewall). Access to individual intervention codes and laboratory data will be restricted to the IES in charge of the analyses.

The firewall will review the unblinded summaries to prevent the potential risk of unblinding at participant level. If the summary results may lead to the unblinding of some specific participants (e.g., in case an event occurred only in 1 group), the blinding of results will be managed by the IES. In this situation, exact results per group will not be provided to the study team. Only blinded data will be released to the blinded study team members and investigators. Further details of this approach can be found in the firewall charter. The firewall team will no longer be active as of the implementation of Protocol Amendment 4 as of which point study statisticians will perform the analyses and manage the blinding of results for blinded study team members and investigators.

No individual data listings with the participant numbers information will be disseminated to the investigators at this point of time.

5. VE Analysis 4: end of Season 2 in NH and SH

An analysis will be performed to evaluate the efficacy, safety and immunogenicity objectives over 2 seasons, when all participants in NH and SH have been followed until the end of second season (S2) in SH.

6. **VE Analysis 5: end of Season 3 in NH**

An analysis will be performed to evaluate the efficacy, safety and immunogenicity objectives over 3 seasons, when all participants in NH have been followed until the end of third season (S3) in NH.

7. **VE Analysis 6: End of Study analysis**

This analysis will be performed at the end of the study, i.e., when all participants (except drop-outs) will have completed the last study visit: end of Season 3 (S3) in NH (Visit 7NH) and end of study in SH (Visit 5SH).

Individual data listings will only be generated at this stage.

9.6. Independent Data Monitoring Committee (IDMC) (Amended)

Unblinded evaluation of safety data will be performed by an IDMC on a regular basis. In preparation of the IDMC meetings, unblinded analyses will be performed by an IES to maintain the study blind. Only the outcomes and recommendations of the IDMC will be communicated to the study team. Operational details will be provided in the IDMC Charter.

A firewall team will be set up in order to allow the planned analyses to be performed and results shared with the IDMC, while the study blind is maintained to the whole team and participants. All details of this approach can be found in the firewall charter. As of implementation of ***the*** Protocol Amendment 4, the firewall team will no longer be active. Refer to Section 6.3.5 for further details.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator for review and approval. These documents will be signed and dated by the investigator before the study is initiated.
- Any protocol amendments will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
  - Notifying the IRB/IEC of SAE(s) 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 financial interest information prior initiation of the center and at the end of the study. Investigators are responsible for providing a Financial Disclosure update if their financial interests change at any point during their participation in a study and for 1 year after completion of the study.

10.1.3. Informed consent process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary.

Freely given and written/witnessed informed consent must be obtained from each participant and/or each participant's witness, prior to participation in the study. The participant's informed consent may be obtained prior to Visit 1. In addition, in case a caregiver is assigned by the participant to help with the study procedures, the caregiver must receive an information letter prior to supporting study participant, that describes the role and data that will be collected from the caregiver.

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

The medical record must include a statement that written or witnessed informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) or an ICF addendum during their participation in the study.

A copy of the ICF(s) must be provided to the participants.

10.1.4. Data protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets 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.

The participants must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law.

The participants must be informed of their rights regarding the use of their personal data in accordance with the data privacy Section of the ICF.

The participants must be informed that his/her 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.

GSK will also ensure protection of the personal data of the investigator and site staff which will be collected within the framework and for the purpose of the study in accordance with the Data Privacy Notice that will be sent to the site staff.

10.1.5. Committees structure

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

10.1.6. Dissemination of clinical study data

The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study register in compliance with the 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 trial registers.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis (end of study analysis).

GSK intends to make anonymized patient-level data from this trial 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 trial participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data quality assurance

The investigator should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential trial documents may be added or removed where justified (in advance of trial initiation) based on their importance and relevance to the trial. When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.

All participant data relating to the study will be recorded in the eCRF 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 electronically signing the eCRF.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants (Section 10.5.2 for the exact definition of source documents) that supports information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents or certified copies.

The sponsor or designee is responsible for the data management of this study including quality checking of the source data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). The safety and rights of participants must be protected, and study be conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Trial records and source documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report /equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Investigator should maintain a record of the location(s) of their source documents.

Data 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 needs to ensure that relevant source documents are available on site. The investigator may need to request previous medical records, current medical records or transfer records, depending on the study.

Definition of what constitutes source data and source documents can be found in Section 10.5.2.

10.1.9. Study and site closure

GSK or its 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, provided there is sufficient notice given to account for patient's safe exit from study participation. Study sites regular closure will occur upon study completion. A study site is considered closed when all required data/documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and 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:

- 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 recruitment of participants by the investigator
- Discontinuation of further study intervention development.

The investigator will:

- Review data collected to ensure accuracy and completeness
- Complete the Study Conclusion screen in the eCRF.

10.1.10. Publication policy

GSK aims to submit for publication the results of the study in searchable, peer reviewed scientific literature within 18 months from Last Participant Last Visit (LPLV) for interventional studies and follows the guidance from the International Committee of Medical Journal Editors.

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 layer of Vero cells (African Green Monkey, kidney, Cercopitheus aethiops, ATCC CCL 81) and incubated for 2 days to allow infection of the Vero cells by non-neutralized virus and the formation of plaques in the cell layer. Following a fixation step, RSV-infected cells are detected using a primary antibody directed against RSV (Polyclonal anti-RSV A/B IgG) and a secondary antibody conjugated to horseradish peroxidase (HRP), allowing the visualization of plaques after coloration with *TrueBlue* peroxidase substrate. Viral plaques are counted using an automated microscope coupled to an image analyzer (Scanlab system with a Reading software). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at each serum dilution and the number of plaques in the virus control wells (no serum added). The serum 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]. The ED60 neutralizing titers will also be converted in concentration in International Units per milliliter (IU/mL). Secondary standard calibrated against the international reference (NIBSC 16/284) will be included in the runs.

RSVPreF3 protein IgG ELISA

Responses to the RSVPreF3 antigen will be evaluated by an indirect ELISA allowing the detection and the quantification of RSVPreF3 IgG binding antibodies in human serum samples.

The principle of these assays is as follows: RSVPreF3 protein antigen will be adsorbed onto a 96-well polystyrene microplate. After washing and blocking steps, dilutions of serum samples, controls and standards will be added to the coated microplate. A reference standard curve will be prepared using a pool of commercial human serum containing anti-RSV antibodies. After incubation, the microplate will be washed to remove unbound primary antibodies. Bound IgG will be detected by the addition of a secondary anti-human antibody (total IgG-specific), conjugated to HRP. Bound antibodies are quantified by the addition of the HRP substrate, tetramethylbenzidine (TMB) and hydrogen peroxide, whereby a colored product develops proportionally to the amount of anti-RSVPreF3 protein total IgG antibodies present in the serum sample. The optical density of each sample dilution is then interpolated on the reference standard. The corresponding antibody concentration, corrected for the dilution factor, is expressed in arbitrary ELISA Laboratory Units per milliliter (ELU/mL).

Any further exploratory immunology testing might be performed to investigate RSV and/or hMPV-related immune responses.

10.2.2. Laboratory assays for molecular biology

Quantitative 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 (absolute quantitation). The RSV viral load is reported as copies of RSV RNA per mL of sample.

Qualitative multiplex RT-PCR for detection of a panel of viruses including hMPV

A qualitative multiplex RT-PCR assay is used for the detection and identification of multiple respiratory virus nucleic acids in the nasal/throat swabs. The following virus types and subtypes can be identified in the assay:

- Human adenovirus (AdV)
- Human metapneumovirus (hMPV)
- Human enterovirus (HEV)
- Human parainfluenza virus including at least types 1, 2, 3 and 4 (PIV1, PIV2, PIV3 and PIV4).

Qualitative multiplex RT-PCR for detection of additional respiratory viruses

A qualitative multiplex RT-PCR assay is used for the detection and identification of multiple respiratory virus nucleic acids in the nasal/throat swabs. The following virus types and subtypes can be identified in the assay:

- Influenza A virus (Flu A)
- Influenza B virus (Flu B)
- Human respiratory syncytial virus A (RSV A)
- Human respiratory syncytial virus B (RSV B)
- Human Influenza A virus subtype H1 (Flu A-H1)
- Human Influenza A virus subtype H3 (Flu A-H3)
- Human Influenza A virus subtype H1pdm09 (Flu A-H1pdm09)
- Human bocavirus ½/3/4 (HBoV)
- Human rhinovirus A/B/C
- Human coronavirus including at least 229E, NL63, OC43 and SARS-CoV-2 species

Following total nucleic acids extraction, viruses are detected by multiplex real-time RT-PCR assays targeting the above-mentioned viruses. A comparative analysis of the fluorescence intensities of each target is performed to detect the viruses present in the sample.

10.3. Appendix 3: Adverse Events: definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. Definition of an Adverse Event (AE)

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of 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 study intervention.

10.3.1.1. Events meeting the AE definition

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study vaccine administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs or symptoms temporally associated with study vaccine administration.
- Signs, symptoms that require medical attention (e.g., hospital stays, physician visits and emergency room visits).
- Pre- or post- intervention events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).
- Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs.
- AEs to be recorded as solicited events are described in the Section 10.3.3. All other AEs will be recorded as UNSOLICITED AEs.

10.3.1.2. Events NOT meeting the AE definition
• Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, admission for routine examination). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Pre-existing conditions or signs and/or symptoms present in a participant prior to the first study vaccination. These events will be recorded in the medical history Section of the eCRF. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline. • Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the participant's condition, or that are present or detected at the start of the study and do not worsen.

10.3.2. Definition of a Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:	
a.	Results in death.
b.	Is life-threatening Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
c.	Requires hospitalization or prolongation of existing hospitalization Note: In general, hospitalization signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalization are also considered as AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred, or was necessary, the AE should be considered serious.
d.	Results in disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza-like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e.	Is a congenital anomaly/birth defect in the offspring of a study participant.

f. Other situations

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

10.3.3. Solicited events

a. Solicited administration site events

The following administration site events will be solicited from participants in the reactogenicity and immunogenicity subset:

Table 33 Solicited administration site events

Pain
Erythema
Swelling

b. Solicited systemic events

The following systemic events will be solicited from participants in the reactogenicity and immunogenicity subset:

Table 34 Solicited systemic events

Fever
Headache
Fatigue
Myalgia
Arthralgia

Note: Participants will be instructed to measure and record the oral, axillary or tympanic body temperature in the evening. Should additional temperature measurements be performed at other times of day, participants will be instructed to record the highest temperature in the paper diary card.

10.3.4. Unsolicited adverse events

An unsolicited AE is an adverse event that was not solicited and that was spontaneously communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.

Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report

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

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

10.3.5. Adverse events of special interest (AESIs)

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

10.3.5.1. Potential immune-mediated diseases

pIMDs are a subset of AESIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 35 (refer to Section 10.3.8.1 for reporting details).

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

Table 35 List of potential immune-mediated diseases (pIMDs)

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

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

Medical Concept	Additional Notes
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis • Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease • Felty's syndrome
Sjögren's syndrome	
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blenorrhagica • Psoriatic spondylitis • Reactive Arthritis (Reiter's Syndrome) • Undifferentiated spondyloarthritis
Systemic Lupus Erythematosus	• Includes Lupus associated conditions (e.g., Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)
Systemic Scleroderma (Systemic Sclerosis)	• Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants	Includes the following: • Acute necrotising myelitis • Bickerstaff's brainstem encephalitis • Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) • Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis
Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	Including but not limited to: • Cranial nerve neuritis (e.g. Optic neuritis) • Idiopathic nerve palsies/paresis (e.g., Bell's palsy) • Melkersson-Rosenthal syndrome • Multiple cranial nerve palsies/paresis
Multiple Sclerosis (MS)	Includes the following: • Clinically isolated syndrome (CIS) • Malignant MS (the Marburg type of MS) • Primary-progressive MS (PPMS) • Radiologically isolated syndrome (RIS)

Medical Concept	Additional Notes
	• Relapsing-remitting MS (RRMS) • Secondary-progressive MS (SPMS) • Uhthoff's phenomenon
Myasthenia gravis	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy
Peripheral inflammatory demyelinating neuropathies and plexopathies	Including but not limited to: • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) • Antibody-mediated demyelinating neuropathy • Chronic idiopathic axonal polyneuropathy (CIAP) • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g., multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) • Multifocal motor neuropathy (MMN)
Transverse myelitis(TM)	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
Lichen planus	• Includes liquen planopilaris
Localised Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	

Medical Concept	Additional Notes
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Takayasu's arteritis
Medium sized and/or small vessels vasculitis	Including but not limited to: • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Behcet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis) • Erythema induratum (also known as nodular vasculitis) • Henoch-Schonlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis • Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Wegener's granulomatosis
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• Frequently used related terms include: "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"
Goodpasture syndrome	• Frequently used related terms include: "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"
Immune-mediated enhancement of disease	• Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)"
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	Including but not limited to: • Kawasaki's disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Raynaud's phenomenon	
Sarcoidosis	• Includes Loefgren syndrome
Susac's syndrome	

10.3.5.2. *Atrial fibrillation*

AEs of AF are considered as AESI in this study.

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.

10.3.6. Clinical laboratory parameters and other abnormal assessments qualifying as AEs or SAEs

In the absence of a diagnosis, abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments the investigator considers clinically significant will be recorded as an AE or SAE if they meet the definition of an AE or SAE (refer to the Sections 10.3 and 10.3.2).

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

10.3.7. Events or outcomes not qualifying as AEs or SAEs

10.3.7.1. Pregnancy

Not applicable for the study population.

10.3.8. Recording and follow-up of AEs, SAEs, AESIs (including pIMDs and AF) (Amended, 12 July 2023)

The participants will be instructed to contact the investigator immediately should the participants manifest any signs or symptoms they perceive as serious.

When an AE/SAE/AESI (including pIMDs and AF) occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE/AESI (including pIMDs and AF) in the eCRF. The investigator is not allowed to send photocopies of the participant's medical records to GSK instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all participant identifiers will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE/AESI (including pIMDs and AF) and not the individual signs/symptoms.

A paper diary will be used in this study to capture solicited administration site or systemic events in participants in the reactogenicity and immunogenicity subset and unsolicited AEs in all participants. The participant should be trained on how and when to

complete each field of the paper diary. If a participant is unable or not willing to complete the paper diary him/herself, he/she may be helped by a caregiver (refer to Section 10.5.2 for the definition of caregiver).

Any individual(s) who performs the measurements of administration site or systemic events and who will enter the information into the paper diary, e.g. the study caregiver, should have received a caregiver information letter explaining the role of the caregiver prior to completing the diary card. If any other individual than the participant is making entries in the paper diary, their identity should be documented in the participant's source record.

- Collect and verify completed diary cards during discussion with the participant on Visit 2 (Day 31 post-Dose 1), Visit 4 (Day 31 post-Dose 2) and Visit 6NH (Day 31 post-Dose3)*.
- Any unreturned diary cards 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.

**** Not applicable for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 and will not receive any study intervention at pre-Season 3 visit (Visit 5NH).***

Refer to the SPM for more information regarding the use of the paper diary.

10.3.8.1. Time period for collecting and recording AEs, SAEs, AESIs (including pIMDs and AF)

Refer to Table 23 in Section 8.3.1 for an overview of the protocol-required reporting periods for AEs, SAEs and pIMDs. AF reporting will follow the same reporting periods as for AEs and SAEs.

All solicited events with an onset during the 4-day period following each study vaccine administration in participants enrolled in the reactogenicity and immunogenicity subset must be recorded into the paper diary, irrespective of intensity.

All unsolicited AEs with an onset during the 30-day period following each study vaccine administration in all participants must be recorded into the paper diary, irrespective of intensity or whether or not they are considered vaccination-related. All other AEs occurring within this time frame should be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

Non-serious AF with an onset during the 30-day period following each study vaccine administration will be collected.

SAEs, serious AF and pIMDs will be collected and recorded from the day of vaccination up to 6 months post-vaccination for each dose.

All SAEs and pIMDs considered vaccination-related, any fatal SAEs and AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of receipt of first study vaccine until the participant is discharged from the study. In addition, SAEs related to study participation or to a concurrent GSK medication/vaccine will be collected from the time of consent obtained until the participant is discharged from the study.

10.3.8.2. Follow-up of AEs, SAEs, AESIs (including pIMDs and AF)

After the initial report of an AE/SAE/pIMD or any other event of interest for the study, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, AESIs (including pIMDs and AF) (as defined in Section 10.3.5), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Refer to Section 10.3.10 for timeframes and further information on how to report SAEs, pIMDs and other events.

10.3.8.2.1. Follow-up during the study

AEs (serious or non-serious), 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 the end of the study or the participant is lost to follow-up.

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

10.3.8.2.2. Follow-up after the participant is discharged from the study

The investigator will provide any new or updated relevant information on previously reported SAE/pIMD to GSK using a paper/electronic Expedited Adverse Events Report, as applicable. For AF cases, the investigator will provide any new or updated relevant information on previously reported AF to GSK using a paper/electronic Expedited Adverse Events Report and the AF follow-up questionnaire as applicable.

The investigator is obliged to perform or arrange for the conduct of supplemental clinical examinations/tests and/or evaluations to elucidate the nature and/or causality of the AE or SAE as fully as possible.

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

When additional SAE, AESI (including pIMD and AF) information is received after removal of write access to the participant's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Section 8.3.4 or to GSK Clinical Safety and Pharmacovigilance department within the defined reporting time frames specified in the Table 24.

10.3.9. Assessment of intensity and toxicity

10.3.9.1. Assessment of intensity

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

Table 36 Intensity scales for solicited events in adults

Event	Intensity grade	Parameter
Pain at the injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities
	2	Moderate: Painful when limb is moved and interferes with every day activities
	3	Severe: Significant pain at rest. Prevents normal every day activities
Erythema at the injection site		Record greatest surface diameter in mm
Swelling at the injection site		Record greatest surface diameter in mm
Temperature*		Record temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Myalgia	0	Normal
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity
Arthralgia	0	Normal
	1	Mild: Arthralgia that is easily tolerated
	2	Moderate: Arthralgia that interferes with normal activity
	3	Severe: Arthralgia that prevents normal activity

* Fever is defined as a temperature ≥ 38.0°C/100.4°F by any route. The route for measuring temperature can be oral, axillary or tympanic.

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

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

The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator's clinical judgment.

The intensity should be assigned to 1 of the following categories:

1 (mild)	=	An AE which is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (In adults, such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.)

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

10.3.9.2. Assessment of causality

The investigator must assess the relationship between the study vaccine and the occurrence of each unsolicited AE/SAE using clinical judgment. Where several different vaccines/products were administered, the investigator should specify, when possible, if the unsolicited AE/SAE could be causally related to a specific vaccine/product (i.e., investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine/product cannot be determined, the investigator should indicate the unsolicited AE/SAE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccine will be considered and investigated. The investigator will also consult the IB to determine his/her assessment.

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

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

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

If an event meets the criteria to be determined as 'serious' (see Section 10.3.2), additional examinations/tests will be performed by the investigator to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.

- Other medication.
- Protocol-required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccine, if applicable.
- Erroneous administration.
- Other cause (specify).

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. However, it is very important to record an assessment of causality for every event before submitting the Expedited Adverse Events Report to GSK.

The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality after receiving additional information and update the SAE information accordingly.

10.3.9.3. Medically attended visits

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

10.3.9.4. Assessment of outcomes

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

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

10.3.10. Reporting of SAEs, AESIs (including pIMDs and AF)

10.3.10.1. Events requiring expedited reporting to GSK

Once an investigator becomes aware that an SAE has occurred in a study participant, the investigator (or designee) must complete information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event.

Even if the investigator does not have all information regarding an SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS. The investigator will always provide an assessment of causality at the time of the initial report.

Refer to the Table 24 for the details on timeframes for reporting of SAEs/AESIs (including pIMDs and AF).

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

Refer to the Section 10.3.10.2 for the back-up system in case the electronic reporting system does not work.

10.3.10.2. Back-up system in case facsimile or electronic reporting system does not work

In rare circumstances if the electronic reporting system does not work, the investigator (or designee) must fax completed, dated and signed paper Expedited Adverse Events Report to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Clinical Safety and Pharmacovigilance department within 24 hours.

Investigator (or designee) must complete the electronic Expedited Adverse Events Report within 24 hours upon electronic reporting system is resumed. The information reported through the electronic SAE reporting system will be considered valid for regulatory reporting purposes.

10.4. Appendix 4: Country-specific requirements

10.4.1. Japan

10.4.1.1. 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.

10.4.1.2. Informed consent

Prior to participation in the study, the investigator (or sub-investigator) should fully inform the potential participant including the written approval given by the IRB. The investigator (or sub-investigator) should provide the participant ample time and opportunity to inquire about details of the study. The participant should sign and personally date the consent form. If the participant wishes to consider the content of the written information at home, he/she may sign the consent form at home. The person who conducted the informed consent discussion and the study collaborator giving supplementary explanation, where applicable, should sign and personally date the consent form. The investigator (or designee) should retain this signed and dated form (and other written information) together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the participant.

10.4.1.3. Study administrative structure

Sponsor Information and List of Medical Institutions and Investigators are included in Exhibit 1 and Exhibit 2, respectively.

10.4.1.4. Unapproved medical device

If unapproved medical devices are used in the study, further details will be added in Exhibit 3. In case no unapproved medical devices are used, Exhibit 3 will not be attached.

10.4.2. Germany

10.4.2.1. Explanatory statement concerning gender distribution (Article 7, Paragraph 2 (12) of the German GCP order)

Recruitment will include both males and females with a balance between both gender. It is intended to enroll at least 40% of participants from each gender; the remaining 20% can be distributed freely between the 2 gender.

There is no intention to conduct specific analyses investigating the relationship between the gender of the participants and the efficacy, immunogenicity or safety of GSK's RSVPreF3 OA investigational vaccine.

10.4.2.2. Remote Monitoring and Source Data Verification

When onsite monitoring is not permissible due to site/local restrictions (e.g., in case of an epidemic and/or pandemic), remote monitoring may be employed that ensures all of the following requirements are met:

- Monitoring plan and execution details [remote source data verification (rSDV) method and scope of activities] are outlined in the Study Remote Monitoring Plan and Study Specific Risk Register.

- Remote monitoring method to be employed is permitted by local regulations, agreed upon by study site and approved by IRB/EC.
- Appropriate security systems/provisions are in place to ensure protection of patient data and shared information.
- Participants sign ICF including disclosure of remote monitoring for (redacted/anonymized) patient data with security provisions in place.

Prior to any rSDV activity, a written agreement by the Investigator will be obtained. The agreement includes the extent and the method of rSDV activities.

The Monitoring Plan and Study Specific Risk Register will be updated to include rSDV activities. Clinical Research Associates will be guided for the conduct of rSDV.

10.4.3. Republic of Korea

10.4.3.1. Study participants exclusion criteria for enrollment

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 enrollment/first study vaccination.

10.4.3.2. Safety monitoring

In addition, the following points should be noted concerning safety monitoring:

- No safety "holding rules" or criteria for pausing or early termination have been defined for this study.
- An Independent Data Monitoring Committee (IDMC) has been put in place and will be in charge of reviewing unblinded safety data on an agreed schedule.
- It will be at the IDMC discretion to recommend, if deemed necessary, that the study recruitment is paused or terminated based on their unblinded data reviews.
- In addition to the IDMC reviews, GSK's SRT will perform regular reviews of blinded data and may request the IDMC to perform ad-hoc unblinded reviews if any potential safety concern is suspected based on blinded data. As of the implementation of Protocol Amendment 4, SRT will review unblinded safety data.

10.5. Appendix 5: Abbreviations and glossary of terms

10.5.1. List of abbreviations (Amended, 12 July 2023)

AE:	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
ANOVA:	Analysis of Variance
ARI:	Acute Respiratory Illness
AS01$_B$:	Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 µg QS-21)
AS01$_E$:	Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 µg QS-21)
BMI:	Body Mass Index
CD:	Community Dwelling
CHF:	Congestive Heart Failure
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
COPD:	Chronic Obstructive Pulmonary Disease
COVID-19:	Coronavirus Disease 2019
DLP	Data Lock Point
eCRF:	electronic Case Report Form
ELISA:	Enzyme-Linked Immunosorbent Assay
EQ-5D:	EuroQol 5 dimension health questionnaire
ES :	Exposed Set
FLU-PRO :	InFLUenza Patient-Reported Outcome
GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titer

GSK:	GlaxoSmithKline Biologicals SA
HCP:	Healthcare Provider
HCRU:	Healthcare Resource Utilization
HLT:	High Level Term
hMPV:	Human Metapneumovirus
HRP:	Horseradish Peroxidase
HR-QoL:	Health-Related Quality of Life
IB:	Investigator Brochure
ICF:	Informed Consent Form
IDMC:	Independent Data Monitoring Committee
IEC:	Independent Ethics Committee
IES:	Independent External Statistician
IgG:	Immunoglobulin G
IRB:	Institutional Review Board
LL:	Lower Limit
LML:	Local Medical lead
LRTD:	Lower Respiratory Tract Disease
LSMEANS:	Least Squares Mean
LTCF:	Long-Term Care Facility
MedDRA:	Medical Dictionary for Regulatory Activities
mES:	modified Exposed Set
MGI:	Mean Geometric Increase
MI:	Myocardial Infarction
MPL:	3-O-desacyl-4'- monophosphoryl lipid A (produced by GSK)
NH:	Northern Hemisphere

PCR:	Polymerase Chain Reaction
PGI-C:	Patient Global Impression of Change
PGI-S:	Patient Global Impression of Severity
pIMD:	Potential Immune-Mediated Disease
PPSe:	Per Protocol Set for efficacy
PPSi:	Per Protocol Set for immunogenicity
PT:	Preferred Term
QS-21:	Quillaja saponaria Molina, fraction 21 (Licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
RNA:	Ribonucleic Acid
rSDV:	remote Source Data Verification
RSV:	Respiratory Syncytial Virus
RSVPreF3 OA:	RSV PreFusion protein 3 Older Adult
RT-PCR:	Reverse Transcription Polymerase Chain Reaction
S1/S2/S3:	Season ½/3
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SBIR:	Source data Base for Internet Randomization
SF-12:	A Short Form 12-item health survey
SH:	Southern Hemisphere
SOC:	System Organ Class
SPM:	Study Procedures Manual
SRT:	Safety Review Team
ULOQ:	Upper Limit Of Quantification
US:	United States

VE:	Vaccine Efficacy
WHO:	World Health Organization
YOA:	Years Of Age

10.5.2. Glossary of terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An 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 one or more parties to the trial 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 trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an 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 intervention assignment.
Caregiver:	A 'caregiver' is a person who has a continuous caring role for a participant or may be a person having substantial periods of contact with a participant and/or is engaged in his/her daily health care (e.g.**,** a relative of the participant including family members or friends, a nurse or LTCF staff

	who helps with daily activities in case of residence in a LTCF). In the context of this study, a caregiver can be appointed by the participant to oversee and support the participant's compliance with protocol-specific procedures (such as transcribing responses to questionnaires and diaries, receiving phone calls, planning study visits, performing the nasal self-swab, etc.). However, at no time, the caregiver should evaluate the participant's health status while answering diaries and/or questionnaires or make decisions on behalf of the participant.
Certified copy:	A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
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.
Current smoker:	A person who is currently smoking or who has stopped smoking within 6 months before study start.
Designee:	A qualified person appointed by the investigator or sponsor to take over a specific part of their trial-related duties or responsibilities.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled participant:	'Enrolled' means a participant's/LAR's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. Refer to the Section 9.3 for the definition of 'enrolled' applicable to the study.
Essential documents:	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
eTrack:	GSK's tracking tool for clinical trials.

Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the per protocol analysis (see Section 9.3 for details on criteria for evaluability).
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.
Immunological correlate of protection:	A correlate of risk that has been validated to predict a certain level of protection from the targeted endpoint.
Intervention:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant.
Intervention number:	A number identifying an intervention to a participant, according to intervention allocation.
Invasive medical device:	A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body.
Investigational vaccine:	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use. Synonym: Investigational Medicinal Product.

Investigator:	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate trial-related duties and functions conducted at the trial site to qualified individual or party to perform those trial-related duties and functions.
Long-term care facility:	A collective institutional setting (i.e., where some aspects of daily life, such as having meals, are shared) where care is provided for older people who reside in the facility 24 hours a day, 7 days a week, for an indefinite period of time. On-site personal assistance with activities of daily living is provided, while nursing and medical care may be provided on-site or by nursing and medical professionals from an organization external to the setting. The term long-term care facility may include nursing homes, care homes, elderly care centers, assisted living facilities and/or others.
Participant:	Term used throughout the protocol to denote an individual who has been contacted to participate or participates in the clinical study, either as a recipient of the vaccine or as a control. Synonym: subject.
Participant number:	A unique identification number assigned to each participant who consents to participate in the study.
Primary completion date:	The date that the final participant was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study.

Randomization:	Process of random attribution of intervention to participants to reduce selection bias.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited event:	Events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the participant or an observer during a specified post-vaccination follow-up period.
Source data:	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents:	Original legible documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
Study vaccine/product:	Any investigational vaccine/product being tested and/or any authorized use of a vaccine/product/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also, any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

10.5.3. List of trademarks

Trademarks of the GSK group of companies	Generic description
Shingrix	Herpes zoster vaccine (recombinant, adjuvanted)

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
TrueBlue Peroxidase Substrate (Seracare Life Sciences Inc.)	A highly sensitive chromagenic substrate for visualization of horseradish peroxidase-labeled reporter reagents

10.6. Appendix 6: Protocol Amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY	
Document	Date of Issue
Original Protocol	16 October 2020
Amendment 1	25 February 2021
Amendment 2	6 October 2021
Amendment 3	24 January 2022
Amendment 4	23 March 2023
Amendment 5	***12 July 2023***

Amendments summary of changes table:

Document	Date of issue	Section # and title	Description of change	Brief rationale
Amendment 1	25 February 2021	1.1. (Synopsis), 2.1. (Study rationale), 3. (Objectives and endpoints), 4.1. (Overall design), 6.1. (Study interventions administered), 9. (Statistical considerations), 10.5.1. (List of abbreviations)	The lot-to-lot consistency evaluation has been removed.	To implement the outcome of consultations with regulatory authorities.
Amendment 1	25 February 2021	2.3. (Benefit/Risk assessment), 4.1. (Overall design), 4.1.1. (Overview of the recruitment plan), 6.1. (Study interventions administered), 6.3.2. (Randomization to study intervention), 6.3.3. (Intervention allocation to the participant), 9.2. (Sample size determination)	A second part with a 4th RSVPreF3 group (Lot 4) and additional placebo recipients has been added for a total sample size up to 23 000 (randomization ratio 1:1) in NH. The target sample size in SH remains unchanged. The study design, study intervention and sample size have been adapted accordingly.	To increase the sample size to mitigate a potential lower attack rate of circulating respiratory viruses observed during the COVID-19 pandemic.
Amendment 1	25 February 2021	1.1. (Synopsis), 1.3. (Schedule of activities), 4.1. (Overall design), 8.1.1. (Efficacy assessments)	ARI surveillance period will start on the day of vaccination (Visit 1) instead of 1 month post-vaccination (Visit 2).	To collect data for all ARI cases starting from the day of vaccination.
Amendment 1	25 February 2021	3. (Objectives and endpoints), 8.1.2. (Immunogenicity assessments), 8.1.5. (Immunological read-outs), 8.1.7. (Immunological correlates of protection)	Neutralization assay was added as test which may be performed to investigate a correlate of protection.	To implement the outcome of consultations with regulatory authorities.
Amendment 1	25 February 2021	4.2.1. (Case definitions for evaluation of vaccine efficacy)	A second case definition for severe LRTD was added.	To implement the outcome of consultations with regulatory authorities.
Amendment 1	25 February 2021	6.1. (Study interventions administered)	The antigen dose was removed from the presentation of the RSVPreF3 OA investigational vaccine lots.	The antigen dose is not required for the presentation, which should only reflect the formulation dose form and formulation unit of presentation.
Amendment 1	25 February 2021	6.3.3. (Intervention allocation to the participant)	Minimization factors were updated to exclude sex and setting and subset as stratification factor was added.	To implement the outcome of consultations with regulatory authorities.
Amendment 1	25 February 2021	8. (Study assessments and procedures)	An additional measure was added to allow collection of swab samples by another person than the site staff, in case this is required to comply with	To allow study conduct in line with guidance from local public health or other competent

Document	Date of issue	Section # and title	Description of change	Brief rationale
			local guidelines (e.g., during the COVID-19 pandemic).	authorities during special circumstances such as the COVID-19 pandemic.
Amendment 1	25 February 2021	9.4.3. (Primary endpoint)	Wording for sensitivity analysis of the primary efficacy endpoint for RSV cases confirmed by the GSK qRT-PCR was added.	To implement the outcome of consultations with regulatory authorities.
Amendment 1	25 February 2021	1.3. (Schedule of activities), 9.5.1. (Sequence of analyses)	Order of the analyses has changed. A first analysis of the safety and immunogenicity objectives will be performed when all safety data up to 6 months post-vaccination will be available for all participants in NH.	To evaluate safety data as soon as possible to build knowledge for the benefit/risk profile assessment.
Amendment 1	25 February 2021	10.4. (Appendix 4: Country-specific requirements)	Country-specific guidance for the Republic of Korea was included.	To comply with legislation from the Republic of Korea.
Amendment 2	6 October 2021	3. (Objectives and endpoints)	The primary objective wording was updated to allow the assessment of the primary vaccine efficacy (VE) after having accrued at least 56 cases (case-driven only), which could happen before reaching the end of Season 1. The evaluation of VE at the end of Season 1 will be done as part of the secondary confirmatory objective evaluating VE over several seasons. In addition, the tertiary descriptive objective evaluating VE against any ARI and any LRTD has been moved to a secondary descriptive objective.	To allow assessment of the primary objective once the required number of cases have been accumulated.
Amendment 2	6 October 2021	3. (Objectives and endpoints), 9.1.2. (Secondary objectives)	Table structure updated to identify the subcategory for secondary confirmatory objectives and endpoints. The figure on sequential evaluation of primary and confirmatory secondary objectives was updated accordingly to indicate the confirmatory objectives to be analyzed.	To implement the outcome of consultations with regulatory authorities.
Amendment 2	6 October 2021	3. (Objectives and endpoints), 8.1.2. (Immunogenicity assessments), 8.1.4.2.	The evaluation of neutralizing antibody titers against RSV B was added to the secondary and tertiary immunogenicity endpoints for the pre-	To implement the outcome of consultations with regulatory authorities.

Document	Date of issue	Section # and title	Description of change	Brief rationale
		(Laboratory assays for immunogenicity assessment), 8.1.5. (Immunological read-outs)	vaccination (Day 1), 30 days post-vaccination (Day 31), pre-Season 2 and pre-Season 3 time points.	
Amendment 2	6 October 2021	9. (Statistical consideration)	The sequence of analyses and power for analyses were updated based on the trigger for analysis of the primary objective (case-driven only) and to include an optional interim analysis in case the number of cases triggering the final analysis of the primary objective is not achieved at the end of Season 1 in NH. The methodology for sample size re-assessment for enrollment of a second cohort before Season 2 in NH was also updated.	To allow assessment of the primary objective once the required number of cases have been accumulated. To allow an interim assessment of the primary objective at the end of Season 1 in NH or later if the trigger for the final primary analysis is not reached at the end of Season 1 in NH.
Amendment 2	6 October 2021	9.3. (Populations for analyses)	The case counting for the analysis on the modified Exposed Set was updated to start on Day 15 after vaccination.	To implement the outcome of consultations with regulatory authorities.
Amendment 2	6 October 2021	10.4. (Appendix 4: Country-specific requirements)	Guidance on remote monitoring and source data verification was added.	To comply with local regulations in Germany.
Amendment 3	24 January 2022	1.3. (Schedule of activities), 8.3.1. (Time period and frequency for collecting AE, SAE and other safety information)	Study visits/contacts and time points were added for all participants at 1 and 6 months post each annual revaccination dose.	To collect solicited adverse events during the 4-day follow-up period after each dose in the reactogenicity and immunogenicity subset, unsolicited adverse events during the 30-day follow-up period after each dose and SAEs/pIMDs during the 6-month follow-up period after each dose.
Amendment 3	24 January 2022	2.1. (Study rationale), 3. (Objectives and endpoints)	The confirmatory assessment of VE of annual revaccination doses and the descriptive evaluation of year-by-year VE for the annual revaccination doses were added. In addition, the safety and reactogenicity objectives were updated to include the additional assessment timepoints.	To allow assessment of the vaccine efficacy and safety following annual revaccinations with the RSVPreF3 OA vaccine.

Document	Date of issue	Section # and title	Description of change	Brief rationale
Amendment 3	24 January 2022	3. (Objectives and endpoints)	A confirmatory secondary efficacy objective was added to assess VE against RSV subtypes A and B separately over 3 seasons, conditionally to the number of cases accrued for both types.	To allow the confirmatory demonstration of VE by RSV subtype at the end of Season 3.
Amendment 3	24 January 2022	3. (Objectives and endpoints)	The assessment of VE against hMPV was upgraded from secondary descriptive to secondary confirmatory objective.	To implement the outcome of consultations with regulatory authorities.
Amendment 3	24 January 2022	4. (Study design), 8.1.5. (Immunological read-outs), 8.2. (Safety assessments)	The following items were added: • Re-randomization of the RSVPreF3 group prior to Season 2 into 2 sub-groups (RSV_annual group receiving annual revaccinations and RSV_1dose group receiving single dose vaccination followed by placebo) in a (1:1) ratio. • Annual revaccination with placebo for participants in the Placebo group. • Addition of study visits/contacts for all participants at 1 and 6 months post each annual revaccination dose. Addition of safety (for all participants) and reactogenicity (for participants in the reactogenicity and immunogenicity subset) follow-up after each annual revaccination dose.	To allow assessment of the efficacy and safety following annual revaccinations with the RSVPreF3 OA vaccine.
Amendment 3	24 January 2022	5. (Study population) 7.1. (Discontinuation of study intervention), 7.1.2. (Contraindications to subsequent vaccine administration)	The sections were adapted following the inclusion of annual revaccination doses.	To comply with implementation of annual revaccination doses throughout the protocol.
Amendment 3	24 January 2022	6. (Study intervention)	The numbers of doses to be administered per group and intervention allocation (randomization) was updated to include annual revaccination doses.	To allow assessment of the efficacy and safety following annual revaccinations with the RSVPreF3 OA vaccine.
Amendment 3	24 January 2022	9. (Statistical consideration)	The sequence of analyses and power for analyses were updated based on the inclusion of confirmatory assessment of VE of annual revaccination doses, and the confirmatory assessment of VE against hMPV.	To implement the outcome of consultations with regulatory authorities and allow assessment of the efficacy and safety following annual revaccinations with the RSVPreF3 OA vaccine.

Document	Date of issue	Section # and title	Description of change	Brief rationale
Amendment 3	24 January 2022	10.3.5 (Potential immune-mediated diseases)	The table with list of pIMDs has been updated.	To include emerging possible immune-mediated events of interest in the context of COVID-19 vaccine safety monitoring.
Amendment 4	23 March 2023	1.1 Synopsis; 1.3 Schedule of activities; 4.1 Overall design; 4.2.1 Case definitions for evaluation of vaccine efficacy; 6.5 Concomitant therapy; 8.1.6. Molecular biology read-outs; 10.5.1. List of abbreviations	ARI is defined as acute respiratory illness instead of acute respiratory infection.	The case definition for ARI includes the clinical manifestations of symptoms/signs in addition to positive reverse transcription polymerase chain reaction (RT-PCR) test results.
Amendment 4	23 March 2023	1.3 Schedule of activities; 6.5 Concomitant therapy; 8.1.1.5. Scheduled site staff contacts; 8.3.1. Time period and frequency for collecting AE, SAE and other safety information; 8.3.2 Method of detecting AEs and SAEs and other events; 8.3.3. Regulatory reporting requirements for SAEs and other events; 8.3.4. Contact information for reporting SAEs, AESIs (including potential immune-mediated diseases [pIMDs] and AF); 8.3.5. Treatment of adverse events; 9.4.1.4. Reactogenicity/Safety; 10.3.5. Adverse events of special interest; 10.3.5.2. Atrial fibrillation; 10.3.8. Recording and follow-up of AEs, SAEs, AESIs (including pIMDs and AF); 10.3.8.1. Time period for collecting and recording AEs, SAEs, AESIs (including pIMDs and AF);	AF adverse events meeting the AEs or serious adverse events (SAEs) definitions will be considered as AESI in this study and additional information on these events is to be reported in the AF follow-up questionnaire in electronic case report form (eCRF).	An imbalance in cases of AFs in the 30-days post Dose 1 was observed. These safety data were reviewed by the SRT and the IDMC, and no safety signals were identified. However, GSK is of the opinion that a detailed assessment of all AF cases is required.

Document	Date of issue	Section # and title	Description of change	Brief rationale
		10.3.8.2. Follow-up of AEs, SAEs, AESIs (including pIMDs and AF); 10.3.8.2.1. Follow-up during the study; 10.3.8.2.2. Follow-up after the participant is discharged from the study; 10.3.8.3. Updating of SAE, AESI (including pIMD and AF) information after removal of write access to the participant's eCRF; 10.3.10. Reporting of SAEs, AESIs (including pIMD and AF); 10.5.1. List of abbreviations; 10.5.2. Glossary of terms		
Amendment 4	23 March 2023	10.3.5.1. pIMDs	The list of pIMDs has been updated.	The list has been updated following a regular safety review and in line with Medical Dictionary for Regulatory Activities (MedDRA) updates
Amendment 4	23 March 2023	3 Objectives and endpoints; 9.1.2. Secondary objectives; 9.2.2. Secondary objectives; 9.2.2.1 Expected number of RSV-confirmed LRTD cases; 9.3 Population for analyses; 9.4.4.1. Efficacy; 9.4.5.1 Efficacy;	The secondary confirmatory objective of vaccine efficacy (VE) against human metapneumovirus (hMPV) over 3 seasons has been removed and the secondary descriptive objective evaluating VE against hMPV after Season 2 and Season 3 has been downgraded to tertiary objective.	As no VE against hMPV was observed at VE Analysis 1.
Amendment 4	23 March 2023	3 Objectives and endpoints; 4.3 Justification for dose; 8.1.2. Immunogenicity assessments; 8.1.4.2. Laboratory assays for immunogenicity assessment; 8.1.5. Immunological read-outs; 10.2.1 Laboratory assays for immune response;	The terminology for respiratory syncytial virus (RSV) A/RSV B neutralizing titers and RSVPreF3-binding IgG has been clarified.	This nomenclature more precisely reflects what is indeed measured by the neutralization assay and the enzyme-linked immunosorbent assay (ELISA) respectively.
Amendment 4	23 March 2023	6.3.5 Blinding and unblinding; 6.3.5.1 Emergency blinding; 8.2.3. Safety monitoring;	As of the implementation of Protocol Amendment 4, GSK RSV OA team members will be unblinded at the individual participant level with the exception	To simplify the blinding procedures at the sponsor level

Document	Date of issue	Section # and title	Description of change	Brief rationale
		9.5.1. Sequence of analyses 9.6 Independent Data Monitoring Committee 10.4.3.2 Safety monitoring	of GSK RSV OA team members involved in clinical evaluation (i.e., data review and validation, ARI/LRTD case review and adjudication, and laboratory testing) as well as investigators and study participants who will remain blinded until the end of study. The firewall team will no longer be active as of the implementation of Protocol Amendment 4 as of which point study statisticians will perform the analyses and manage the blinding of results for blinded study team members and investigators. As of the implementation of Protocol Amendment 4, SRT can review unblinded data.	to reduce complexity in sharing study-related information.
Amendment 4	23 March 2023	9.5.1. Sequence of analyses	The following analyses have been added: • VE Analysis 4: end of season 2 in Northern hemisphere (NH) and Southern hemisphere (SH): An analysis will be performed to evaluate the efficacy, safety and immunogenicity objectives over 2 seasons, when all participants in NH and SH have been followed until the end of second season (S2) in SH. • VE Analysis 5: end of season 3 in NH: An analysis will be performed to evaluate the efficacy, safety and immunogenicity objectives over 3 seasons, when all participants in NH have been followed until the end of third season (S3) in NH. VE Analysis 4 End of Study Analysis becomes VE Analysis 6.	To evaluate persistence of VE more regularly and to support discussions with recommending bodies.
Amendment 4	23 March 2023	10.4 Country-specific requirements	Country specific requirements for Brazil and France have been removed.	These countries that were initially planned, finally did not participate in this study.
Amendment 4	23 March 2023	6.3.5.1. Emergency unblinding;	The section has been updated to reflect that GSK's Global Safety staff may unblind the	For alignment with current protocol template.

Document	Date of issue	Section # and title	Description of change	Brief rationale
			intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.	
Amendment 4	23 March 2023	9.3 Population for analyses	Modified exposed set (mES) specific definition for hMPV was removed and mES definition after each dose was clarified.	As no VE against hMPV was observed at VE Analysis 1, the confirmatory objective was removed and no specific mES for hMPV will be used for analysis. Clarification of mES by dose for RSV endpoints was added to be aligned with the statistical analysis plan (SAP).
Amendment 4	23 March 2023	9.4.4.1 Efficacy	The reporting periods for RSV-confirmed LRTD cases for the VE analysis by year have been clarified.	For alignment with the SAP, and to take into account the revaccination.
Amendment 4	23 March 2023	3 Objectives and endpoints 9.4.4.1 Efficacy	It has been clarified that VE in the prevention of hospitalization and complications will be evaluated during RSV seasons and during the entire follow-up.	To cover the entire period post-vaccination as for the other endpoints.
Amendment 4	23 March 2023	9.4.4.3 Safety	The section has been updated to clarify that SAEs, pIMDs, fatal SAEs, causally related SAEs and causally related pIMDs occurring within 6 months post-vaccination will be tabulated after each dose, and that causally related SAEs, fatal SAEs and causally related pIMDs will be tabulated after each dose from Day 1 up to study end.	For alignment with the SAP, and to take into account the revaccination.
Amendment 4	23 March 2023	8.1.1.1 ARI surveillance period and methods	Addition of flexibility in defining the data lock point (DLP) for the upcoming analyses for the ongoing and/or subsequent seasons.	To take into consideration the RSV circulation.

Detailed description of the current Protocol Amendment:

Title	A Phase 3, randomized, placebo-controlled, observer blind, multi-country study to demonstrate the efficacy of a single dose and annual revaccination ~~doses~~ of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above.
Sponsor signatory	Marie Van Der Wielen***, MD*** Clinical Project Lead,~~ MD~~ RSV Older Adults

Section 1. PROTOCOL SUMMARY

Section 1.1. Synopsis

GlaxoSmithKline Biologicals SA (GSK) ~~is developing an investigational vaccine,~~ ***has developed a new RSV PreFusion protein F3 Older Adult (***RSVPreF3 OA***) vaccine*** against ~~respiratory syncytial virus (~~RSV~~)~~-associated (subtypes A and B) disease in adults ≥ 60 years of age (YOA).

Section 1.3. Schedule of activities

For participants who will have the Visit 5NH (pre-Season 3 visit) taking place BEFORE the approval of this Protocol Amendment 5, the study procedures should be performed according to the previously approved protocol amendment version. Refer to Table 1 for details.

For participants who will have the Visit 5NH (pre-Season 3 visit) taking place AFTER the approval of this Protocol Amendment 5, the study procedures should be performed according to the current Protocol Amendment 5: Dose 3 administration should be cancelled as well as other procedures related to Dose 3 administration. Visit 6NH and Contact 5 should be cancelled for these participants. Blood sample should be collected for all participants at Visit 5NH. Refer to Table 2 for details.

Timeframe for Visit 5NH are defined in Table 5.

Table 1 Schedule of activities for ~~all~~ participants in Northern hemisphere *that have their Visit 5NH BEFORE approval of this Protocol Amendment 5*

Type of contact for NH[1]	V1	V2	C1[2]	C2	V3	V4	C3[2]	C4	V5NH	V6NH	C5[2]	V7NH	Notes for more information and details
Timepoint	Day 1 Dose 1	Day 31 Post-D1	Month 6 Post-D1	End S1	Pre S2 Dose 2	Day 31 Post-D2	Month 6 Post-D2	End S2	Pre S3 Dose 3	Day 31 Post-D3	Month 6 Post-D3	End S3	
Study group and intervention number allocation	○				○				○				**See Sections 6.3.2 and 6.3.3**

Note: The double-line borders indicate the analyses, which will be performed on data that are as clean as possible: VE Analysis 2 at the end of Season 1 in NH, Safety analysis when all safety data up to 6 months post-Dose 1 will be available for all participants in NH and SH, VE Analysis 3 after at least 2 seasons in NH and 1 season in SH, and VE Analysis 4 ***6*** after 3 seasons in NH and 2 seasons in SH (end of study). VE Analysis 1 will be case-driven. ***Additional analyses, not indicated in this table, will be performed as detailed in*** ~~refer to~~ Section 9.5.1 ~~for details~~.

[3] Freely given and written informed consent must be obtained from each study participant prior to participation in the study. The participant's informed consent may be obtained prior to Visit 1 ~~and Visit 3.~~ ***In addition, participants should sign the ICF addendum for revaccination (Protocol Amendment 3) at Visit 3.***

[4] In case the participant does not agree to continue the study for the annual revaccination~~s~~, the study conclusion page of the eCRF should be completed.

[11] 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. For AF that were reported before the implementation of ***the*** ~~this~~ Protocol Amendment 4, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

Table 2 Schedule of activities for participants in Northern hemisphere that have their Visit 5NH AFTER the approval of this Protocol Amendment 5

Type of contact for NH[1]	*V1*	*V2*	*C1[2]*	*C2*	*V3*	*V4*	*C3[2]*	*C4*	*V5NH*	*V6NH[11]*	*C5[11]*	*V7NH*	*Notes for more information and details*
Timepoint	*Day 1 Dose 1*	*Day 31 Post-D1*	*Month 6 Post-D1*	*End S1*	*Pre S2 Dose 2*	*Day 31 Post-D2*	*Month 6 Post-D2*	*End S2*	*Pre S3 Dose 3*	*Day 31 Post-D3*	*Month 6 Post-D3*	*End S3*	
Study participant informed consent	●[3]												*See Section 10.1.3*
Study participant informed consent for annual revaccination					●								
Study participant informed consent addendum for Protocol Amendment 5									●				
Distribution of participant card	○												*See Section 8.3.6*
Check inclusion/exclusion criteria	●												*See Sections 5.1 and 5.2*
Check with participant if he/she will appoint a caregiver and distribute information letter(s) to caregiver, when applicable	○	○			○	○			○				*See Sections 5.3 and 10.1.3*
Baseline and demography assessments													
Collect demographic data	●												*See Section 8.2.1.1*
Measure/record height and weight	●												*See Section 8.2.1.2*
Record medical history	●												*See Section 8.2.1.3*
Record history of vaccine administration[4]	●												*See Section 8.2.1.4*
Physical examination/Vital signs	●	○[5]			●	○[5]			●			○[5]	*See Section 8.2.2*
Lung auscultation	○	○[5]			○	○[5]			○			○[5]	*See Section 8.2.2.3*
Record oxygen saturation	●				●				●				*See Section 8.2.2.4*

Type of contact for NH[1]	*V1*	*V2*	*C1[2]*	*C2*	*V3*	*V4*	*C3[2]*	*C4*	*V5NH*	*V6NH[11]*	*C5[11]*	*V7NH*	*Notes for more information and details*
Timepoint	*Day 1 Dose 1*	*Day 31 Post-D1*	*Month 6 Post-D1*	*End S1*	*Pre S2 Dose 2*	*Day 31 Post-D2*	*Month 6 Post-D2*	*End S2*	*Pre S3 Dose 3*	*Day 31 Post-D3*	*Month 6 Post-D3*	*End S3*	
Record smoking status and smoking exposure history (including electronic smoking devices)	●												*See Section 8.2.1.5. Refer to Section 10.5.2 for definitions of current and former smoker.*
Clinical specimens for laboratory assays													
Blood sampling in all participants (~20 mL)	●[6]	●							●[12]				*See Section 8.1.3.2*
Blood sampling in subset (~20 mL)[7]					●[6]				●				*See Section 8.1.3.2*
Vaccine(s)													
Check criteria for temporary delay for enrollment and/or vaccination	○				○								*See Section 7.1.1*
Check contraindications to vaccination					○								*See Section 7.1.2*
Study group and intervention number allocation	○				○								*See Sections 6.3.2 and 6.3.3*
Record pre-vaccination body temperature	●				●								*The route for measuring temperature can be oral, axillary or tympanic (see Section 8.2.1.6).*
Vaccine administration (including 30-minute post-vaccination observation)	●				●								*See Section 6.1*
Safety assessments													
Distribute paper diary cards[8]	○				○								*See Section 8.2.1.7*
Return of paper diary cards		○				○							*See Section 10.3.8*

Type of contact for NH[1]	*V1*	*V2*	*C1[2]*	*C2*	*V3*	*V4*	*C3[2]*	*C4*	*V5NH*	*V6NH[11]*	*C5[11]*	*V7NH*	*Notes for more information and details*
Timepoint	*Day 1 Dose 1*	*Day 31 Post-D1*	*Month 6 Post-D1*	*End S1*	*Pre S2 Dose 2*	*Day 31 Post-D2*	*Month 6 Post-D2*	*End S2*	*Pre S3 Dose 3*	*Day 31 Post-D3*	*Month 6 Post-D3*	*End S3*	
Record solicited administration site and systemic events (Days 1-4) in the reactogenicity subset	●	●			●	●							*See Section 10.3.8*
Record unsolicited AEs (Days 1-30) in all participants[10]	●	●			●	●							*See Section 10.3.8*
Record concomitant medications/vaccinations	●	●	●	●	●	●	●	●	●			●	*See Table 15 for specific collection period and Section 6.5*
Record intercurrent medical conditions	●	●	●	●	●	●	●	●	●			●	*See Section 9.3.1.1*
Record all SAEs and pIMDs[10]	●	●	●		●	●	●		●				*See Section 10.3.8*
Record fatal SAEs, SAEs related to study vaccination, COVID-19 cases and pIMDs related to study vaccination[10]	●	●	●	●	●	●	●	●	●			●	*See Section 10.3.8*
Record AEs/SAEs leading to withdrawal from the study	●	●	●	●	●	●	●	●	●			●	*See Section 10.3.8*
Record SAEs related to study participation, or to a concurrent GSK medication/vaccine[9]	●	●	●	●	●	●	●	●	●			●	*See Section 10.3.8*
ARI surveillance													
Instruct/remind participants of ARI surveillance	○	○	○	○	○	○	○	○	○				*See Section 8.1.1*
Nasal self-swab training with the study participant		○											*See Section 8.1.1.1.1*
Distribute material for nasal self-swab collection (including instructions)		○			○				○				*See Section 8.1.1*

Type of contact for NH[1]	*V1*	*V2*	*C1[2]*	*C2*	*V3*	*V4*	*C3[2]*	*C4*	*V5NH*	*V6NH[11]*	*C5[11]*	*V7NH*	*Notes for more information and details*
Timepoint	*Day 1 Dose 1*	*Day 31 Post-D1*	*Month 6 Post-D1*	*End S1*	*Pre S2 Dose 2*	*Day 31 Post-D2*	*Month 6 Post-D2*	*End S2*	*Pre S3 Dose 3*	*Day 31 Post-D3*	*Month 6 Post-D3*	*End S3*	
Frailty status													
Assess frailty status with Gait Speed test	●												*See Section 8.4*
HR-QoL questionnaires													
Distribute the daily health questionnaires for participants to complete at home in case of ARI		○			○				○				*See Section 8.10.1*
Completion of daily health questionnaires by the participant		●											*See Section 8.10.1*
Completion of EQ-5D and SF-12 questionnaires by the participant	●				●				●				*See Section 8.10.1*
Study conclusion for NH												●	*See Section 4.4*

Note: The double-line borders indicate the analyses, which will be performed on data that are as clean as possible: VE Analysis 2 at the end of Season 1 in NH, Safety analysis when all safety data up to 6 months post-Dose 1 will be available for all participants in NH and SH, VE Analysis 3 after at least 2 seasons in NH and 1 season in SH, and VE Analysis 6 after 3 seasons in NH and 2 seasons in SH (end of study). VE Analysis 1 will be case-driven. Additional analyses, not indicated in this table, will be performed as detailed in Section 9.5.1.

Note: If following the sample size re-assessment an additional cohort needs to be enrolled before the next season in NH (see Section 9.2.3), the participants enrolled in this cohort will follow the same schedule of activities as indicated in this table.

ARI: acute respiratory illness; C: Contact; D: Dose; EQ-5D: EuroQol 5-dimension health questionnaire; HR-QoL: health-related quality of life; pIMDs: potential immune-mediated diseases; S: Season; SAE: serious adverse event; SF-12: Short Form 12-item health survey; Pre-S1: pre-Season 1; Pre-S2: pre-Season 2; Pre-S3: pre-Season 3; V: Visit.

● 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. ***Study visits should preferably be done on site or in the LTCF. If deemed necessary, study visits can be done at home. 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, or via a visit for LTCF participants. 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. ***Contacts 1 and 3 must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months after each vaccination for each participant. These contacts can be combined with another contact or visit.***

3. ***Freely given and written informed consent must be obtained from each study participant prior to participation in the study. The participant's informed consent may be obtained prior to Visit 1. In addition, participants should sign the ICF addendum for revaccination (Protocol Amendment 3) at Visit 3 and ICF addendum for Protocol Amendment 5 at Visit 5NH.***
4. ***Any vaccination administered up to 1 year before administration of the first study vaccine dose should be recorded in the eCRF. Administration of Shingrix at any timepoint (even if longer than 1 year before the first study vaccination) should be recorded in the eCRF.***
5. ***If deemed necessary by the investigator.***
6. ***The blood samples at Visits 1 and 3 should be taken prior to vaccine administration.***
7. ***The blood samples at Visit 3 should only be taken from participants in the reactogenicity and immunogenicity subset.***
8. ***A paper diary will be distributed to all study participants on each vaccination day (at Visits 1 and 3). All participants will record unsolicited AEs and concomitant medications/products on the day of each vaccination and for 29 subsequent days (Days 1-30). In addition, participants in the reactogenicity subset will be asked to record solicited events on the day of each vaccination and for 3 subsequent days (Days 1-4).***
9. ***SAEs related to study participation, or to a concurrent GSK medication/vaccine should be collected from the time of consent obtained (prior to administration of the first study vaccine dose) up to study end.***
10. ***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) in eCRF. The collection of AF will be performed following the AE/SAE reporting periods. For AF that were reported before the implementation of the Protocol Amendment 4, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.***
11. ***Visit 6NH and Contact 5 are not applicable for participants that did not receive the Dose 3 but are not removed from the schedule of activities table as these timepoints still appear in the eCRFs.***
12. ***At Visit 5NH, a blood sample of 20 mL should be taken from all participants including the participants of the immunogenicity and reactogenicity subset.***

Table 3 Schedule of activities for all participants in Southern hemisphere

Type of contact for SH[1]	V1	V2	V2b[2]	C1[3]	C2	V3	V4	C3[3]	C4	V5SH	Notes for more information and details
Timepoint	Day 1 Dose 1	Day 31 Post-D1	Pre S1	Month 6 Post-D1	End S1	Pre S2 Dose 2	Day 31 Post-D2	Month 6 Post-D2	End S2	End of study	
Study participant informed consent for annual revaccinations[5]						•					

[5] In case the participant does not agree to continue the study for the annual revaccinations, the study conclusion page of the eCRF should be completed.

[12]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. For AF that were reported before the implementation of ~~this~~ ***the*** Protocol Amendment 4, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

Table 4 Schedule of activities for ARI surveillance

10. 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. For AF that were reported before the implementation of ***the*** ~~this~~ Protocol Amendment 4, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

Table 5 Intervals between study visits/contacts for all participants in Northern hemisphere

Interval[3]	Length of interval	Allowed interval
Visit 5NH (Pre-Season 3~~/Dose 3~~)	Between 1 August and 30 September Study Year 3[4,5]	
Visit 5NH → Visit 6NH[6]	30 days	28-42 days[1]
Visit 5NH → Contact 5[6]	180 days	180-210 days[2]

[5] For participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5, in exceptional cases, Visit 5NH can be organized before 30 October.

[6] Visit 6NH and Contact 5 are not applicable for participants who will have their Visit 5NH after the approval of the current Protocol Amendment 5 and did not receive any study intervention (Dose 3) at pre-Season 3 visit (Visit 5NH).

Section 2.1. Study rationale

GSK ~~is developing an investigational vaccine~~ ***has developed a new*** RSVPreF3 OA ***vaccine*** against RSV-associated (subtypes A and B) disease in adults ≥ 60 YOA**.**

The purpose of the current study is to demonstrate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RT-PCR-confirmed LRTD caused by RSV A and/or B in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA vaccine and following annual revaccination ~~doses~~. The vaccine cross-protection against RT-PCR-confirmed LRTD caused by human metapneumovirus (hMPV) will also be evaluated. In addition, the safety and immunogenicity of the vaccine will be assessed after each dose.

Section 2.2. Background

At the time of initiation of this study, ~~There is currently~~ no vaccine ~~or~~ ***nor*** other prophylactic treatment ***was*** available against RSV or hMPV in older adults. ***Since then, GSK's RSVPreF3 OA investigational vaccine was first approved for use in an adults ≥ 60 YOA in the US on 3 May 2023, followed by the European Union on 6 June 2023*** ~~Currently available treatment for RSV and hMPV infections in this age group is generally supportive in nature.~~

Section 2.3.2. Benefit assessment

At the start of this study, the efficacy of the RSVPreF3 OA investigational vaccine was not demonstrated yet. Hence it was unknown if t*~~T~~he participants receiving the RSVPreF3 OA investigational vaccine ~~may not directly~~ ***would benefit from this vaccination ~~because the vaccine efficacy (VE) has not been assessed yet~~. ***Since then, the efficacy of RSVPreF3 OA investigational vaccine was demonstrated and the study primary confirmatory objective was met. One dose of RSVPreF3 OA vaccine has shown a favorable benefit/risk profile. The vaccine was approved for use in an adults ≥ 60 YOA in the US on 3 May 2023, followed by the European Union on 6 June 2023.***

The VE Analysis 3 data showed that revaccination administered approximately 12 months after Dose 1 did not confer additional benefit in prevention of RSV-confirmed LRTD for the overall population of adults ≥ 60 YOA, while the second dose of vaccine has a clinically acceptable safety profile. The clinical development program will continue to evaluate longer term follow-up and the optimal timing for potential revaccination. ~~Hence, it is not known whether the RSVPreF3 OA investigational vaccine is effective in protecting against RSV disease.~~

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

Section 3. OBJECTIVES AND ENDPOINTS

Table 8 Study objectives and endpoints

Objectives	Endpoints
Secondary	
Secondary – Efficacy	
Secondary confirmatory	
To demonstrate the efficacy of a single dose of the RSVPreF3 OA investigational vaccine followed by ***1*** annual revaccination ***before Season 2***~~doses~~ in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA over several seasons. Criterion: The LL of the 2-sided CI for VE is above 20%.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*.
To demonstrate the efficacy of a single dose and ***1*** annual revaccination ***before Season 2*** ~~doses~~ of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 YOA over 3 seasons. Criterion: The LL of the 2-sided CI for VE is above 0%.	First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition*, for RSV subtype A and RSV subtype B separately.
Other secondary descriptive	
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed RSV-associated LRTD, according to the case definition*, for RSV subtype A and RSV subtype B separately.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by age category, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, in the following age categories: ≥ 65 YOA, ≥ 70 YOA and ≥ 80 YOA.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by season in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by season.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by year in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by year.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA by baseline comorbidities, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD according to the case definitions*, by baseline comorbidities.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD by baseline frailty status in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA	First occurrence of RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definition*, by baseline frailty status.

Objectives	Endpoints
investigational vaccine and following annual revaccination ~~doses~~.	
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of severe RSV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated severe LRTD, according to the case definitions*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of any ARI and any LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of ARI or LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of hospitalization due to respiratory diseases in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	• Occurrence of hospitalization due to respiratory diseases or due to a complication related to respiratory diseases during the RSV seasons† and during the entire follow-up. • Occurrence of hospitalization due to RSV-confirmed respiratory diseases or due to a complication related to RSV-confirmed respiratory diseases during the RSV seasons† and during the entire follow-up.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of complications related to RSV-confirmed ARI and any ARI in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	Occurrence of complication related to RSV-confirmed ARI or related to any ARI during the RSV seasons†, according to the case definition* and during the entire follow-up.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on lower respiratory tract symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	Maximum FLU-PRO Chest score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on ARI total symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	Estimated Least Squares mean FLU-PRO total score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on health utility score in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	Estimated Least Squares mean EQ-5D utility score at the ARI visit for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.

Objectives	Endpoints
To evaluate the impact of the RSVPreF3 OA investigational vaccine on physical functioning in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	Estimated Least Squares mean SF-12 Physical Functioning score at the ARI visit for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
Secondary – Immunogenicity	
To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine.	In a subset of participants, at pre-Dose 1 (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (pre-Season 2) and ~~pre-Dose 3 (~~pre-Season 3~~)~~: • RSVPreF3 IgG-binding antibody concentrations. • Neutralizing titers against RSV A. • Neutralizing titers against RSV B.
Tertiary	
Tertiary – Efficacy	
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV and/or hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed RSV and/or hMPV-associated LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~ up to the end of Season 2 and Season 3.	First occurrence of RT-PCR-confirmed hMPV-associated LRTD, according to the case definition*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of severe hMPV-confirmed LRTD in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed hMPV-associated severe LRTD, according to the case definitions*.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI for each RSV subtype (A and B) separately in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed RSV-associated ARI, according to the case definition*, for RSV subtype A and RSV subtype B separately.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI by age category, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*, in the following age categories: ≥ 65 YOA, ≥ 70 YOA and ≥ 80 YOA.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI by season, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definition*, by season.

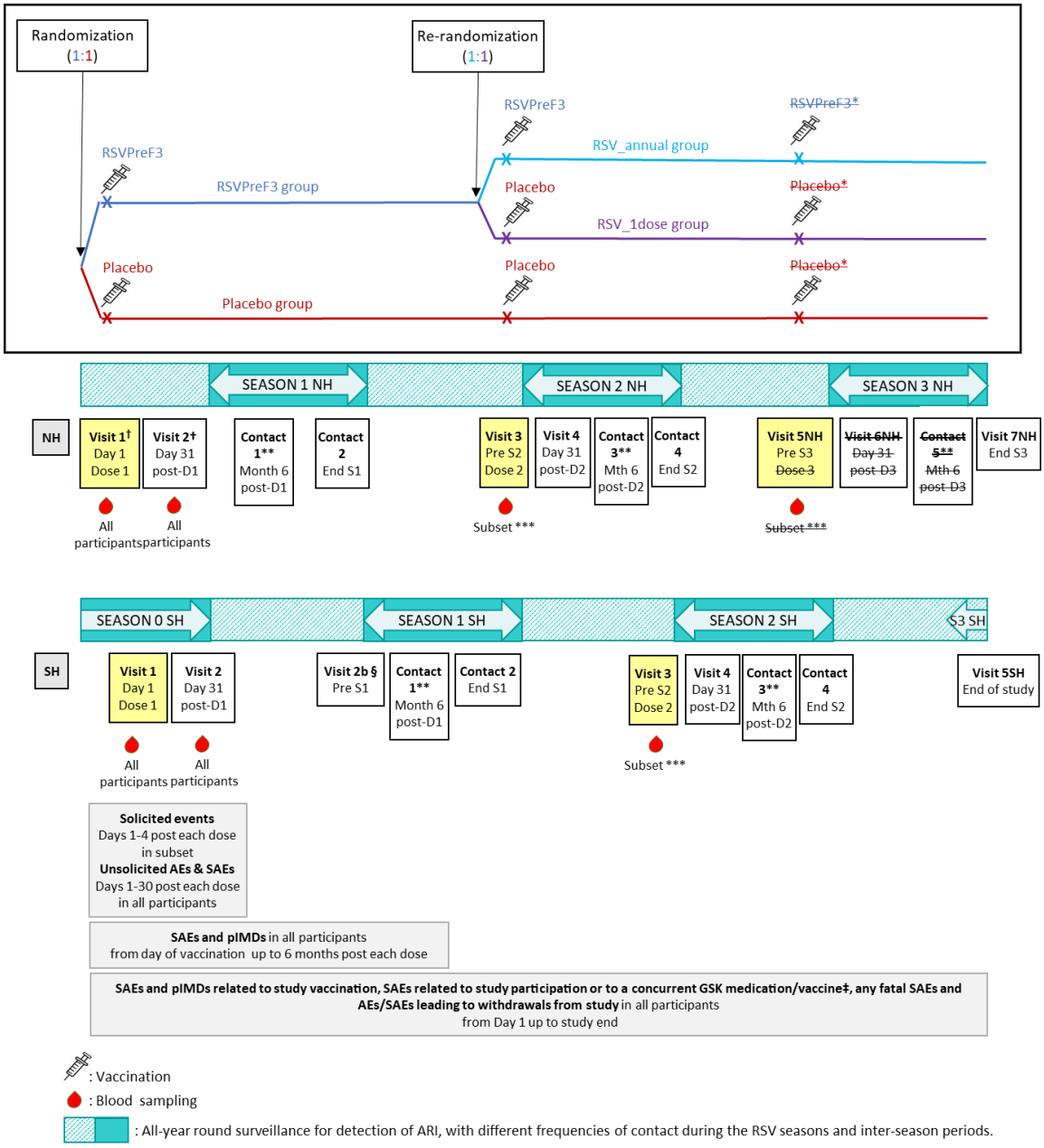
Objectives	Endpoints
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed ARI in adults ≥ 60 YOA by baseline comorbidities, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	First occurrence of RT-PCR-confirmed RSV A and/or B-associated ARI, according to the case definitions*, by baseline comorbidities.
To evaluate the efficacy of the RSVPreF3 OA investigational vaccine in the prevention of all-cause mortality during the RSV seasons† in adults ≥ 60 YOA, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	Occurrence of any death during the RSV seasons†.
To estimate the proportion of participants with > 1 case of ARI or LRTD by season and participants reporting respiratory diseases in consecutive seasons, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	Number of participants with > 1 case of ARI, LRTD, RT-PCR-confirmed RSV A and/or B-associated ARI and RT-PCR-confirmed RSV A and/or B-associated LRTD, according to the case definitions* by season and in consecutive seasons.
To estimate the proportion of co-infections with other viral pathogens for RSV-confirmed or hMPV-confirmed ARI cases, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	Number of participants with other viral pathogens (detected by RT-PCR) co-existing with RSV or hMPV among RT-PCR-confirmed RSV or RT-PCR-confirmed hMPV ARI episodes.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on upper respiratory tract symptoms in participants with RSV-confirmed ARI in the RSVPreF3 groups compared to the Placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	Maximum FLU-PRO upper respiratory symptom score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated ARI.
To assess the impact of the RSVPreF3 OA investigational vaccine on healthcare resource utilization (HCRU) for participants with RSV-confirmed ARI and any ARI, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	• Hospitalization rate during the ARI episode for participants with RT-PCR-confirmed RSV A and/or B-associated ARI and any ARI, according to the case definitions*. • Antibiotic use during the ARI episode for participants with RT-PCR-confirmed RSV A and/or B-associated ARI and any ARI, according to the case definitions*.
To evaluate the impact of the RSVPreF3 OA investigational vaccine on patient-reported severity of respiratory symptoms in participants with RSV-confirmed LRTD in the RSVPreF3 groups compared to the Placebo group, following a single dose of the RSVPreF3 OA investigational vaccine and following annual revaccination ~~doses~~.	Maximum patient global impression of severity (PGI-S) score during the first 7 days from the onset of ARI symptoms for participants with RT-PCR-confirmed RSV A and/or B-associated LRTD.
Tertiary - Immunogenicity and Safety	
To assess the correlation of the humoral immune response to the RSVPreF3 OA investigational vaccine at 30 days post-Dose 1 with protection against RSV disease.	RSVPreF3 IgG-binding antibody concentrations at pre-Dose 1 (Day 1), ~~and~~ 30 days post-Dose 1 (Day 31) ***and pre-Season 3*** in all participants with RSV disease compared to a subset of controls.‡

Objectives	Endpoints
To evaluate the humoral immune response to the RSVPreF3 OA investigational vaccine by baseline frailty status.	In a subset of participants, at pre-Dose 1 (Day 1), 30 days post-Dose 1 (Day 31), pre-Dose 2 (pre-Season 2) and ~~pre-Dose 3 (~~pre-Season 3~~)~~: • RSVPreF3 IgG-binding antibody concentrations classified by baseline frailty score. • Neutralizing titers against RSV A classified by baseline frailty score. • Neutralizing titers against RSV B classified by baseline frailty score.

***** Blood sample at pre-Season 3 is applicable for all participants in the NH who have their Visit 5NH after the approval of the current Protocol Amendment 5.***

Section 4.1. Overall design

Figure 1 Study design overview



** Contacts 1 ***and*** 3 ~~*and 5*~~ must not be performed before the 6-month post-vaccination time point to allow collection of safety data up to at least 6 months after each vaccination for each participant. These contacts can be combined with another contact or visit.

†† ***Some participants in the NH may have Visit 5NH before the approval of the current Protocol Amendment 5. These participants should receive Dose 3 pre-Season 3 and all subsequent study procedures should be performed as planned in Protocol Amendment 4. Please refer to the Table 1 for the details of the procedures to be performed in participants that have their Visit 5NH before the approval of this amendment.***

**** ***For participants in the NH who have their Visit 5NH before the approval of the current Protocol Amendment 5, a blood sample should be taken only if the participant is in the reactogenicity and***

immunogenicity subset. Please refer to the Table 1 for the details of the procedures to be performed in participants that have their Visit 5NH before the approval of this amendment.

Each of the 4 RSVPreF3 groups in both parts will be randomized before Season 2 into 2 sub-groups (RSV_annual group and RSV_1dose group) with a 1:1 ratio. The RSV_annual group will receive an additional dose of RSVPreF3 OA vaccine before each subsequent season, while the RSV_1dose group will receive 1 dose of placebo at the same timepoints. To maintain the study blind, participants who were initially randomized to the Placebo group will also receive additional doses of placebo at the same timepoints.

At the time of pre-Season 3 (Visit 5NH), participants in the NH who will have their Visit 5NH before approval of the current Protocol Amendment 5, will receive the study intervention as planned according to their group allocation. Participants having their Visit 5NH after approval of the current Protocol Amendment 5 will not receive any study intervention at pre-Season 3 visit (Visit 5NH).

- **Randomization for the additional cohort enrolled in NH after sample size re assessment:** If following sample size re-assessment an additional cohort needs to be enrolled before the next season in NH (see Section 9.2.3), the participants in this additional cohort will be enrolled in 3 study groups (RSV_annual group, RSV_1dose group and Placebo group) according to a 1:1:2 randomization ratio and will follow the same study design as indicated in Figure 1. They will have a blood sampling at Visit 1 and Visit 2 as for all study participants. There will be no subset for immunogenicity and reactogenicity for this cohort.

  Note: Blood sample at Visit 5NH is not applicable for this cohort because it was never enrolled.

Table 9 Study groups, intervention and blinding foreseen in the study

For annual revaccination ~~doses~~							
RSV_L1_annual	Up to 5 750	375-500	Up to 6 250	≥ 60 years	RSVPreF3 OA investigational vaccine		X
RSV_L2_annual							X
RSV_L3_annual							X

- **Vaccination schedule:** First dose of study vaccine (RSVPreF3 OA investigational vaccine or placebo) on Day 1 followed by annual revaccination ~~doses~~ of study vaccine (RSVPreF3 OA investigational vaccine or placebo) as follows:
  - Participants from the NH ***who will have their Visit 5NH before the approval of the current Protocol Amendment 5,*** will receive 2 additional doses, 1 before Season 2 and 1 before Season 3.
  - ***Participants from the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5, will not receive any study intervention at pre-Season 3 visit (Visit 5NH). These participants had received 1 additional dose before Season 2.***
  - Participants from the SH will receive 1 additional dose before Season 2**.**

Section 4.2. Scientific rationale for study design

The study is designed as a Phase 3, observer-blind, placebo-controlled study enrolling adults ≥ ~~3~~ 60 YOA, who will be followed up for 3 consecutive RSV seasons in the NH and at least 2 consecutive RSV seasons in the SH.

The results of VE Analysis 3 evaluating the efficacy and safety up to the end of Season 2 in the NH, showed that 1 dose of the RSVPreF3 OA vaccine is efficacious against RSV-LRTD and severe LRTD at least over 2 RSV seasons, and that a second dose of the study vaccine administered before Season 2 did not confer additional benefit in prevention of RSV-confirmed LRTD. Safety and reactogenicity data post-Dose 2 were consistent with previous results from the Phase 3 program.

Based on this observation, the study design was modified to remove the next annual revaccination dose of study vaccine (Dose 3 pre-Season 3) in the NH. The clinical development program will continue to evaluate longer term follow-up and the optimal timing for revaccination.

Section 4.2.2. Rationale for the use of placebo

As there ~~is~~ ***was*** ~~currently~~ no licensed RSV vaccine available ***at the time of initiation of this study***, a placebo group (receiving saline solution) ***is*** ~~will~~ ~~be~~ used as control for the efficacy, safety/reactogenicity and immunogenicity assessments.

Section 6.1. Study interventions administered

After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be prepared and administered as shown in Table 10 for Dose 1 and Table 11 for the annual revaccination ~~doses~~. Refer to Section 4.1 for the schedule of vaccine administration.

For the annual revaccination ~~doses~~:

The RSV_annual group will receive an additional dose of RSVPreF3 OA vaccine before each subsequent RSV season while the RSV_1dose and Placebo groups will receive 1 dose of placebo at the same timepoints*. Refer to Section 4.1 for details on the study design.

**** Participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5, will not receive any study intervention at pre-Season 3 visit (Visit 5NH).***

Table 12 Study interventions administered for annual revaccination ~~doses~~

Number of doses to be administered for annual revaccination~~s~~	RSV_annual group: 2 doses in NH*†* 1 dose in SH	RSV_1dose and Placebo groups: 2 doses in NH*†* 1 dose in SH

† Participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5, will not receive any study intervention at pre-Season 3 visit (Visit 5NH).

Section 6.3.2. Randomization to study intervention

At Visit 3 (pre-Season 2), all participants who received 1 of the RSVPreF3 vaccine lots will be re-randomized in a 1:1 ratio into 2 sub-groups (RSV_annual group and RSV_1dose group) to receive annual revaccination ~~doses~~ (Dose 2 and Dose 3* in NH and Dose 2 in SH).

**** Participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 will not receive any study intervention at pre-Season 3 visit (Visit 5NH).***

Table 13 Number of participants in reactogenicity and immunogenicity subset

For immunogenicity pre-Season 3 ~~For Dose 3~~				
	RSV_annual group	**RSV_1dose group**	**Placebo**	**Total**
NH	~405	~405	~810	~1620

Section 6.5. Concomitant therapy

- Any prophylactic medication (e.g., analgesics, antipyretics) administered on each study vaccination day (Day 1, pre-Season 2 and pre-Season 3*) in the absence of ANY symptom and in anticipation of a reaction to the vaccination.

  **** Not applicable for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 and will not receive any study intervention at pre-Season 3 visit (Visit 5NH)***.

Table 15 Timing of collection of concomitant medication to be recorded

	Dose 1 Day 1 post-D1	Day 30 post-D1	Dose 2 Day 1 post-D2	Day 30 post-D2	Dose 3* Day 1 post-D3	Day 30 post-D3	Study Conclusion
All concomitant medication, except vitamins and dietary supplements					***	***	
Any prophylactic medication					***		
All concomitant medication including vaccines/products which may explain/cause/be used to treat an SAE/pIMD/AF**							

****** Not applicable for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 and will not receive any study intervention at pre-Season 3 visit (Visit 5NH).***

Section 7.1. Discontinuation of study intervention

Participants who do not consent for the annual revaccinations will be considered withdrawals from the study.

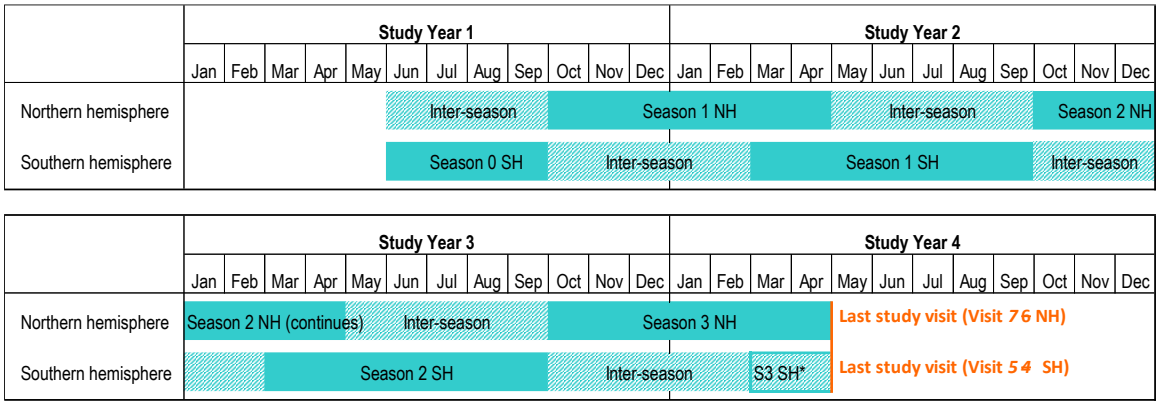
Section 7.1.2. Contraindications to subsequent vaccine administration

Note: This section is not applicable at pre-Season 3 visit for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 and will not receive any study intervention at pre-Season 3 visit (Visit 5NH).

Section 8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timings are summarized in Table 1 and ***Table 2*** for participants in NH, Table 3 for participants in SH and Table 4 for ARI surveillance (Section 1.3).

Figure 2 ARI surveillance in Northern and Southern hemispheres



* The last study visit in SH (Visit 54 SH) will occur approximately 2 months after the start of Season 3 in SH; yet the site staff surveillance contacts will be performed monthly during these last months (i.e., continuation of the inter-season frequency of contacts).

Section 8.1.3.2. Biological samples for immunogenicity assessment

A blood sample will be taken from all participants in both hemispheres at pre-Dose 1 (Day 1), ~~and~~ 1-month post-Dose 1 (Day 31) ***and from all participants at Visit 5NH**** to allow the evaluation of a potential correlate of protection. In addition, the immune response to the RSVPreF3 OA investigational vaccine will be further evaluated at other timepoints in a subset of participants (see Table 18).

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

- ~60 mL (3 x 20 mL) for participants in the reactogenicity and immunogenicity subset from SH,
- ~80 mL (4 x 20 mL) for participants in the reactogenicity and immunogenicity subset from NH,

- ~40 mL (2 x 20 mL) for all other participants in SH ~~and NH~~.
- ***~60 mL (3 x 20 mL) for all other participants in NH****

**** Applicable after the approval of the current Protocol Amendment 5.***

Table 18 Biological samples for immunogenicity assessment

Sample type	Quantity	Unit	Timepoint	Subset name*
Blood for correlate of protection	~20	mL	Visit 1 (Day 1, pre-Dose 1) Visit 2 (Day 31, post-Dose 1)	All participants
	~20	***mL***	***Visit 5NH (Pre Season 3)***	***All participants****
Blood for antibody measurement	~20	mL	Visit 3 (Pre Season 2, pre-Dose 2) Visit 5NH (Pre Season 3~~, pre-Dose 3~~)	Immunogenicity subset**

****All participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 including participants in the immunogenicity subset.***

Note: After the approval of the current Protocol Amendment 5, participants from the immunogenicity subset will still provide only 1 blood sample at Visit 5NH. This sample will be used for both the assessment of humoral immune response and evaluation of correlate of protection.

Section 8.1.5. Immunological read-outs

Table 21 Immunological read-outs

Blood sampling time point		Subset tested	No. samples tested	Component	Components priority rank
Type of contact and time point	Sampling time point				
Visit 5NH (Pre S3)	Pre-~~Dose 3~~ ***Season 3***	Immunogenicity subset*	~1620	RSV A neutralizing antibody	1
				RSV B neutralizing antibody	2
				RSVPreF3-binding IgG antibody	3
		All participants with RSV disease + Subset of controls*	***Case-driven****	***RSVPreF3-binding IgG antibody***	***-***

** A blood sample will be taken in all participants at Visit 1 and Visit 2 to allow the evaluation of a potential correlate of protection. RSVPreF3 ELISA will be tested on all participants with RSV-confirmed disease and in a subset of control participants. Additional testing such as but not limited to neutralization assay(s) and systems serology testing might be performed on the same subset of participants to investigate a correlate of protection. ***After approval of this Protocol Amendment 5, a blood sample will also be taken at Visit 5NH.***

8.1.7. Immunological correlates of protection

This study will attempt to correlate humoral immune responses at Day 31 post-Dose 1 ***and at pre-Season 3 (Visit 5NH)*** with protection against RSV-confirmed disease (see Section 9.4.5.4.1).

Section 8.2.1.7. Distribution of paper diary cards

A paper diary card will be distributed as follows:

- To all participants at Visit 1 (Day 1), Visit 3 (pre-Season 2) and Visit 5NH (pre-Season 3)* to note down any unsolicited AE as well as any medication and vaccination taken in the 30-day period following vaccination.
- To participants in the reactogenicity and immunogenicity subset at Visit 1 (Day 1), Visit 3 (pre-Season 2) and Visit 5NH (pre-Season 3)* to note down any solicited event, any unsolicited AE as well as any medication and vaccination taken in the 30-day period following vaccination.

Not applicable for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5. Refer to Table 2 for details.

Section 8.2.2.3. Lung auscultation

Lung auscultation at Visit 2 (Day 31 post-Dose 1/pre-Season 1), Visit 4 (Day 31 post-Dose 2), Visit 6NH (Day 31 post-Dose 3)*, Visit 5SH (end of study) and Visit 7NH (end Season 3) 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.

**** Visit 6NH is not applicable for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5. Refer to Table 2 for details.***

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

Table 23 Timeframes for collecting and reporting of safety information

	Pre-Vacc *	Dose 1 Day 1 post-Dose 1	Day 4 post-Dose 1	Day 30 post-Dose 1	6 months post-Dose 1***	Dose 2 Day 1 post-Dose 2	Day 4 post-Dose 2	Day 30 post-Dose 2	6 months post-Dose 2***	Dose 3# Day 1 post-Dose 3#	Day 4 post-Dose 3#	Day 30 post-Dose 3#	6 months post-Dose 3***, #	Study conclusion
Solicited administration site and systemic events**										‡	‡			
Unsolicited AEs†										‡	‡	‡		
All SAEs†										‡	‡	‡	‡	
All pIMDs										‡	‡	‡	‡	

 # Dose 3 is only applicable for participants in the NH who will have their Visit 5NH before the approval of the current Protocol Amendment 5.

‡For participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5, solicited and unsolicited AEs and all SAEs and pIMDs occurring after Visit 5NH will not be collected.

† Atrial fibrillation (AF) will be considered as AESI in this study and will be additionally reported in the AF follow-up questionnaire in eCRF. The reporting of non-serious AF will be performed according to the unsolicited AE reporting period. The reporting of AF meeting the SAE definition will be performed according to the SAE reporting period. Fatal AF and Serious AF judged as related to study vaccination will be performed according to the fatal SAE and related SAE reporting period, respectively. For AF that were reported before the implementation of ***the*** ~~this~~ Protocol Amendment 4, additional available information should be encoded in the specific AF follow-up questionnaire retrospectively.

Section 9. STATISTICAL CONSIDERATIONS

9.1.2. Secondary objectives

- To demonstrate the efficacy of a single dose of RSVPreF3 OA investigational vaccine followed by ***1*** annual revaccination~~s~~ ***before Season 2*** in the prevention of RSV-confirmed LRTD in adults ≥ 60 YOA over several seasons.

  Criterion: The LL of the 2-sided CI for VE is above 20%.

- To demonstrate the efficacy of a single dose and ***1*** annual revaccination ***before Season 2*** ~~doses~~ of RSVPreF3 OA investigational vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 YOA over 3 seasons.

  Criterion: The LL of the 2-sided CI for VE is above 0%.

VE of the *1* annual revaccination *given before Season 2* over 2 and 3 seasons:

- The confirmatory secondary objective assessing VE of the annual revaccination ***given before Season 2*** with RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 years after Season 2 in NH (S1+A2NH) will be evaluated conditionally to the success of the previous objective evaluating VE after Season 1 in NH (see Figure 4). A Bonferroni adjustment of alpha for multiplicity will be applied. Therefore, this analysis will be done using a 1-sided test at alpha=1.25% level.
- The confirmatory secondary objective assessing VE of ~~an~~ ***the*** annual revaccination ***given before Season 2*** with RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD in adults ≥ 60 years after Season 3 in NH (S1+A2+A3NH) will be evaluated conditionally to the success of the annual revaccination objective after Season 2 (see Figure 4). This analysis will be done using a 1-sided test at alpha=1.25% level.
- The confirmatory secondary objective assessing VE of ~~an~~ **the** annual revaccination ***given before Season 2*** with RSVPreF3 OA vaccine in the prevention of RSV-confirmed LRTD for each RSV subtype (A and B) separately in adults ≥ 60 years after Season 3 in NH (S1+A2+A3NH) will be evaluated conditionally to the success of the RSV objective of annual revaccination after Season 3 (see Figure 4).

  Analysis will be case-driven and will be performed if at least 49 cases are accrued for each subtype (RSV A and RSV B). The RSV A objective will be tested first, and if demonstrated, the RSV B objective will also be tested (see Figure 4).

Note that participants who received a third dose of RSVPreF3 OA investigational vaccine will not be included in the evaluation of annual revaccination over 3 seasons.

Figure 4 Sequential evaluation of primary and confirmatory secondary objectives

A2/A3 = Annual evaluation during Season 2/3 (after ***1*** revaccination ***given before Season 2***)

Section 9.2.2. Secondary objectives

- a VE against RSV-confirmed LRTDs of 70% over 1 season after ***Dose 1 (Season 1) and after 1 revaccination dose (Season 2)*** ~~each dose~~, ***VE of 65% at Season 3***.

Table 28 Power to demonstrate secondary confirmatory objectives

Endpoint (success criterion)	Sample size	AR	Analysis	Expected number of cases	Power (1-sided alpha=1.25%)
RSV-confirmed LRTDs (LL>20%)	16000+1500	0.6%	S1+A2NH	101	97.7%
			S1+A2+A3NH	13***7*** ~~6~~	99.***1***~~6~~%
			S1+S2NH	102	95.8%
			S1+S2+S3NH	139	98.2%
	23000+2000	0.6%	S1+A2NH	144	99.8%
			S1+A2+A3NH	19***6*** ~~5~~	≥99.9%
			S1+S2NH	146	99.5%
			S1+S2+S3NH	198	99.8%

S1/S2/S3 = Seasons 1/2/3***;*** A2/A3=Annual evaluation during Season 2/3 ***(after 1 revaccination given before Season 2)***; LL = lower limit

Table 30 Expected number of RSV-confirmed LRTD cases for the evaluation of VE of the annual revaccination

Season	N at start of season			Expected vaccine efficacy	Attack rate		Expected number of cases*
	RSVPreF3 group	RSV_annual group	Placebo group		Placebo group	Vaccine group	
A3NH	-	2560	5120	~~70~~ **65%**	0.60%	0.18%	3***2*** ~~1~~

A3NH= End of Season 3 in the Northern Hemisphere for participants receiving ~~2~~***1*** revaccination dose~~s~~ ***before Season 2.***

Section 9.3. Populations for analyses

Exposed Set Dose 2 and Exposed Set Dose 3 including all participants who received the 2nd and the 3rd dose, respectively, will also be used to report analysis on post-Dose 2/3 data.

mES will be defined by dose as follows:

- mES: participants who received Dose 1 and who did not report RSV ARI within 15 days post-Dose 1,
- mES Dose 2: participants who received Dose 2 and who did not report RSV ARI within 15 days post-Dose 2,
- mES Dose 3: participants who received Dose 3 and who did not report RSV ARI within 15 days post-Dose 3.

Note that participants who received a third dose of RSVPreF3 OA investigational vaccine will not be included in the primary evaluation of annual revaccination over 3 seasons. Details will be provided in the SAP.

- **Per Protocol set for efficacy (PPSe):** the PPSe will include all participants included in the mES who:

- received at least the first dose of the study vaccine to which they were randomized,
- ~~have data available for efficacy endpoint measures,~~
- did not have protocol deviations leading to exclusion.

Section 9.4.4.1. Efficacy

The same methodology as described for the primary endpoint (see Section 9.4.3) will be used to analyze the secondary efficacy endpoints described below. For the analysis over 2 or 3 seasons ~~(VE Analysis 3 and 4)~~, the model will include season as covariate, in addition to age category and region. The first occurrence of the event meeting the case definition according to the endpoint will be considered for the primary analysis of those secondary efficacy endpoints.

The following endpoints will be evaluated following a single dose of the RSVPreF3 OA investigational vaccine and following ***1*** annual revaccination dose~~s~~ ***given before Season 2***.

Note that participants who received a third dose of RSVPreF3 OA investigational vaccine will not be included in the primary evaluation of annual revaccination over 3 seasons. Secondary analysis of the annual revaccination on participants who received 3 doses of RSVPreF3 OA investigational vaccine might be performed depending on the number of participants who will receive the Dose 3. Details will be provided in the SAP.

Other secondary objectives

- VE during the second year post-vaccination (Year 2) in NH and SH, including first occurrence of cases reported from Day 15 post-Dose 2 ~~up to Dose 3 administration in NH, and~~ up to 12 months post-Dose 2 ***in NH and SH, or up to Dose 3 administration in NH*** ~~in SH~~;
- VE during the third year post-vaccination (Year 3) in NH and SH, including first occurrence of cases reported from ***12 months*** ~~Day 15~~ post-Dose ***2***~~3~~ in NH up to study end.

Section 9.4.4.4. Quality of life

The endpoints will be evaluated following a single dose of the RSVPreF3 OA investigational vaccine and following ***the*** annual revaccination dose~~s~~.

Section 9.4.5.1. Efficacy

The same methodology as described for the primary and secondary endpoints (see Sections 9.4.3 and 9.4.4.1, respectively) will be used to analyze the tertiary endpoints. The following endpoints will be evaluated following a single dose of the RSVPreF3 OA investigational vaccine and following ***the*** annual revaccination ***given before Season 2*** ~~doses~~:

Section 9.4.5.4.1. Correlate of protection

For that purpose, blood samples for humoral immune response will be collected from all participants at pre-Dose 1 (Day 1) ~~and~~, 1-month post-Dose 1 (Day 31) ***and at Visit 5NH**** and may be tested for correlate of protection analysis in all participants with RSV-confirmed disease and in a subset of control participants.

**** The blood sample at Visit 5NH is applicable after approval of the current Protocol Amendment 5.***

Section 9.5.1. Sequence of analyses

5. VE Analysis 4: end of Season 2 in NH and SH

~~6.~~ An analysis will be performed to evaluate the efficacy, safety and immunogenicity objectives over 2 seasons, when all participants in NH and SH have been followed until the end of second season (S2) in SH.

~~7~~ 6. **VE Analysis 5: end of Season 3 in NH**

An analysis will be performed to evaluate the efficacy, safety and immunogenicity objectives over 3 seasons, when all participants in NH have been followed until the end of third season (S3) in NH.

7. VE Analysis 6: End of Study analysis

Section 9.6. Independent Data Monitoring Committee (IDMC)

A firewall team will be set up in order to allow the planned analyses to be performed and results shared with the IDMC, while the study blind is maintained to the whole team and participants. All details of this approach can be found in the firewall charter. As of implementation of ***the~~is~~*** Protocol Amendment 4, the firewall team will no longer be active. Refer to Section 6.3.5 for further details.

Section 10.3.8. Recording and follow-up of AEs, SAEs, AESIs (including pIMDs and AF)

- Collect and verify completed diary cards during discussion with the participant on Visit 2 (Day 31 post-Dose 1), Visit 4 (Day 31 post-Dose 2) and Visit 6NH (Day 31 post-Dose 3)*.

**** Not applicable for participants in the NH who will have their Visit 5NH after the approval of the current Protocol Amendment 5 and will not receive any study intervention at pre-Season 3 visit (Visit 5NH).***

Section 10.5.1. List of abbreviations

AS01$_B$:	Adjuvant System containing MPL, QS-21 and liposome (50 µg MPL and 50 ***µ~~m~~***g QS-21)
AS01$_E$:	Adjuvant System containing MPL, QS-21 and liposome (25 µg MPL and 25 ***µ~~m~~***g QS-21)
DLP	***Data Lock Point***

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