Protocol Amendment 1

Study ID: 212496

Official Title of Study: A phase 3, randomized, open-label, multi-country study to evaluate the immunogenicity, safety, reactogenicity and persistence of a single dose of the RSVPreF3 OA investigational vaccine and different revaccination schedules in adults aged 60 years and above.

NCT number: NCT04732871

EudraCT number: 2019-004680-51

Date of Document: 01-APR-2022

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

Primary Study vaccine and number	GlaxoSmithKline Biologicals SA (GSK)'s investigational respiratory syncytial virus (RSV) vaccine BIO RSV OA=ADJ (GSK3844766A)
eTrack study number and abbreviated title	212496 (RSV OA=ADJ-004)
EudraCT number	2019-004680-51
Date of protocol	Final: 20 October 2020
Date of protocol amendment	Amendment 1 Final: 01 April 2022
Title	A phase 3, randomized, open-label, multi-country study to evaluate the immunogenicity, safety, reactogenicity and persistence of a single dose of the RSVPreF3 OA investigational vaccine and different revaccination schedules in adults aged 60 years and above.
Short title	Immunogenicity, safety, reactogenicity and persistence of an investigational respiratory syncytial virus (RSV) vaccine in adults aged 60 years and above.

Based on GSK Biologicals' Protocol WS v17.0

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and abbreviated title	212496 (RSV OA=ADJ-004)
EudraCT number	2019-004680-51
Date of protocol	Final: 20 October 2020
Date of protocol amendment	Amendment 1 Final: 01 April 2022
Title	A phase 3, randomized, open-label, multi-country study to evaluate the immunogenicity, safety, reactogenicity and persistence of a single dose of the RSVPreF3 OA investigational vaccine and different revaccination schedules in adults aged 60 years and above.
Sponsor signatory	Veronica Hulstrøm Clinical and Epidemiology R&D Project Lead RSV Older Adults
Signature	_____
Date	_____

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

Protocol Amendment 1 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 Biologicals SA (GSK).
- 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 representative(s) of GSK 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	212496 (RSV OA=ADJ-004)
EudraCT number	2019-004680-51
Date of protocol	Final: 20 October 2020
Date of protocol amendment	Amendment 1 Final: 01 April 2022
Title	A phase 3, randomized, open-label, multi-country study to evaluate the immunogenicity, safety, reactogenicity and persistence of a single dose of the RSVPreF3 OA investigational vaccine and different revaccination schedules in adults aged 60 years and above.

Investigator name _____

Signature _____

Date _____

PPD

name, function and title _____

Signature _____

Date _____

GSK Japan study representative name, function and title _____

Signature _____

Date _____

SPONSOR INFORMATION

1. Sponsor

GlaxoSmithKline Biologicals SA
Rue de l'Institut, 89
1330 Rixensart, Belgium

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 8.3.3.1.

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

5. GSK Helpdesk for Emergency Unblinding

Refer to the protocol Section 6.3.5.1**.**

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document history

Document	Date
Amendment 1	01 April 2022
Original Protocol	28 October 2020

Amendment 1: 01 April 2022

Overall rationale for the Amendment:

Immunogenicity data from other studies using the same study intervention showed that following a two-dose vaccination schedule (0-2-month schedule), the immune response gradually declines over time but remains above baseline value up to 18 months post-Dose 2 and that a re-vaccination at 18 months post-Dose 2 (i.e., 20 months post-Dose 1) induced humoral and cellular immune responses.

Consequently, as there are unknowns about (1) the persistence of the immune response to the RSVPreF3 OA investigational vaccine administered as a single dose and (2) the level of immune response that may be required for protection, the RSV OA=ADJ-004 (212496) Protocol has been amended to define the timing of the revaccination for participants in the RSV_flexible revaccination group. The revaccination will be administered in this group at Month 24 (i.e., approximately two years after the first dose).

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Section 1.3. Schedule of Activities	Table 2 was updated with the addition of (1) a revaccination (and related study procedures) at Month 24 and (2) a new follow-up visit at Month 25.	The timing of the revaccination with RSVPreF3 OA investigational vaccine for participants in the RSV_flexible revaccination group ~2 years after the first one was implemented.
	Tables 1, 2 and 3 were updated to clarify that (1) on vaccination days, blood samples were to be taken before vaccination and (2) that the 6-month post-vaccination safety follow-up should be performed at least 6 months after each vaccination.	Some study procedures were clarified.
	New interval (Month 24 → Month 25) for the RSV_flexible revaccination group was added in Table 5.	A new follow-up visit after revaccination has been added for these participants.

Section # and title	Description of change	Brief rationale
Section 4.1. Overall design Section 4.2 Scientific rationale for study design Section 6.1. Study interventions administered (Table 8) Section 6.5. Concomitant therapy Section 7.1.2. Contra-indications to subsequent vaccine administration Section 8.1. Efficacy and/or immunogenicity assessments Section 10.3.8. Recording and follow-up of AEs, SAEs and pIMDs	Where applicable, it was stated that participants from the RSV_flexible revaccination group will receive an additional dose of the RSVPreF3 OA investigational vaccine at Month 24 and that they will need to come to the study site for an additional follow-up visit one month later (Month 25). Consequently, some sections were adapted/aligned with the implementation of this revaccination timing.	Results from previous studies using the same study intervention showed that participants from this group might benefit from an additional dose at that timepoint.
Section 9.2. Sample size calculation Section 9.2.5. Evaluation of humoral immune response at Month 25 (secondary objective) Section 9.2.6. Evaluation of cellular immune response at Month 25 (secondary objective) Section 9.2.7. Evaluation of reactogenicity and safety profile following revaccination in the RSV_annual and RSV_flexible revaccination groups Section 9.4.1. General considerations Section 9.5.1.1. Analyses for objectives and endpoints	These sections were updated where applicable following the implementation of a revaccination with an additional dose of the RSVPreF3 OA investigational vaccine at Month 24 for participants from the RSV_flexible revaccination group.	Results from previous studies using the same study intervention showed that participants from this group might benefit from an additional dose at that timepoint.

Section # and title	Description of change	Brief rationale
Section 9.3. Population for analyses Section 9.4.1.2. Immunogenicity Section 9.4.2. Demographics and participants' disposition Section 9.4.3.1. Humoral immune response – up to Month 12 Section 9.4.4.1. Humoral immune response Section 9.4.4.2. Cell-mediated immune response Section 9.4.4.3. Safety analysis	Analyses were updated.	Following the addition of a revaccination at Month 24 for the RSV_flexible revaccination group, and to align with other Phase 3 RSV OA studies, some immunogenicity and safety analyses were updated/clarified.
Section 10.3.5.1. Potential immune-mediated diseases	The list of pIMDs has been revised.	The list has been updated following a regular safety review and to include possible immune-mediated adverse events of special interest.
Section 10.4.2. Requirements for Germany	Remote Source Data Verification (rSDV) during exceptional situations in Germany was added.	Instructions with regards to remote monitoring were added to allow this study procedure to be performed even in case of exceptional circumstances (e.g., in case of a lockdown).

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale:

GlaxoSmithKline Biologicals SA (GSK) is developing a new RSV PreFusion protein 3 Older Adult (RSVPreF3 OA) investigational vaccine against respiratory syncytial virus (RSV)-associated (subtypes A and B) disease in adults ≥ 60 years of age (YOA).

The RSVPreF3 OA investigational vaccine was administered intramuscularly for the first time to adults 60-80 YOA according to a 0, 2-month vaccination schedule in another clinical study (RSV OA=ADJ-002). The vaccine formulation and schedule to be used in the present study was selected based on safety and immunogenicity data from the RSV OA=ADJ-002 study.

The RSV OA=ADJ-004 is conducted to evaluate the safety, reactogenicity, immunogenicity profile and long-term persistence of the immune response up to 3 years following a single dose vaccination regimen of the RSVPreF3 OA investigational vaccine in adults ≥ 60 YOA. Considering the uncertainty on the persistence of the immune response, this study is also designed to evaluate the immunogenicity, safety and reactogenicity of additional vaccine doses according to different revaccination schedules (annual revaccination or revaccination at a later stage). The rationale for the study design is presented in Section 4.2.

Objectives and Endpoints: Refer to Table 6.

1.2. Schema

Refer to Figure 1 for a schematic presentation of the study design.

1.3. Schedule of Activities (Amended: 01 April 2022)

Study visits should preferably be done on site. ***As of Protocol Amendment 1 implementation***, if deemed necessary, ***local regulations allow, and quality of study procedures is maintained,*** study visits during the follow-up phases can be done at home or at the long-term care facility (LTCF), as per local regulation. **Home visits are not allowed for the cell-mediated immunity (CMI) subset** (due to sensitivity of CMI samples), except in special circumstances and with the approval of the GSK Central study team. For participants without blood sample collections (i.e., for participants only being followed up for safety), contact should be attempted only if site visit is not possible at Months 6, 18, 30 and 36. For contacts, multiple formats can be proposed by the study site. These contacts may be done via email, text message, or phone call for example. The most appropriate format should be agreed between site staff and the study participant. Messaging services and email 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, then 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.

Table 1 Schedule of activities: RSV_annual* (Amended: 01 April 2022)

Type (V = visit, C = contact)**	V	V	V/C	V	V	V/C[7]	V	V	V/C[7]	V/C	Notes
Timepoint	**D1**	**D31**	**M6**	**M12**	**M13**	**M18[7]**	**M24**	**M25**	**M30[7]**	**M36**	
Study participant informed consent[1]	●										See Section 10.1.3 for details
Check with participant if he/she will appoint a caregiver and distribute caregiver information letter, when applicable	O	O	O	O	O	O	O	O	O	O	See Section ***5.2.5*** for details
Distribution of participant card	O										See Section 8.3.5 for details
Check inclusion/exclusion criteria	●										See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Collect demographic data	●										See Section 8.2.1.1 for more information
Recording smoking status and smoking exposure history, including electronic smoking devices	●										See Section 8.2.1.4 for more information. Refer to the Glossary of terms for definitions of current and former smoker
Recording medical history	●										See Section 8.2.1.2 for more information
Recording history of any vaccine administration[2]	●										See Section 8.2.1.3 for more information
Vaccine											
Randomization	●										See Section 6.3 for more information
Check criteria for temporary delay for enrolment and vaccination	O			O			O				See Section 7.1.1 for more information
Check contraindications to vaccination				O			O				See Section 7.1.2 for more information
Recording pre-vaccination body temperature	●			●			●				See Section 8.2.1.6 for more information. The route for measuring temperature can be oral, axillary or tympanic. Fever is defined as temperature ≥38.0°C/100.4°F regardless the location of measurement
History-directed physical examination	O			O			O				See Section 8.2.1.5 for more information
Study group and intervention number allocation	O										See Sections 6.3.2 and 6.3.3 for more information
Intervention number allocation for subsequent doses				O			O				See Section 6.3.3 for more information
Recording of administered intervention number	●			●			●				The number of each administered study intervention must be recorded in the eCRF

Type (V = visit, C = contact)**	V	V	V/C	V	V	V/C[7]	V	V	V/C[7]	V/C	Notes
Timepoint	**D1**	**D31**	**M6**	**M12**	**M13**	**M18[7]**	**M24**	**M25**	**M30[7]**	**M36**	
Vaccine administration (including 30-minute post-vaccination observation)	●			●			●				See Section 6.1 for more information
Clinical specimens for laboratory assays											
Blood sampling for antibody determination, **from HI subset[3]** (~10 mL)	●	●	●	●	●	●	●[6]	●	●	●	See Section 8.1.1 for more information
Blood sampling for CMI, **from CMI subset[3]** (~25 mL)	●	●	●	●	●	●	●[6]	●	●	●	See Section 8.1.1 for more information
Safety assessments											
Recording any concomitant medication/vaccination	●	●	●	●	●	●	●	●	●	●	See Section 6.5 for more information
Recording any intercurrent medical conditions	●	●	●	●	●	●	●	●	●	●	See Section 9.3.1.1 for more information
Distribution of paper diary cards for solicited events and unsolicited AEs	O			O			O				See Section 8.2.1.7 for more information
Return of paper diary cards		O			O			O			
Recording of solicited events (Days 1–4 post-vaccination)	●	●		●	●		●	●			See Section 10.3.8 for more information
Recording of unsolicited AEs (Days 1–30 post-vaccination)	●	●		●	●		●	●			See Section 10.3.8 for more information
Recording of pIMDs and SAEs[4]	●	●	●	●	●	●	●	●	●		See Section 10.3.8 for more information
Recording of fatal SAEs, SAEs related to study vaccination and pIMDs related to study vaccination	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Recording AEs/SAEs leading to withdrawal from the study	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[5]	●	●	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Study Conclusion										●	See Section 4.4 for more information

Note: The double-line borders indicate analyses which will be performed on all data obtained up to these timepoints.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
V = visit, C = contact; D = day; M = month; AE = adverse event; CMI = cell-mediated immunity; pIMDs = potential immune-mediated diseases; SAE = serious adverse event; eCRF = electronic case report form.

*Refer to Table 7 for the description of study groups.

Study visits should preferably be done on site. ***As of Protocol Amendment 1 implementation,* if deemed necessary, ***local regulations allow, and quality of study procedures is maintained,*** study visits during the follow-up phases can be done at home or at the LTCF, as per local regulation. **Home visits are not allowed for the CMI subset** (due to sensitivity of CMI samples), except in special circumstances and with the approval of the GSK Central study team. For participants without blood sample collections (i.e., for participants only being followed up for safety), contact should be attempted only if site visit is not possible at Months 6, 18, 30 and 36. For contacts, multiple formats can be proposed by the study site. These contacts may be done via email, text message, or phone call for example. The most appropriate format should be agreed between site staff and the study participant. Messaging services and email 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, then 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.

[1] 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.

[2] Any vaccination administered up to 1 year before administration of the first dose of study vaccine should be recorded in the eCRF. Administration of *Shingrix* at any timepoint (even if longer than 1 year before the first study dose) should be recorded in the eCRF.

[3] Blood samples for humoral immunity (HI) and for CMI will be taken from the same ~345 participants. The remaining ~645 participants will have no blood draws. Refer to Section 6.3.4 for details.

[4] Recording of any SAE or any pIMD should only be done in the 6-month post-vaccination period, i.e., from Day 1 to Month 6, from Month 12 to Month 18, and from Month 24 to Month 30.

[5] 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 Dose 1) up to study end.

[6] Blood sampling should be performed prior to vaccination (this has been clarified for the vaccination visit occurring after implementation of Protocol Amendment 1).

[7] Visits/contacts at Month 18 and Month 30 must not be performed before the 6-month post-vaccination timepoint to allow collection of safety data up to at least 6 months after each vaccination for each participant (this has been clarified for the vaccination visit occurring after implementation of Protocol Amendment 1).

Table 2 Schedule of activities: RSV_flexible revaccination* (Amended: 01 April 2022)

Type *(V = visit)***	V	V	V	V	V	V	*V*	V[8]	V	Notes
Timepoint	**D1**	**D31**	**M6**	**M12**	**M18**	**M24**	***M25***	**M30[8]**	**M36**	
Study participant informed consent[1]	●									See Section 10.1.3 for details
Check with participant if he/she will appoint a caregiver and distribute caregiver information letter, when applicable	O	O	O	O	O	O	***O***	O	O	See Section ***5.2.5*** for details
Distribution of participant card	O									See Section 8.3.5 for details
Check inclusion/exclusion criteria	●									See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Collect demographic data	●									See Section 8.2.1.1 for more information
Recording smoking status and smoking exposure history, including electronic smoking devices	●									See Section 8.2.1.4 for more information. Refer to the Glossary of terms for definitions of current and former smoker
Recording medical history	●									See Section 8.2.1.2 for more information
Recording history of any vaccine administration [2]	●									See Section 8.2.1.3 for more information
Vaccine										
Randomization	●									See Section 6.3 for more information
Check criteria for temporary delay for enrolment and vaccination	O					***O***				See Section 7.1.1 for more information
Check contraindications to vaccination						***O***				***See Section 7.1.2 for more information***
Recording pre-vaccination body temperature	●					●				See Section 8.2.1.6 for more information. The route for measuring temperature can be oral, axillary or tympanic. Fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement
History-directed physical examination	O					***O***				See Section 8.2.1.5 for more information
Study group and intervention number allocation	O									See Sections 6.3.2 and 6.3.3 for more information
Intervention number allocation for subsequent dose						***O***				***See Section 6.3.3 for more information***
Recording of administered intervention number	●					●				The number of each administered study intervention must be recorded in the eCRF

Type *(V = visit)***	V	V	V	V	V	V	*V*	V[8]	V	Notes
Timepoint	**D1**	**D31**	**M6**	**M12**	**M18**	**M24**	***M25***	**M30[8]**	**M36**	
Vaccine administration (including 30-minute post-vaccination observation)	●					●				See Section 6.1 for more information
Clinical specimens for laboratory assays										
Blood sampling for antibody determination, **from all participants**[3] (~10 mL)	●	●	●	●	●	●[7]	●	●	●	See Section 8.1.1 for more information
Blood sampling for CMI, **from CMI subset**[4] (~25 mL)	●	●	●	●	●	●[7]	●	●	●	See Section 8.1.1 for more information
Safety assessments										
Recording any concomitant medication/vaccination	●	●	●	●	●	●	●	●	●	See Section 6.5 for more information
Recording any intercurrent medical conditions	●	●	●	●	●	●	●	●	●	See Section 9.3.1.1 for more information
Distribution of paper diary cards for solicited events and unsolicited AEs	O					***O***				See Section 8.2.1.7 for more information
Return of paper diary cards		O					***O***			
Recording of solicited events (Days 1–4 post-vaccination)	●	●				●	●			See Section 10.3.8 for more information
Recording of unsolicited AEs (Days 1–30 post-vaccination)	●	●				●	●			See Section 10.3.8 for more information
Recording of pIMDs and SAEs[5]	●	●	●			●	●	●		See Section 10.3.8 for more information
Recording of fatal SAEs, SAEs related to study vaccination and pIMDs related to study vaccination	●	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Recording AEs/SAEs leading to withdrawal from the study	●	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[6]	●	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Study Conclusion									●	See Section 4.4 for more information

Note: The double-line borders indicate analyses which will be performed on all data obtained up to these timepoints.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
V = visit, D = day; M = month; AE = adverse event; CMI = cell-mediated immunity; pIMDs = potential immune-mediated diseases; SAE = serious adverse event; eCRF = electronic case report form.

*Refer to Table 7 for the description of study groups.
Study visits should preferably be done on site. ***As of Protocol Amendment 1 implementation,* if deemed necessary, ***local regulations allow, and quality of study procedures is maintained,*** study visits during the follow-up phases for the humoral subset can be done at home or at the LTCF, as per local regulation. **Home visits are not allowed for the CMI subset** (due to sensitivity of CMI samples) except in special circumstances and with the approval of the GSK Central study team.
[1] 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.
[2] Any vaccination administered up to 1 year before administration of the first dose of study vaccine should be recorded in the eCRF. Administration of *Shingrix* at any timepoint (even if longer than 1 year before the first study dose) should be recorded in the eCRF.
[3] Blood samples for humoral immunity will be taken from all participants. Refer to Section 6.3.4 for details.
[4] CMI blood samples should only be taken from ~115 participants. Refer to Section 6.3.4 for details.
[5] Recording of any SAE or any pIMD should only be done ***in the 6-month post-vaccination period, i.e.,*** from Day 1 to Month 6 ***and from Month 24 to Month 30***.
[6] 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 Dose 1) up to study end.
[7] ***Blood sampling should be performed prior to vaccination (this has been clarified for the revaccination visit occurring after implementation of Protocol Amendment 1).***
[8] ***Visits at Month 30 must not be performed before the 6-month post-vaccination timepoint to allow collection of safety data up to at least 6 months after each vaccination for each participant (this has been clarified for the revaccination visit occurring after implementation of Protocol Amendment 1).***

Table 3 Schedule of activities: RSV_1dose* (Amended: 01 April 2022)

Type *(V = visit)***	V	V	V	V	V	V	V	V	Notes
Timepoint	**D1**	**D31**	**M6**	**M12**	**M18**	**M24**	**M30**	**M36**	
Study participant informed consent[1]	●								See Section 10.1.3 for details
Check with participant if he/she will appoint a caregiver and distribute caregiver information letter, when applicable	O	O	O	O	O	O	O	O	See Section ***5.2.5*** for details
Distribution of participant card	O								See Section 8.3.5 for details
Check inclusion/exclusion criteria	●								See Sections 5.1 and 5.2 for Inclusion and Exclusion criteria
Collect demographic data	●								See Section 8.2.1.1 for more information
Recording smoking status and smoking exposure history, including electronic smoking devices	●								See Section 8.2.1.4 for more information. Refer to the Glossary of terms for definitions of current and former smoker
Recording medical history	●								See Section 8.2.1.2 for more information
Recording history of any vaccine administration [2]	●								See Section 8.2.1.3 for more information
Vaccine									
Randomization	●								See Section 6.3 for more information
Check criteria for temporary delay for enrolment and vaccination	O								See Section 7.1.1 for more information
Recording pre-vaccination body temperature	●								See Section 8.2.1.6 for more information. The route for measuring temperature can be oral, axillary or tympanic. Fever is defined as temperature ≥38.0°C/100.4°F regardless the location of measurement
History-directed physical examination	O								See Section 8.2.1.5 for more information
Study group and intervention number allocation	O								See Sections 6.3.2 and 6.3.3 for more information
Recording of administered intervention number	●								The number of each administered study intervention must be recorded in the eCRF
Vaccine administration (including 30-minute post-vaccination observation)	●								See Section 6.1 for more information

Type *(V = visit)***	V	V	V	V	V	V	V	V	Notes
Timepoint	**D1**	**D31**	**M6**	**M12**	**M18**	**M24**	**M30**	**M36**	
Clinical specimens for laboratory assays									
Blood sampling for antibody determination, **from all participants**[3] (~10 mL)	●	●	●	●	●	●	●	●	See Section 8.1.1 for more information
Blood sampling for CMI, **from CMI subset**[4] (~25 mL)	●	●	●	●	●	●	●	●	See Section 8.1.1 for more information
Safety assessments									
Recording any concomitant medication/vaccination	●	●	●	●	●	●	●	●	See Section 6.5 for more information
Recording any intercurrent medical conditions	●	●	●	●	●	●	●	●	See Section 9.3.1.1 for more information
Distribution of paper diary cards for solicited events and unsolicited AEs	O								See Section 8.2.1.7 for more information
Return of paper diary cards		O							
Recording of solicited events (Days 1–4 post-vaccination)	●	●							See Section 10.3.8 for more information
Recording of unsolicited AEs (Days 1–30 post-vaccination)	●	●							See Section 10.3.8 for more information
Recording of pIMDs and SAEs[5]	●	●	●						See Section 10.3.8 for more information
Recording of fatal SAEs, SAEs related to study vaccination and pIMDs related to study vaccination	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Recording AEs/SAEs leading to withdrawal from the study	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Recording of SAEs related to study participation, or to a concurrent GSK medication/vaccine[6]	●	●	●	●	●	●	●	●	See Section 10.3.8 for more information
Study Conclusion								●	See Section 4.4 for more information

Note: The double-line borders indicate analyses which will be performed on all data obtained up to these timepoints.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
O is used to indicate a study procedure that does not require documentation in the individual eCRF.
V = visit, D = day; M = month; AE = adverse event; CMI = cell-mediated immunity; pIMDs = potential immune-mediated diseases; SAE = serious adverse event; eCRF = electronic case report form.
*Refer to Table 7 for the description of study groups.

Study visits should preferably be done on site. ***As of Protocol Amendment 1 implementation,* if deemed necessary, ***local regulations allow, and quality of study procedures is maintained,*** study visits during the follow-up phases for the humoral subset can be done at home or at the LTCF, as per local regulation. **Home visits are not allowed for the CMI subset** (due to sensitivity of CMI samples) except in special circumstances and with the approval of the GSK Central study team.

[1] 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.

[2] Any vaccination administered up to 1 year before administration of the first dose of study vaccine should be recorded in the eCRF. Administration of *Shingrix* at any timepoint (even if longer than 1 year before the first study dose) should be recorded in the eCRF.

[3] Blood samples for humoral immunity will be taken from all participants. Refer to Section 6.3.4 for details.

[4] CMI blood samples should only be taken from ~115 participants. Refer to Section 6.3.4 for details.

[5] Recording of any SAE or any pIMD should only be done from Day 1 to Month 6.

[6] 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 Dose 1) up to study end.

Table 4 Intervals between study visits for group RSV_annual

Interval	Length of interval	Allowed interval
Day 1 → Day 31	30 days	30-42 days
Day 1 → Month 6	180 days	180-210 [1] days
Day 1 → Month 12	365 days	350-380 days
Month 12 → Month 13	30 days	30-42 days
Month 12 → Month 18	180 days	180-210 [1] days
Day 1 → Month 24	730 days	715-745 days
Month 24 → Month 25	30 days	30-42 days
Month 24 → Month 30	180 days	180-210 [1] days
Day 1 → Month 36	1095 days	1080-1110 days

[1] Visit must not be performed before the 6-month post-vaccination timepoint to allow collection of safety data up to at least 6 months post-vaccination for each participant.
For the intervals, exclusion from the per-protocol set will be defined in the Statistical Analysis Plan (SAP).

Table 5 Intervals between study visits for groups RSV_flexible revaccination and RSV_1dose (Amended: 01 April 2022)

Interval	Length of interval	Allowed interval
Day 1 → Day 31	30 days	30-42 days
Day 1 → Month 6	180 days	180-210 [1] days
Day 1 → Month 12	365 days	350-380 days
Month 12 → Month 18	180 days	180-210 days
Day 1 → Month 24	730 days	715-745 days
Month 24 → Month 25 [2]	***30 days***	***30-42 days***
Month 24 → Month 30	180 days	180-210 [1] days
Day 1 → Month 36	1095 days	1080-1110 days

[1] Visit must not be performed before the 6-month post-vaccination timepoint to allow collection of safety data up to at least 6 months post-vaccination for each participant. ***Note that the 6-month safety follow-up following revaccination at Month 24 is only applicable for the RSV_flexible revaccination group***.
[2] Only applicable for the RSV_flexible revaccination group.
For the intervals, exclusion from the per-protocol set will be defined in the SAP.

2. INTRODUCTION

2.1. Study Rationale

GlaxoSmithKline Biologicals SA (GSK) is developing a new RSV PreFusion protein 3 Older Adult (RSVPreF3 OA) investigational vaccine against respiratory syncytial virus (RSV)-associated (subtypes A and B) disease in adults ≥ 60 years of age (YOA).

The RSVPreF3 OA investigational vaccine was administered intramuscularly for the first time to adults 60–80 YOA according to a 0, 2-month vaccination schedule in another clinical study (RSV OA=ADJ-002). The vaccine formulation and schedule to be used in the present study was selected based on safety and immunogenicity data from the RSV OA=ADJ-002 study.

The RSV OA=ADJ-004 is conducted to evaluate the safety, reactogenicity, immunogenicity profile and long-term persistence of the immune response up to 3 years following a single dose vaccination regimen of the RSVPreF3 OA investigational vaccine in adults ≥ 60 YOA. Considering the uncertainty on the persistence of the immune response, this study is also designed to evaluate the immunogenicity, safety and reactogenicity of additional vaccine doses according to different revaccination schedules (annual revaccination or revaccination at a later stage).

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

2.2. Background

RSV is a ribonucleic acid virus of which 2 antigenically distinct subgroups exist, RSV-A and RSV-B [Borchers, 2013]. It is a highly contagious pathogen that causes respiratory tract infections in people of all ages. In temperate climates throughout the world, it 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 from 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 infection in older adults 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).

There is currently no vaccine or other prophylactic treatment available against RSV in older adults. Currently available treatment for RSV in this age group is generally supportive in nature, as detailed in the IB. Please refer to the current IB for information regarding pre-clinical and clinical studies of the RSVPreF3 OA investigational vaccine.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

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

All participants will remain under observation at the clinical center for at least 30 minutes after vaccination.

Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This may typically include pain at administration 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 4.2.

2.3.2. Benefit Assessment

The participants may not directly benefit from vaccination with the RSVPreF3 OA investigational vaccine because vaccine efficacy has not been established yet. 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.

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

2.3.3. Overall Benefit/Risk Conclusion

The RSVPreF3 OA 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 6 Study objectives and endpoints

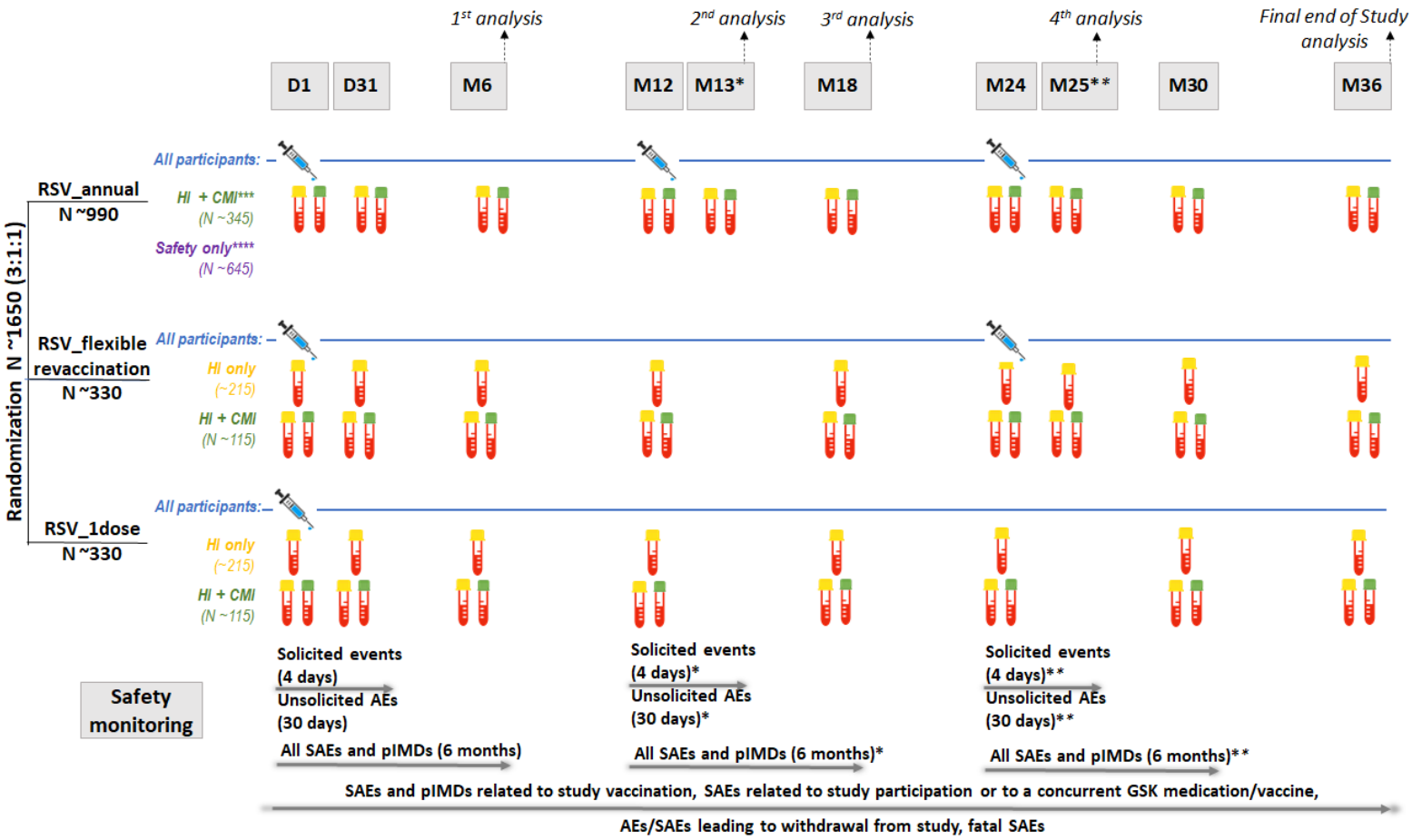
Objectives	Endpoints
Primary	
To evaluate the humoral immune response following a 1-dose primary schedule of RSVPreF3 OA investigational vaccine up to 12 months post-Dose 1.	Humoral immune response at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), and at 6 and 12 months post-Dose 1 (Months 6 and 12), in a subset of participants: – Neutralizing antibody titers against RSV-A – Neutralizing antibody titers against RSV-B.
Secondary	
To further evaluate the humoral immune response following a 1-dose primary schedule of RSVPreF3 OA investigational vaccine up to 12 months post-Dose 1.	Humoral immune response at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), and at 6 and 12 months post-Dose 1 (Months 6 and 12), in a subset of participants: – RSVPreF3-specific Immunoglobulin G (IgG) antibody concentrations.
To evaluate the humoral immune response following 1 dose of the RSVPreF3 OA investigational vaccine and following revaccination doses, up to study end.	Humoral immune response at Months 18, 24, 30 and 36 post-Dose 1, and at 1 month after each revaccination dose (Months 13 and 25), in a subset of participants: – Neutralizing antibody titers against RSV-A and RSV-B – RSVPreF3-specific IgG antibody concentrations.
To evaluate the CMI response following 1 dose of the RSVPreF3 OA investigational vaccine and following revaccination doses up to study end.	CMI response at pre-vaccination (Day 1), 30 days post-Dose 1 (Day 31), at Months 6, 12, 18, 24, 30 and 36 post-Dose 1, and at 1 month after each revaccination dose (Months 13 and 25), in a subset of participants: – Frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17.
To evaluate the safety and reactogenicity of each vaccination schedule of the RSVPreF3 OA investigational vaccine in all participants.	• Occurrence of each solicited administration site and systemic event during a 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) after each vaccination. • Occurrence of any unsolicited AE during a 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) after each vaccination. • Occurrence of all SAEs and pIMDs up to 6 months after each vaccination. • Occurrence of fatal SAEs, related SAEs and related pIMDs from first vaccination (Day 1) up to study end (Month 36).
Tertiary	
To further characterize immune responses to the RSVPreF3 OA investigational vaccine.	• Any further exploratory immunology in a subset of participants, such as, but not limited to: – Antibodies against specific protein F epitopes. – Potential new immunological markers for protection. – Frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing one or any combination of immune marker(s).

CMI = cell-mediated immunity, AE = adverse event, SAE = serious adverse event, pIMD = potential immune-mediated disease.

4. STUDY DESIGN

4.1. Overall Design

Figure 1 Study design overview (Amended: 01 April 2022)



N = number of participants; D = day; M = month; AE = adverse event; HI = humoral immunity; CMI = cell-mediated immunity; pIMD = potential immune-mediated disease; SAE = serious adverse event.

 = blood sample for humoral immune responses (only applicable for ~ 345 participants of the RSV_annual group; and for all participants of the RSV_flexible revaccination and RSV_1dose groups)

 = blood sample for CMI (only applicable for ~345 participants of the RSV_annual group, and for ~115 participants each from the RSV_flexible revaccination and RSV_1dose groups).

Note: For group RSV_annual: Revaccination Year 1 = Month 12; Revaccination Year 2 = Month 24***; for group RSV_flexible revaccination: Revaccination Year 2 = Month 24***.

*Visit and follow-up of solicited events, unsolicited AEs, SAEs and pIMDs are only applicable for RSV_annual group.

****Visit and follow-up of solicited events, unsolicited AEs, SAEs and pIMDs are only applicable for RSV_annual and RSV_flexible revaccination groups.***

***For the RSV_annual group, the same ~345 participants will be part of both the HI and CMI subsets. The remaining ~645 participants will have no blood draws and will only be followed up for safety and reactogenicity.

****For those participants in the RSV_annual group without blood sample collections, visits at Months 6, 18, 30 and 36 may be held through a contact. However, contact should be attempted only if site visit is not possible at Months 6, 18, 30 and 36.

- **Type of study**: Self-contained.
- **Experimental design**: Phase 3, randomized, open-label, multi-country study with 3 parallel groups (see Figure 1).
- **Duration of the study**: ~36 months for each participant.
- **Primary completion date**: Month 12.
- **Control**: None.
- **Blinding**: Open-label. 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 participant Diary card (paper Diary card).
- **Safety monitoring**: The study will be conducted with oversight by the project Safety Review Team (SRT). Please refer to Section 8.2.2 for the description of review of safety data by the SRT.
- **Study groups**: refer to Figure 1 and Table 7 for an overview of the study groups.

Table 7 Study groups, intervention and blinding foreseen in the study (Amended: 01 April 2022)

Study groups	Number of participants	Age	Intervention			Blinding
			Primary vaccination	Revaccination Year 1 (Month 12)	Revaccination Year 2 (Month 24)	Open
RSV_annual	~990	≥ 60 years	RSVPreF3 OA investigational vaccine	RSVPreF3 OA investigational vaccine	RSVPreF3 OA investigational vaccine	X
RSV_flexible revaccination	~330	≥ 60 years	RSVPreF3 OA investigational vaccine	***(none)***	***RSVPreF3 OA investigational vaccine***	X
RSV_1dose	~330	≥ 60 years	RSVPreF3 OA investigational vaccine	(none)	(none)	X

4.1.1. Overview of the recruitment plan

No screening visit is planned for this study. The study is planned to be conducted at sites in multiple countries. Recruitment plan will be defined by each participating site.

The recruitment plan may be adapted based on the actual number of participants enrolled in each country. In case a site/country would fall behind in participant recruitment, a redistribution of the enrolment target per site/country may be made. This would allow the other participating sites/countries to enroll additional participants in an effort to ensure full and timely enrolment 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.

4.2. Scientific rationale for study design (Amended: 01 April 2022)

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. The study RSV OA=ADJ-004 has been designed to consider the possibility of a decline in the immune response through the assessment of persistence over 3 years, while also evaluating revaccination as early as the second year to generate data, should an annual revaccination be required.

For that reason, the study is designed not only to evaluate the safety, the reactogenicity, the immunogenicity profile and the long-term persistence of the immune response up to 3 years following a single dose vaccination regimen of the RSVPreF3 OA investigational vaccine in adults ≥60 YOA, but also to evaluate the immunogenicity, safety and reactogenicity of an additional vaccine dose through different revaccination schedules (annual revaccination or revaccination at a later stage):

- RSV_annual group will receive the first dose (Dose 1) at Day 1, followed by revaccination doses at 12 months post-Dose 1 and at 24 months post-Dose 1.
- RSV_flexible revaccination group will receive the first dose (Dose 1) at Day 1. A revaccination dose will be given ***24 months post-Dose 1. Immunogenicity data from other studies using the same study intervention showed that following a two-dose vaccination schedule (0–2-month schedule), the immune response gradually declines over time but remains above baseline value up to 18 months post-Dose 2 and that a re-vaccination at 18 months post-Dose 2 (i.e., 20 months post-Dose 1) induced humoral and cellular immune responses.***
- RSV_1dose group will receive a single dose (Dose 1) at Day 1.

The study will include the target population of older adults ≥ 60 YOA living in the community (community dwelling [CD]) or living in a LTCF and presenting with medically stable condition.

The vaccine formulation was selected in a previous study, where the vaccine was administered intramuscularly according to a 0, 2-month vaccination schedule. Please refer to the IB for details.

4.3. Justification for dose

A 2-dose vaccination regimen with an interval of 2 months between doses was evaluated in the RSV OA=ADJ-002 study. This regimen was supported by available data from several clinical studies in GSK's Herpes Zoster and chronic obstructive pulmonary disease vaccine development programs [Chlibek, 2013; Leroux-Roels, 2016] conducted with an AS01-adjuvanted protein in older adults.

In the RSV OA=ADJ-002 study, the peak response for both IgG and neutralizing antibodies was observed at 1 month post-Dose 1. Comparisons of the mean responses 1 month post-Dose 2 versus 1 month post-Dose 1, in terms of neutralizing antibodies

against RSV-A and in terms of frequencies of CD4+ T cells expressing at least 2 markers did not show any added value of the second dose.

Based on safety, reactogenicity and immunogenicity data (humoral and cellular immune response) of the RSV OA=ADJ-002 study, the 120 µg RSVPreF3/AS01$_E$ formulation as a single dose was selected for the Phase 3 clinical development.

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 as described in the protocol.

End of Study (EoS): Last testing results released of samples collected at Month 36, i.e. Last Subject Last Visit (LSLV). In these cases, EoS must be achieved no later than 8 months after LSLV.

5. STUDY POPULATION

5.1. Inclusion criteria for enrolment

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 first vaccination, who live in the community (CD participants) or in a LTCF (LTCF participants).

  Please refer to the Glossary of terms for the definition of 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, attend regular phone calls/study site visits, 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, 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 will the site staff or caregiver evaluate the participant's health status while answering diaries or make decisions on behalf of the participant. Refer to the Glossary of terms 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. Patients 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 enrolment

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.
- 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 diary cards, attend regular phone calls/study site visits).
- 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.
- 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 Examination (MMSE), Mini-Cog or Montreal Cognitive Assessment (MoCA) to determine cognition levels of the participant.

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 dose of study vaccine, 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, split virion 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 dose of study vaccine 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 vaccine dose 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 the Glossary of terms 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 participation in the trial until the study end. This includes:
  - Planned move during the study period to another LTCF that will prohibit participation in the trial until study end.
  - Planned move from the community to a LTCF that will prohibit participation in the trial until study end.
- Participation of any study personnel or their immediate dependents, family, or household members.

5.2.5. Caregiver support

Study participants may decide to assign a caregiver to help them fulfilling the study procedures. Please refer to the Glossary of terms for the definition of a caregiver.

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

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

5.3. Lifestyle considerations

This section is not applicable.

5.4. Screen failures

This section is 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 (including vaccine reconstitution).

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 8.

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

Table 8 Study intervention administered (Amended: 01 April 2022)

Study intervention name:	RSVPreF3 OA interventional vaccine
Vaccine/Product name*:	RSVPreF3 (120 µg)
	$AS01_E$
Presentation:	RSVPreF3 (120 µg): Vial; Powder for suspension for injection
	$AS01_E$: Vial; Suspension for injection
Vaccine formulation:	RSVPreF3 (120 µg) $AS01_E$: QS-21* (25 µg), MPL (25 µg), liposomes; Water for injections q.s. 0.5 mL
Route of administration:	Intramuscular
Location:	Deltoid
Laterality:**	Non-dominant
Number of doses to be administered:	RSV_annual: 3 doses RSV_flexible revaccination: ***2*** dose***s*** RSV_1dose: 1 dose
Volume to be administered:	0.5 mL
Packaging, labeling and TM:	Refer to SPM for more details
Manufacturer:	GSK Biologicals

*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.
SPM: Study Procedures Manual

Refer to Section 4 for the schedule of vaccine administration.

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.

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 sequentially to the participants who have consented to take part in the study, according to the range of participant identification numbers allocated to each study center.

6.3.2. Randomization to study intervention

Approximately 1650 eligible participants will be randomly assigned (3:1:1) to the 3 study groups (RSV_annual, RSV_flexible revaccination, or RSV_1dose) at the first study visit (Day 1).

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).

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

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. The SBIR's randomization algorithm will use minimization procedure accounting for age, sex, center, setting (CD and LTCF participants) and CMI subset. Minimization factors will have equal weight in the minimization algorithm.

Participants will be enrolled in 3 age categories reflecting an approximate age distribution in the general population, with 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.

Upon providing the participant identification number, the age category, the sex, the setting and the subset, the randomization system will determine the study group and will provide the intervention number to be used for the first vaccination. The intervention number(s) to be used for subsequent dose administration(s) will also be provided by SBIR. The site will record the study intervention assignment on the applicable case report form, if required.

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

Allocation of participants to assay subsets will be performed using SBIR. The subsets are detailed below.

	RSV_annual	RSV_flexible revaccination	RSV_1dose
HI subset	~345*	All participants (~330)	All participants (~330)
CMI subset	~345*	~115	~115

*For the RSV_annual group, the same ~345 participants will be part of both the HI and CMI subsets. The remaining ~645 participants will have no blood draws and will only be followed up for safety and reactogenicity.

- **HI subset:** ~345 participants from the RSV_annual group, and all participants from the RSV_flexible revaccination and RSV_1dose groups. These participants will have blood samples collected for testing of humoral immunity at each visit applicable for their study group.

- **CMI subset**: ~345 participants from the RSV_annual group, and ~115 participants each from the RSV_flexible revaccination and RSV_1dose groups. These participants will have additional blood samples collected for CMI testing at each visit applicable for their study group.

6.3.5. Blinding and unblinding

This is an open-label study.

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. More specifically, for each sample, a different randomly selected code will be used at each timepoint. This sample coding will prevent the testing laboratory personnel from linking the consecutive visits/timepoints to a specific participant.

6.3.5.1. Emergency unblinding

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

The emergency process enables the investigator to have unrestricted, immediate and direct access to the participant's individual study intervention via an automated Internet-based system, e.g., SBIR.

The investigator may contact a GSK Helpdesk (refer to the Table 9) if he/she needs help to perform the unblinding process (i.e., if the investigator is unable to access the SBIR).

A physician other than the investigator (e.g. an emergency room physician) or participant/care giver/family member may also request emergency access to the participant's individual study intervention either via the investigator (preferred option) or via the GSK Helpdesk (back-up option). The subject/participant card provides contact information for the investigator, his/her back-up and GSK Helpdesk.

Table 9 Contact information for emergency unblinding

GSK Helpdesk Available 24/24 hours and 7/7 days
The Helpdesk is available by phone, fax and email Toll-free numbers: Germany and Taiwan: 00 800 4344 1111 Finland: 999 800 4344 1111 Japan: 00 531 320 109 United States: 1 844 446 3133 Fax : +32 2 401 25 75 Email: rix.ugrdehelpdesk@gsk.com

6.4. Study intervention compliance (Amended: 01 April 2022)

Study intervention ***will be administered to the participants*** directly from the investigator or designee, under medical supervision. The date of each dose administered will be recorded in the source documents and in the eCRF.

6.5. Concomitant therapy (Amended: 01 April 2022)

At each study contact, the investigator or designee should question the participant about any medications/products taken and vaccinations received by the participant.

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

- All concomitant medication including vaccines/products, except vitamins and dietary supplements, administered during the period of 30 days post each vaccine dose (Day 1 to Day 31 for all groups, Month 12 to Month 12 + 30 days ***for the RSV_annual group*** and Month 24 to Month 24 + 30 days for the RSV_annual ***and RSV_flexible revaccination*** group***s***).
- 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 10.3.8.2. These must also be recorded on the Expedited Adverse Event report.
- Any prophylactic medication (e.g., analgesics, antipyretics) administered on the day of study vaccination (Day 1 for all groups; Month 12 ***for the RSV_annual group*** and Month 24 for the RSV_annual ***and RSV_flexible revaccination*** group***s***) and in the absence of ANY symptom and in anticipation of a reaction to the vaccination.
- 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).
- *Shingrix* or any AS01-containing vaccine throughout the entire study.

Refer to Table 10 for an overview of the timing for recording of concomitant medication during the study.

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

Table 10 Timing of collection of concomitant medication (Amended: 01 April 2022)

	Day 1	Day 30		Month 12	Month 12 + 30 days		Month 24	Month 24 + 30 days	Study conclusion
All concomitant medication including vaccines/products, except vitamins and dietary supplements				*RSV_annual only*	*RSV_annual only*		*RSV_annual* ***and RSV_flexible revaccination*** *only*	*RSV_annual* ***and RSV_flexible revaccination*** *only*	
All concomitant medication including vaccines/products which may explain/cause/be used to treat an SAE/pIMD									
Any prophylactic medication				*RSV_annual only*			*RSV_annual* ***and RSV_flexible revaccination*** *only*		
All concomitant medications including vaccines/products leading to discontinuation of the study intervention or an elimination from the analysis									
Shingrix or any AS01-containing vaccine									
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									

Note: The collection period for the concomitant medications to be recorded in eCRF for all groups is indicated in grey.

6.6. Dose modification

This section is not applicable.

6.7. Intervention after the end of the study

During the study conclusion visit, the investigator might ask each participant if they are interested in participating in an additional extension study on longer term follow-up. If a participant is not interested in joining an additional extension study, 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

'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 or revaccination, 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:

- AE 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 the Glossary of terms for the definition of intervention.

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

Vaccination may be postponed within the permitted time interval until transient circumstances cited below are resolved:

- Acute disease and/or fever at the time of vaccination. Refer to the Schedule of Activities for fever definition and preferred location for measuring temperature in this study.
- Participants with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be vaccinated at the discretion of the investigator.

- Participants with symptoms suggestive of active Coronavirus Disease 2019 (COVID-19) infection (e.g., fever, cough, etc.). The return of the participant to the site will follow the specific guidance from local public health and other competent authorities (e.g., free of symptoms, COVID-19 negative testing, etc.).
- Participants with known COVID-19 positive contacts within the past 14 days should be delayed for at least 14 days since the exposure, and if the participant remains symptom free.

Refer to Table 4 for the permitted time intervals.

7.1.2. Contraindications to subsequent vaccine administration (Amended: 01 April 2022)

Participants in the RSV_annual ***and RSV_flexible revaccination*** group***s*** must be evaluated to confirm they are eligible 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 and 5.2.2 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 study vaccine or non-study 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.
- Anaphylaxis following the administration of vaccine.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- 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 for the definition of pIMDs.

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 (please 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

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.3).

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.

The investigator is not allowed to do testing on samples outside of what has been agreed upon by the IEC/IRB.

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.

Procedures conducted as part of routine clinical management (e.g. hematologic profiles) and obtained before the participant signed the Informed Consent Form (ICF) may be used for establishing a clinical baseline, provided the procedure met protocol-specified criteria and was performed within the timeframe defined in the Schedule of Activities (Section 1.3).

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 means and/or conventional mail.
- 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.

  *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 site 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 site staff at a site other than the designated study site. Refer to European Medicines Agency (EMA) Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version ***5***, ***10 February 2022***) ***and to the Food and Drug Administration Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency (updated 30 August 2021)*** for more details. **(Amended: 01 April 2022)**

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

Impact on the per-protocol set for immunogenicity will be determined on a case by case basis.

8.1. Efficacy and/or immunogenicity assessments

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.

8.1.1. Biological samples (Amended: 01 April 2022)

Table 11 Biological samples (Amended: 01 April 2022)

Sample type	Quantity	Unit	Timepoint	Subset name*
Blood for humoral immune response	~10	mL	Day 1 Day 31 Month 6 Month 12 Month 13** Month 18 Month 24 Month 25*** Month 30 Month 36	HI subset
Blood for CMI	~25	mL	Day 1 Day 31 Month 6 Month 12 Month 13** Month 18 Month 24 Month 25*** Month 30 Month 36	CMI subset

CMI: cell-mediated immunity
*Refer to Section 6.3.4 for subset description.
**Only applicable for the RSV_annual group
***Only applicable for the RSV_annual and RSV_flexible revaccination groups*

The approximate overall volume that will be collected per participant during the entire 3-year study period is as follows:

Group	Participant subset	Number of participants	Total volume of blood	Notes
RSV_annual group	HI subset	~345	10x10 mL = ~100 mL	The same ~345 participants will be part of both the HI and CMI subsets. The participants from this group who are not part of the subset will not have blood draws
	CMI subset	~345	10x25 mL = ~250 mL	
RSV_flexible revaccination group	All participants	~330	***9***x10 mL = ~***90*** mL	
	CMI subset	~115	***9***x25 mL = ~***225*** mL	
RSV_1dose	All participants	~330	8x10 mL = ~80 mL	
	CMI subset	~115	8x25 mL = ~200 mL	

Refer to the Table 11 and Schedule of Activities for details of volumes collected for different assessments.

8.1.2. Laboratory assays

Table 12 Laboratory assays

Assay type	System	Component	Challenge	Method	Laboratory*
Cell-mediated Immunity	PBMC	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	Peptide pool covering RSVPreF3	ICS	GSK**
Humoral Immunity (antibody determination)	Serum	Respiratory Syncytial Virus A antibody		Neutralization	GSK**
	Serum	Respiratory Syncytial Virus B antibody		Neutralization	GSK**
	Serum	RSVPreF3-specific IgG antibody		ELISA	GSK**

PBMC = peripheral blood mononuclear cells; ICS = intracellular cytokine staining; ELISA = enzyme-linked immunosorbent assay
*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 Contract Research Organization

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.

8.1.3. Immunological read-outs

Table 13 Immunological read-outs (Amended: 01 April 2022)

Blood sampling timepoint		Subset name	No. participants	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Humoral immunity (on serum samples)					
Day 1	Pre-Vacc	Humoral immunity subset	~1005	RSV-A neutralizing antibody	1
				RSV-B neutralizing antibody	2
				RSVPreF3-specific IgG antibody	3
Day 31	Day 31	Humoral immunity subset	~1005	RSV-A neutralizing antibody	1
				RSV-B neutralizing antibody	2
				RSVPreF3-specific IgG antibody	3
Month 6	Month 6	Humoral immunity subset	~1005	RSV-A neutralizing antibody	1
				RSV-B neutralizing antibody	2
				RSVPreF3-specific IgG antibody	3
Month 12	Month 12	Humoral immunity subset	~1005	RSV-A neutralizing antibody	1
				RSV-B neutralizing antibody	2
				RSVPreF3-specific IgG antibody	3
Month 13[1]	Month 13[1]	Humoral immunity subset	~345	RSV-A neutralizing antibody	1
				RSV-B neutralizing antibody	2
				RSVPreF3-specific IgG antibody	3
Month 18	Month 18	Humoral immunity subset	~1005	RSV-A neutralizing antibody	1
				RSV-B neutralizing antibody	2
				RSVPreF3-specific IgG antibody	3
Month 24	Month 24	Humoral immunity subset	~1005	RSV-A neutralizing antibody	1
				RSV-B neutralizing antibody	2
				RSVPreF3-specific IgG antibody	3
Month 25 [2]	Month 25 [2]	Humoral immunity subset	***~675***	RSV-A neutralizing antibody	1
				RSV-B neutralizing antibody	2
				RSVPreF3-specific IgG antibody	3
Month 30	Month 30	Humoral immunity subset	~1005	RSV-A neutralizing antibody	1
				RSV-B neutralizing antibody	2
				RSVPreF3-specific IgG antibody	3
Month 36	Month 36	Humoral immunity subset	~1005	RSV-A neutralizing antibody	1
				RSV-B neutralizing antibody	2
				RSVPreF3-specific IgG antibody	3
Cell-mediated immunity (on PBMC samples)					
Day 1	Pre-Vacc	CMI subset	~575	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	-
Day 31	Day 31	CMI subset	~575	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	-
Month 6	Month 6	CMI subset	~575	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	-
Month 12	Month 12	CMI subset	~575	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	-
Month 13[1]	Month 13[1]	CMI subset	~345	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	-

Blood sampling timepoint		Subset name	No. participants	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Month 18	Month 18	CMI subset	~575	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	-
Month 24	Month 24	CMI subset	~575	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	-
Month 25 [2]	Month 25 [2]	CMI subset	***~460***	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	-
Month 30	Month 30	CMI subset	~575	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	-
Month 36	Month 36	CMI subset	~575	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	-

PBMC = peripheral blood mononuclear cells; CMI = cell-mediated immunity.
[1] Only applicable for the RSV_annual group.
[2] Only applicable for the RSV_annual and RSV_flexible revaccination groups.

8.1.4. Immunological correlates of protection

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

8.2. 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 intervention or study.

8.2.1. Pre-vaccination procedures

8.2.1.1. Collection of demographic data

Record demographic data such as year of birth, sex, race, ethnicity and type of residence (CD/LTCF) in the participant's eCRF.

8.2.1.2. Medical history

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.

8.2.1.3. Vaccination history

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 administration of the first dose of study vaccine should be recorded in the eCRF. For history of influenza vaccination, information about the vaccine formulation (e.g., adjuvanted or non-adjuvanted, or high-dose) should be recorded if known.

Administration of *Shingrix* at any timepoint (even if longer than 1 year before the first study dose) should be recorded in the eCRF. The date of vaccination should be collected and recorded in the eCRF.

8.2.1.4. Smoking status and smoking exposure history

Obtain the participant's smoking status and smoking history by interviewing the participant, differentiating tobacco use (cigarettes, cigars, cigarillos, pipes …) and use of electronic smoking devices (e-cigarettes). Refer to the Glossary of terms for 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.

8.2.1.5. History-directed physical examination

Perform a history-directed physical examination. If the investigator determines that the participant's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the allowed interval for this visit (refer to Table 4 for the allowed intervals).

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

8.2.1.6. Pre-vaccination body temperature

The axillary, oral or tympanic body temperature of each participant needs to be measured prior to any study vaccine administration and recorded in the eCRF. If the participant has fever (fever is defined as temperature ≥ 38.0°C/100.4°F regardless the location of measurement) on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 4).

8.2.1.7. Distribution of paper diary cards

Paper diary cards will be distributed at each vaccination visit for the participants to record any solicited event in the 4-day period following each vaccination, and any unsolicited AE they may have experienced as well as any medication taken in the 30-day period following each vaccination. Refer to Section 10.3.8 for guidelines.

8.2.2. Safety monitoring

The project's SRT will perform the safety monitoring in this study.

As the RSVPreF3 OA investigational vaccine will be administered for the first time in adults older than 80 years, an initial safety assessment will be performed by the SRT on the 30 days post-Dose1 data of the first 50 participants aged 80 years and above who received one dose of study intervention.

8.3. AEs, SAEs and other events of interest

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

An overview of the protocol-required reporting periods for AEs, SAEs and pIMDs is given in Table 14.

Table 14 Timeframes for collecting and reporting of safety information

	Pre-Dose 1*	Dose 1**			6 months after vaccination (M6)	Revaccination Year 1 (Month 12)**				Revaccination Year 2 (Month 24)**				Study Conclusion (M36)
	D1	D1	D4	D30		M12	M12 + D4	M13	M18	M24	M24 + D4	M25	M30	
Solicited administration site and systemic events														
Unsolicited AEs														
All SAEs/pIMDs														
SAEs/pIMDs related to study vaccination														
SAEs related to study participation or concurrent GSK medication/vaccine														
Fatal SAEs														
AEs/SAEs leading to withdrawal from the study														
Intercurrent medical conditions														

D = day; M = month; Vacc = vaccination; AE = adverse event; SAE = serious adverse event; pIMD = potential immune-mediated disease
*i.e. consent obtained on Day 1 (prior to vaccination).
**Solicited administration site and systemic events up to 4 days, unsolicited AEs up to 30 days and SAEs/pIMDs up to 6 months will be collected only after vaccination.
Note: COVID-19 cases will be collected during the same timeframes as those used for collecting and reporting the other safety information (unsolicited AEs/SAEs, etc.).

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 14. 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 the Table 16.

8.3.2. Method of detecting AEs, SAEs and other events

Methods of detecting and recording AEs/SAEs/pIMDs are detailed in the Section 10.3.8. The assessment of AEs/SAEs intensity, causality and outcome are provided in the Section 10.3.9.

Open-ended and non-leading verbal questioning of the participant is the preferred method of acquiring information related to an AE/SAE/pIMD.

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/pIMD, he/she must report it to GSK using the required documentation, and within the timeframes, mentioned in the Table 15. 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/pIMDs, the investigator will always provide an assessment of causality at the time of the initial report, as defined in the 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/pIMDs.

Table 15 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
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 an 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.

8.3.3.1. Contact information for reporting of SAEs and pIMDs

Table 16 Contact information for reporting of SAEs and pIMDs (Amended: 01 April 2022)

Study contact for questions regarding SAEs and pIMDs
Refer to the local study contact information document
Back-up study contact for reporting SAEs and pIMDs
Available 24/24 hours and 7/7 days:
GSK Clinical Safety & Pharmacovigilance
Outside US sites:
Fax: +32 2 656 51 16 or +32 2 656 80 09
Email address: ***ogm28723@gsk.com***
US sites only:
Fax: 1-610-787-7053

8.3.4. 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).

8.3.5. 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/their possession at all times throughout the study. In an emergency, this card serves to inform the responsible attending physician/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator.

8.4. Treatment of overdose

This section is not applicable.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in the current study. For participants who consent to participate in genetic research in future studies, the obtained blood samples may be used at a later stage in future studies for research such as B cell receptor repertoire analysis (B cell receptor sequencing).

8.8. Biomarkers

Biomarkers for pharmacogenetics are not evaluated in this study.

8.9. Health outcomes

Economic outcome measures such as health care resource utilization data associated with healthcare encounters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

Not applicable as this study is descriptive.

9.2. Sample size determination (Amended: 01 April 2022)

This study is planned to enroll ~1650 participants randomized according to 3:1:1 ratio to 1 of the 3 study groups: RSV_annual, RSV_flexible revaccination, and RSV_1dose respectively.

The proposed sample size is based on the following considerations:

- Ensure a sufficient number of participants to evaluate with adequate precision the immunogenicity after a single dose regimen up to 12 months post-vaccination (based on the 3 pooled *RSV_annual*, *RSV_flexible revaccination* and *RSV_1dose* groups) but also the immunogenicity after revaccination (based on RSV_annual ***and RSV_flexible revaccination*** group***s***).

- Ensure adequate description of the antibody kinetics after a single dose keeping the flexibility to give a revaccination to a part of the participants.
- Ensure an adequate sample size for evaluation of reactogenicity and safety profile following revaccination.

Approximately 345 participants will be enrolled in the humoral subset in the RSV_annual ***group*** and approximately 330 participants per group in the RSV_flexible revaccination and RSV_1dose ***groups***. Approximately 345, 115 and 115 participants will be enrolled in the CMI subset in the RSV_annual, RSV_flexible revaccination, and RSV_1dose groups, respectively. A total of 990 ***and 330*** participants will be enrolled in the RSV_annual ***and RSV_flexible revaccination*** group***s, respectively,*** for evaluation of reactogenicity and safety profile following revaccination. A 20% rate of non-evaluable participants every year will be considered.

Withdrawals will not be replaced.

9.2.1. Evaluation of humoral immune response up to Month 12 (primary objective and first secondary objective)

At Month 12, the effect of a 1-dose primary schedule will be evaluated in terms of RSV-A/B neutralizing antibody titers and RSVPreF3-specific IgG concentrations. Approximately 804 participants in the (RSV_annual, RSV_flexible revaccination, and RSV_1dose) pooled group receiving a single dose of RSVPreF3 OA investigational vaccine will be evaluable for the humoral immune response at Month 12.

Table 17 shows the precision that can be obtained based on different values of standard deviations in terms of RSV-A/B neutralizing antibody titers, and RSVPreF3-specific IgG antibody concentrations.

Table 17 Precision and 95% confidence interval on the geometric mean antibody titers and concentrations at Month 12 based on different values of standard deviations for 804 evaluable participants in the (RSV_annual, RSV_flexible revaccination and RSV_1dose) pooled groups

Number of enrolled participants in the humoral subset (3 groups pooled*)	Number of evaluable participants in the humoral subset up to Month 12 (3 groups pooled*)	Standard deviation in log10	Width ½ 95% CI in log10	Ratio upper limit 95% CI/GM	Ratio upper limit/ lower limit 95% CI
1005	804	0.30	0.021	1.05	1.10
1005	804	0.35	0.024	1.06	1.12
1005	804	0.40	0.028	1.07	1.14
1005	804	0.45	0.031	1.07	1.15
1005	804	0.50	0.035	1.08	1.17

*At the time of the analysis at Month 12 (RSV_annual, RSV_flexible revaccination and RSV_1dose groups) will be pooled.
Precision estimated using PASS 12.0.10: Confidence interval of a mean, alpha = 5%.
CI = Confidence Interval, LL = Lower Limit, UL = Upper Limit
GM = Geometric Mean

9.2.2. Evaluation of the cellular immune response up to Month 12 (secondary objective)

At Month 12, the effect of a 1-dose primary schedule dose will be evaluated in terms of RSVPreF3-specific CD4+ T cells frequency. Approximately, 460 participants in the pooled groups (RSV_annual, RSV_flexible revaccination, and RSV_1dose groups) receiving a single dose of RSVPreF3 OA investigational vaccine will be evaluable for the CMI response at study Month 12.

Table 18 shows the precision that can be obtained based on different values of standard deviations in terms of the frequency of RSVPreF3-specific CD4+ T cells.

Table 18 Precision and 95% confidence interval on the geometric mean of the frequency of RSVPreF3-Specific CD4+ T cells at Month 12 based on different values of standard deviations for 460 evaluable participants in the (RSV_annual, RSV_flexible revaccination and RSV_1dose) pooled groups

Number of enrolled participants in the CMI subset (3 groups pooled*)	Number of evaluable participants in the CMI subset up to Month 12 (pooled 3 groups pooled*)	Standard deviation in log10	Width ½ 95% CI in log10	Ratio upper limit 95% CI/GM	Ratio upper limit/ lower limit 95% CI
575	460	0.30	0.027	1.06	1.13
575	460	0.35	0.032	1.08	1.16
575	460	0.40	0.037	1.09	1.19
575	460	0.45	0.041	1.10	1.21
575	460	0.50	0.046	1.11	1.24

*At the time of the analysis at Month 12 (RSV_annual, RSV_flexible revaccination and RSV_1dose groups) will be pooled.
Precision estimated using PASS 12.0.10: Confidence interval of a mean, alpha = 5%.
CI = Confidence Interval, LL=Lower Limit, UL=Upper Limit
GM = Geometric Mean

9.2.3. Evaluation of humoral and cellular immune response at Month 13 (secondary objective)

At Month 13 (one month post-revaccination at Month 12), the effect of a revaccination dose will be evaluated. As such ~ 276 participants in the RSV_annual group receiving a revaccination dose of RSVPreF3 OA investigational vaccine will be evaluable for the humoral and cellular immune response at study Month 13.

Table 19 shows the precision that can be obtained based on different values of standard deviations in terms of RSV-A/B neutralizing antibody titers, RSVPreF3-specific IgG antibody concentrations and the frequency of RSVPreF3-specific CD4+ T cells.

Table 19 Precision and 95% confidence interval on the geometric mean antibody titers/concentrations and of the frequency of RSVPreF3-Specific CD4+ T cells at Month 13 based on different values of standard deviations for 276 evaluable participants in the RSV_annual group

Number of enrolled participants in the humoral and CMI subsets in the RSV_annual	Number of evaluable participants in the humoral and CMI subsets at Month 13	Standard deviation in log10	Width ½ 95% CI in log10	Ratio upper limit 95% CI/ GM	Ratio upper limit/ lower limit 95% CI
345	276	0.30	0.036	1.09	1.18
345	276	0.35	0.041	1.10	1.21
345	276	0.40	0.047	1.11	1.24
345	276	0.45	0.053	1.13	1.28
345	276	0.50	0.059	1.15	1.31

Precision estimated using PASS 12.0.10: Confidence interval of a mean, alpha = 5%.
CI = Confidence Interval, LL = Lower Limit, UL = Upper Limit
GM = Geometric Mean

9.2.4. Evaluation of humoral and cellular immune response at Month 25 *in the RSV_annual and RSV_flexible revaccination groups* (secondary objective) (Amended: 01 April 2022)

At Month 25 (one month post-revaccination at Month 24), the effect of revaccination dose will be evaluated.

As such ~220 participants in the RSV_annual group receiving a revaccination dose of RSVPreF3 OA investigational vaccine will be evaluable for the humoral and cellular immune response at study Month 25.

Table 20 shows the precision that can be obtained based on different values of standard deviations in terms of RSV-A/B neutralizing antibody titers, RSVPreF3-specific IgG antibody concentrations and the frequency of RSVPreF3-specific CD4+ T cells.

Approximately 211 participants in the RSV_flexible revaccination group receiving a revaccination dose of RSVPreF3 OA investigational vaccine will be evaluable for the humoral immune response at study Month 25. Table 21 shows the precision that can be obtained based on different values of standard deviations in terms of RSV-A/B neutralizing antibody titers, RSVPreF3-specific IgG antibody concentrations.

Approximately 74 participants in the RSV_flexible revaccination group receiving a revaccination dose of RSVPreF3 OA investigational vaccine will be evaluable for the cellular immune response at study Month 25. Table 22 shows the precision that can be obtained based on different values of standard deviations in terms of the frequency of RSVPreF3-specific CD4+ T cells.

Table 20 Precision and 95% confidence interval on the geometric mean antibody titers/concentrations and of the frequency of RSVPreF3-specific CD4+ T cells at Month 25 based on different values of standard deviations for 220 evaluable participants in the RSV_annual group

Number of enrolled participants in the humoral and CMI subsets in the RSV_annual	Number of evaluable participants in the humoral and CMI subsets at Month 25	Standard deviation in log10	Width ½ 95% CI in log10	Ratio upper limit 95% CI/GM	Ratio upper limit/ lower limit 95% CI
276	220	0.30	0.040	1.10	1.20
276	220	0.35	0.047	1.11	1.24
276	220	0.40	0.053	1.13	1.28
276	220	0.45	0.060	1.15	1.32
276	220	0.50	0.066	1.16	1.36

Precision estimated using PASS 12.0.10: Confidence interval of a mean, alpha = 5%.
CI = Confidence Interval, LL = Lower Limit, UL = Upper Limit
GM = Geometric Mean

Table 21 Precision and 95% confidence interval on the geometric mean antibody titers/concentrations at Month 25 based on different values of standard deviations for 211 evaluable participants in the RSV_flexible revaccination group

Number of enrolled participants in the humoral subset in the RSV_flexible revaccination	*Number of evaluable participants in the humoral subset at Month 13*	*Number of evaluable participants in the humoral subset at Month 25*	*Standard deviation in log10*	*Width ½ 95% CI in log10*	*Ratio UL 95% CI / GM*	*Ratio UL / LL 95% CI*
330	*264*	*211*	*0.30*	*0.041*	*1.10*	*1.21*
330	*264*	*211*	*0.35*	*0.047*	*1.11*	*1.24*
330	*264*	*211*	*0.40*	*0.054*	*1.13*	*1.28*
330	*264*	*211*	*0.45*	*0.061*	*1.15*	*1.32*
330	*264*	*211*	*0.50*	*0.068*	*1.17*	*1.37*

Precision estimated using PASS 2019: Confidence interval for one mean, alpha = 5%.
CI = Confidence Interval, LL = Lower Limit, UL = Upper Limit; GM = Geometric Mean

Table 22 Precision and 95% confidence interval of the frequency of RSVPreF3-specific CD4+ T cells at Month 25 based on different values of standard deviations for 74 evaluable participants in the RSV_flexible revaccination group

Number of enrolled participants in the CMI subset in the RSV_flexible revaccination group	*Number of evaluable participants in the CMI subset at Month 13*	*Number of evaluable participants in the CMI subset at Month 25*	*Standard deviation in log10*	*Width ½ 95% CI in log10*	*Ratio UL 95% CI / GM*	*Ratio UL / LL 95% CI*
115	*92*	*74*	*0.30*	*0.070*	*1.17*	*1.38*
115	*92*	*74*	*0.35*	*0.081*	*1.21*	*1.45*
115	*92*	*74*	*0.40*	*0.093*	*1.24*	*1.53*
115	*92*	*74*	*0.45*	*0.105*	*1.27*	*1.62*
115	*92*	*74*	*0.50*	*0.116*	*1.31*	*1.71*

Precision estimated using PASS 2019: Confidence interval of a mean, alpha = 5%.
CI = Confidence Interval, LL = Lower Limit, UL = Upper Limit; GM = Geometric Mean

9.2.5. Evaluation of reactogenicity and safety profile following revaccination in the RSV_annual *and RSV_flexible revaccination* groups (Amended: 01 April 2022)

As indicated in Table 23, the proposed sample size*s* of 990 participants in the RSV_annual group receiving revaccination on an annual basis ***and 330 participants in the RSV_flexible revaccination group receiving revaccination at Year 2 (Month 24)***, give 99.3% ***and 80.9%*** probabilit***ies, respectively,*** of observing at least one AE if a true incidence rate equals 0.5%. This probability increases to 100% for true incidence rates ≥0.8% ***for the RSV_annual group***. Although lower, the probability remains above 62% to detect at least one AE that would occur at a frequency of 0.1% (1/1000) ***and 0.3% (3/1000) in the RSV_annual and RSV_flexible revaccination groups, respectively***.

Table 23 Probability (%) to observe at least one AE depending on the AE true incidence rate with 990 *and 330* participants *in the RSV_annual and RSV_flexible revaccination groups, respectively*

Incidence rate	Probability to observe at least one AE *in the RSV_annual*	*Probability to observe at least one AE in the RSV_flexible revaccination*
0.01%	9.4%	***3.2%***
0.05%	39.1%	***15.2%***
0.10%	62.9%	***28.1%***
0.15%	77.4%	***39.1%***
0.20%	86.2%	***48.3%***
0.25%	91.6%	***56.2%***
0.30%	94.9%	***62.9%***
0.35%	96.9%	***68.6%***
0.40%	98.1%	***73.4%***
0.50%	99.3%	***80.9%***
0.60%	99.7%	***86.3%***
0.70%	99.9%	***90.2%***
0.80%	100.0%	***92.9%***
0.90%	100.0%	***94.9%***
1.00%	100.0%	***96.4%***

9.3. Populations for analyses (Amended: 01 April 2022)

Table 24 Populations for analyses (Amended: 01 April 2022)

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 1 dose of the study intervention. The allocation in a group is done in function of the administered intervention.
Per-Protocol set (PPS)	All participants who received at least 1 dose of the study intervention to which they are randomized and have post-vaccination ***immunogenicity*** data, minus participants with protocol deviations that lead to exclusion.

The primary analysis for immunogenicity will be performed on the PPS. If in any study group ***and for at least one visit,*** the percentage of vaccinated participants with serological results excluded from the PPS for immunogenicity is at least ***5***%, a second analysis will be performed on the ES. The immunogenicity analysis will be performed, overall, by sex,

by age category (age at Dose 1: ≥ 65 YOA, ≥ 70 YOA, ≥ 80 YOA, 60-69 YOA and 70-79 YOA), and by region.

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 the Sections 7.1.2 (contraindication to subsequent vaccination) or 5.2.1 (medical conditions) or 5.2.2 (concomitant therapy), he/she may be eliminated from per-protocol analysis.

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

9.4. Statistical analyses

The statistical analysis plan (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.

9.4.1. General considerations (Amended: 01 April 2022)

Analysis of data up to Month 12 will be performed by group (RSV_annual, RSV_flexible revaccination and RSV_1dose), and for the 3 groups pooled. ***For*** Month 13 ***and Month 18***, the analysis will be tabulated for RSV_annual ***group*** versus the pooled RSV_flexible revaccination and RSV_1dose groups. ***From Month 25 up to study end, the analysis will be performed by group***.

9.4.1.1. Demography

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

9.4.1.2. Immunogenicity (Amended: 01 April 2022)

- Any missing or non-evaluable immunogenicity measurement will not be replaced. The descriptive analysis performed for each assay at each timepoint will exclude participants with a missing or non-evaluable measurement. ***This is applicable to the standard way of computing geometric mean titers/concentrations (GMTs/GMCs).***
- ***During the computation of GMTs/GMCs from the mixed model, multiple imputation (MI) technique will not be applied for any missing immunogenicity measurement. This is because the mixed model inherently accounts for the missingness, under the assumption that the missing data are missing at random***

(MAR). Thus, considering that "missing data are MAR" is a reasonable assumption for this descriptive clinical trial, then it is not necessary to perform MI [Rubin, 1995]. More details about the mixed-effects model have been described in the SAP.

- The 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) value will be given the ULOQ value for the purpose of GMT/GMC calculation.
- The mean geometric increase (MGI) is calculated by the geometric mean of ratios of antibody titer/concentrations of each post-primary vaccination timepoint over pre-primary vaccination (Day 1).

More details regarding the handling of numerical serology results will be described in the SAP.

9.4.1.3. 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, pIMDs 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.

9.4.2. Demographics and participants' disposition (Amended: 01 April 2022)

Descriptive summaries will be performed for each group (RSV_annual, RSV_flexible revaccination and RSV_1dose) and overall. The same will be performed in each subset (humoral immune subset and CMI subset).

Demographic/baseline characteristics (age at vaccination in years, sex, race, ethnicity, type of residence [CD/LTCF] and smoking status) will be summarized 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 such as age.

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

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

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 Per-Protocol (PP) analyses will be tabulated.
- The numbers of participants withdrawn ***from the study*** will be tabulated according to the reason for withdrawal.

Participant disposition in the ES and PPS will be reported as a whole and per group.

The number and percentage of participants using concomitant medication (any medication, any antipyretic and any antipyretic taken prophylactically, respectively) during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) and during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) will be summarized by group after each vaccine dose and overall, and after the revaccination.

9.4.3. Primary endpoints

9.4.3.1. Humoral immune response – up to Month 12 (Amended: 01 April 2022)

The analysis of the primary vaccination timepoints up to Month 12 will be performed for each group and for the 3 groups pooled. For each timepoint with blood sample collection for humoral immune response up to Month 12 and for each assay (RSV-A/-B neutralization), unless otherwise specified, the following analyses will be performed:

Within groups evaluation:

- Percentage of participants with antibody titers/concentrations above a positivity cut-off and their exact 95% confidence interval (CI) will be tabulated.
- GMTs/GMCs and their 95% CI will be tabulated and represented graphically. Furthermore, to account for all the timepoints at which the blood samples are collected, a mixed ***effects*** model will be fitted, from which the GMTs/GMCs will be computed. ***More details about the mixed model have been defined in the SAP.***
- Antibody titers/concentrations will be displayed using reverse cumulative curves.
- The MGI will be tabulated with 95% CI.

9.4.4. Secondary endpoints

9.4.4.1. Humoral immune response (Amended: 01 April 2022)

The same analyses as described above for the primary endpoint will be performed for ELISA up to Month 12 and for each timepoint with blood sample collection for humoral immune response from study Month 13 up to study end and for each assay (ELISA and RSV-A/-B neutralization). ***For Month 13 and Month 18, the analysis will be tabulated for RSV_annual group versus the pooled RSV_flexible revaccination and RSV_1dose groups. From Month 25 up to study end, the analysis will be performed by group.***

Only the analyses requiring further clarification of the exact timepoints analyzed are summarized below:

Within groups evaluation:

- The MGI, i.e. geometric mean of ratios of antibody titer/concentrations, will be tabulated with 95% CI:
  - For each post-primary vaccination timepoint (at Months 18, 24, 30 and 36 when applicable) over pre-primary vaccination (Day 1),
  - For each post-revaccination timepoint over corresponding pre-revaccination (Months 12/24) in the RSV_annual group,
  - ***For each post-revaccination timepoint over corresponding pre-revaccination (Month 24) in the RSV_flexible revaccination group,***
  - For 1 month post-revaccination at Month 12 (Month 13) over 1 month post-Dose 1 vaccination (Day 31) in RSV_annual group,
  - For 1 month post-revaccination at Month 24 (Month 25) over 1 month post-revaccination at Month 12 (Month 13) in RSV_annual group.
  - ***For 1 month post-revaccination at Month 24 (Month 25) over 1 month post-Dose 1 vaccination (Day 31) in RSV_flexible revaccination group.***

In addition, the following evaluations will be performed:

- The kinetics of GMTs/GMCs will be plotted as a function of time for participants with results available at all post-primary vaccination timepoints.

The immunogenicity analysis will also be performed by age category (age at Dose 1: ≥65 YOA, ≥70 YOA, ≥80 YOA, 60-69 YOA and 70-79 YOA), by sex and by region.

9.4.4.2. Cell-mediated immune response (Amended: 01 April 2022)

Within groups evaluation:

The following parameters will be summarized by group at each timepoint for which blood samples are collected, for the 3 groups pooled for timepoints up to study Month 12. ***For Month 13 and Month 18, the analysis will be tabulated for RSV_annual group versus the pooled RSV_flexible revaccination and RSV_1dose groups. From Month 25 up to study end, the analysis will be performed by group*** using descriptive statistics (N, geometric mean, min, Q1, median, Q3, max) in the CMI subset:

- Frequency of RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17***, measured by intracellular cytokine staining (ICS) using peripheral blood mononuclear cells (PBMCs)***.
- The kinetics of RSVPreF3-specific CD4+ T cells frequencies will be plotted as a function of time for participants with results available at all timepoints.
- Fold increase of the frequency of RSVPreF3-specific CD4+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17***, measured by ICS***, at each post-primary vaccination timepoint over pre-vaccination (Day 1), at each post-revaccination over the corresponding pre-revaccination ***(Month 12/Month 24 in the RSV_annual group and Month 24 in the RSV_flexible revaccination group)*** and at one month post-revaccination over 1 month post-previous dose in the RSV_annual group ***[one month post-revaccination at Month 12 (Month 13) over one month post-Dose 1 vaccination (Day 31) and one month post-revaccination at Month 24 (Month 25) over one month post-revaccination at Month 12 (Month 13)] and in the RSV_flexible revaccination group [one month post-revaccination at Month 24 (Month 25) over one month post-Dose 1 vaccination (Day 31)]***.

The descriptive immunogenicity analysis will also be performed by age category (age at Dose 1: ≥ 65 YOA, ≥ 70 YOA, ≥ 80 YOA, 60-69 YOA and 70-79 YOA), by sex and by region.

9.4.4.3. Safety analysis (Amended: 01 April 2022)

Primary vaccination and revaccination dose:

The safety analysis will be performed on the ES. A descriptive analysis by group, for the 3 groups pooled up to Month 12, for the RSV_flexible revaccination and RSV_1dose groups pooled versus RSV_annual group ***for Month 13 and Month 18, and by group from Month 25 up to study end,*** will present a summary of:

- 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 during the 4-day or 30-day follow-up period will be tabulated with exact 95% CI after each dose. The same computations will be done for Grade 3 AEs, and for Grade 3 non-serious AEs and for AEs resulting in medically attended visit.
- The number and percentage of participants reporting each individual solicited administration site event (any grade, Grade 3 and resulting in medically attended visit) and solicited systemic event (any grade, Grade 3 and resulting in medically attended visit) during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) will be tabulated for each group after each dose.
- For fever, the number and percentage of participants reporting fever by half degree (°C) cumulative increments during the 4-day follow-up period (i.e., on the day of vaccination and 3 subsequent days) will be tabulated for each group after each dose.

- The incidence of each solicited administration site event and solicited systemic event (any grade and Grade 3) will be represented graphically for each group after each dose.
- The number and percentage of participants with any unsolicited AEs during the 30-day follow-up period (i.e., on the day of vaccination and 29 subsequent days) with its exact 95% CI will be tabulated for each dose by group and by Medical Dictionary for Regulatory Activities (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 verbatim reports of unsolicited AEs 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 the MedDRA ***Primary SOC, HLT and*** PTs and reported from Dose 1 up to 6 months post-Dose 1 and from revaccination dose up to 6 months post-revaccination will be tabulated with exact 95% CI.
- The number and percentage of participants with at least one report of causally related SAE classified by the MedDRA ***Primary SOC, HLT and*** PTs and reported during the entire study period will be tabulated with exact 95% CI.
- The same tabulation will be presented for fatal SAEs.
- All SAEs will also be described in detail ***in a tabular listing.***
- ***All AEs/SAEs leading to study/intervention discontinuation from Dose 1 up to study end will be tabulated.***
- The number and percentage of participants with at least one report of pIMD classified by the MedDRA ***Primary SOC, HLT and*** PTs and reported from Dose 1 up to 6 months post-primary and from revaccination dose up to 6 months post-revaccination will be tabulated with exact 95% CI.
- The number and percentage of participants with at least one causally related pIMD classified by the MedDRA ***Primary SOC, HLT and*** PTs and reported during the entire study period will be tabulated with exact 95% CI.
- All pIMDs will also be described in detail ***in a tabular listing***.
- ***The analyses of unsolicited AEs will include SAEs (unless otherwise specified).***

The analysis of safety will also be performed by age category (***age at Dose 1: ≥ 65 YOA, ≥ 70 YOA,*** ≥ 80 YOA, 60-69 YOA and 70-79 YOA) ***and region (North America, Europe, Asia)***.

9.4.5. Tertiary/exploratory endpoints (Amended: 01 April 2022)

Please refer to the SAP for statistical analyses concerning tertiary endpoints and modeling of long-term persistence of post-primary vaccination antibodies (using mixed ***effects*** models for repeated measurements).

9.5. Interim analyses

All analyses will be conducted on final data, as clean as possible.

9.5.1. Sequence of analyses

9.5.1.1. Analyses for objectives and endpoints (Amended: 01 April 2022)

Analyses to evaluate objectives and endpoints will be performed stepwise:

- **Month 6:** A first analysis will be performed on all reactogenicity, safety and immunogenicity data available and as clean as possible, when data for at least primary and secondary endpoints up to Month 6 are available. This analysis will be considered as final for those endpoints.
- **Month 13**: A second analysis will be performed on all reactogenicity, safety and immunogenicity data available and as clean as possible, when data for at least primary and secondary endpoints up to Month 12 are available for all participants, as well as data up to 1 month after the first revaccination (Month 13) in the RSV_annual group. This analysis will be considered as final for those endpoints.
- **Month 18**: A third analysis will be performed on all safety and/or immunogenicity data available and as clean as possible, when data for secondary endpoints up to Month 18 are available for all participants. This analysis will be considered as final for those endpoints. Safety and immunogenicity analysis may be performed at different time depending on data availability.
- **Month 25**: A fourth analysis will be performed on all safety, reactogenicity and immunogenicity data available and as clean as possible, when data for at least primary and secondary endpoints up to Month 24 are available for all participants, as well as data up to 1 month after the second revaccination (Month 25) in the RSV_annual ***group and up to 1 month after the first revaccination (Month 25) in the RSV_flexible revaccination*** group. This analysis will be considered as final for those endpoints.
- The final **End of Study** analysis will be performed when all reactogenicity, safety and immunogenicity data for at least primary and secondary endpoints up to study conclusion are available (Month 36).
- If the data for tertiary endpoints become available at a later stage, (an) additional analysis/analyses will be performed.

9.5.2. Statistical consideration for interim analysis

All analyses will be conducted on final data (all planned results available for the time-points of interest) and therefore no statistical adjustment for interim analyses is required.

9.6. Data Monitoring Committee (DMC)

Not applicable.

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 Organizations 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/IEC.
  - 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 information on financial interests during the course of the study and for 1 year after completion 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. In addition, in case a caregiver is assigned by the participant to help him/her with the study procedures, the caregiver must receive an information letter prior to supporting the participant, that describes the role and data that will be collected from the caregiver.

The content of ICF 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.

Safety oversight will be provided by an unblinded SRT composed of GSK RSV OA project team members.

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 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 (see Glossary of terms for the exact definition of essential and 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, eCRF), the copy should fulfill the requirements for certified copies (see Glossary of terms for the exact definition of certified copies).

All participant data relating to the study will be recorded on 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 (see Glossary of terms 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 (see Glossary of terms for the exact definition of 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 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 the Glossary of terms.

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.

At study or site closure, 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 LSLV 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 (Amended: 01 April 2020)

RSV-A and RSV-B neutralization assays

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

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

and a secondary antibody conjugated to horse-radish 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 or equivalent). For each serum dilution, a ratio, expressed as a percentage, is calculated between the number of plaques at each serum dilution and the number of plaques in the virus control wells (no serum added). The serum neutralizing antibody 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]. For the testing of phase 3 studies, secondary standards calibrated against the international reference (NIBSC 16/284) ***[McDonald, 2018; McDonald, 2020]*** will be included in every run to allow conversion into international units.

RSVPreF3 protein IgG ELISA

Responses to the RSVPreF3 antigen will be evaluated by an indirect ELISA allowing the detection and the quantification of antigen-specific IgG 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).

Intracellular cytokine staining (ICS)

The ICS is used to assess RSVPreF3-specific CD4+ and/or CD8+ T cells expressing at least 2 activation markers including at least one cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17 (secondary endpoint).

As previously described [Moris, 2011], thawed peripheral blood mononuclear cells (PBMCs) are stimulated in vitro in the presence of anti-CD28 and anti-CD49d antibodies either with pools of 15-mer peptides overlapping by 11 amino acids and spanning the sequence of the RSVPreF3 protein, or with medium. After 2 hours of incubation at 37°C, Brefeldin A is added to inhibit cytokine secretion during an additional overnight incubation at 37°C. Cells are subsequently harvested, stained for surface markers (CD4+ and CD8+) and then fixed. Fixed cells are then permeabilized and stained with labeled antibodies specific for the following immune markers:

- CD3+: phenotyping T cells;

- CD40L (CD154), expressed on activated CD4+ T cells, [Chattopadhyay, 2005; Frentsch, 2005; Samten, 2000; Stubbe, 2006];
- IL-2: key for the development, survival and function of T cells [Boyman, 2012];
- TNF-α: anti-viral/intracellular factor, pro-inflammatory cytokine, cytotoxicity [Sedger, 2014];
- IFN-γ: anti-viral factor, associated with the Th1-like profile [Schoenborn, 2007];
- 4-1BB (CD137), expressed on activated CD4+ and CD8+ T cells [Wölfl, 2008];
- IL-13: associated with the Th2-like profile [Bao, 2015];
- IL-17: associated with the Th17-like profile [Korn, 2009].

After staining with the markers above, the cellular samples are analyzed by flow-cytometry allowing to determine the frequency of CD4+ and/or CD8+ T cells expressing the marker(s) of interest per million of CD4+ and/or CD8+ T cells.

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

10.3.1. Definition of an 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 an 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:

Table 25 Solicited administration site events

Pain
Erythema
Swelling

b. Solicited systemic events

The following systemic events will be solicited:

Table 26 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 diary card.

10.3.4. Unsolicited AEs

An unsolicited AE is an AE 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) during the reporting period for safety information, as well as any events that, though not medically attended, are of participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by 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

10.3.5.1. Potential immune-mediated diseases

pIMDs are a subset of AEs of special interest that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in the Table 27 (please refer to the 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 27 List of potential immune-mediated diseases (pIMDs) (Amended: 01 April 2022)

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

Medical Concept	*Additional Notes*
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***

Medical Concept	*Additional Notes*
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	
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	

Medical Concept	*Additional Notes*
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)*

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

Medical Concept	*Additional Notes*
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	

Medical Concept	*Additional Notes*
Stevens-Johnson Syndrome (SJS)	*Including but not limited to:* • *Toxic Epidermal Necrolysis (TEN)* • *SJS-TEN overlap*
Sweet's syndrome	• *Includes Acute febrile neutrophilic dermatosis*
Vitiligo	
Vasculitis	
Large vessels vasculitis	*Including but not limited to:* • *Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION)* • *Giant cell arteritis (also called temporal arteritis)* • *Takayasu's arteritis*
Medium sized and/or small vessels vasculitis	*Including but not limited to:* • *Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified)* • *Behcet's syndrome* • *Buerger's disease (thromboangiitis obliterans)* • *Churg–Strauss syndrome (allergic granulomatous angiitis)* • *Erythema induratum (also known as nodular vasculitis)* • *Henoch-Schonlein purpura (also known as IgA vasculitis)* • *Microscopic polyangiitis* • *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)"*

Medical Concept	*Additional Notes*
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	

10.3.6. 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 10.3.1 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

This section is not applicable for the study population.

10.3.8. Recording and follow-up of AEs, SAEs and pIMDs (Amended: 01 April 2022)

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

When an AE/SAE 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 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 and not the individual signs/symptoms.

A Paper Diary, hereafter referred to as Participant Diary will be used in this study to capture solicited administration site or systemic events and unsolicited AEs. The participant should be trained on how and when to complete each field of the Participant 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 the Glossary of terms 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 Participant Diary should be trained on the use of the Diary; for example, the study caregiver should have received a caregiver information letter explaining the role of the caregiver prior to completing the diary card. This training must be documented in the participant's source record. If any other individual than the participant is making entries in the Participant Diary (i.e., caregiver), their identity should be documented in the participant's source record.

- Collect and verify completed diary cards during discussion with the participant at Day 31 for all groups, and at Month 13 ***for the RSV_annual group only*** and Month 25 for the RSV_annual ***and RSV_flexible revaccination*** group***s***.
- Any unreturned diary cards will be sought from the participant through telephone call(s) or any other convenient procedure.

The investigator or designee will transcribe the required information into the eCRF in English. Refer to the SPM for more information regarding the completion of the paper diary.

10.3.8.1. Time period for collecting and recording AEs, SAEs and pIMDs

All solicited administration site and systemic events that occur during 4 days following administration of each dose of study vaccine must be recorded into the appropriate section of the eCRF, irrespective of intensity. All unsolicited AEs that occur during 30 days following administration of each dose of study vaccine must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs and pIMDs will begin at the first receipt of study vaccine and will end 6 months after study vaccine administration.

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

10.3.8.2. Follow-up of AEs, SAEs, pIMDs or any other events of interest

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 and pIMDs (as defined in the 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) or pIMDs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contact 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. 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 and pIMD information after removal of write access to the participant's eCRF

When additional SAE or pIMD 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 8.3.3.1 or to GSK Clinical Safety and Pharmacovigilance department within the defined reporting timeframes specified in the Table 15.

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 28 Intensity scales for solicited events in adults

Adults		
Event	**Intensity grade**	**Parameter**
Pain at administration site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal everyday activities.
	2	Moderate: Painful when limb is moved and interferes with everyday activities.
	3	Severe: Significant pain at rest. Prevents normal everyday activities.
Erythema at administration site		Record greatest surface diameter in mm
Swelling at administration site		Record greatest surface diameter in mm
Temperature*		Record temperature in °C/°F (with 1 decimal)
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

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

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

	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. 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 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 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 and unsolicited adverse event 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, pIMDs

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 15 for the details on timeframes for reporting of SAEs/pIMD.

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 (refer to Section 8.3.3.1 for contact information).

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. Requirements for 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 27th 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. Requirements for Germany (Amended: 01 April 2022)

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

There is no intention to conduct specific analyses investigating the relationship between the sex of the participants and the immunogenicity and safety of GSK's RSVPreF3 OA investigational vaccine. The ratio of male to female participants recruited into the study RSV OA=ADJ-004 is expected to be in line with the demographics of the population aged 60 years and above in the Member state.

Remote Source Data Verification (rSDV) during exceptional situations in Germany

Frequent in-stream monitoring of safety data by the central study team at GSK is required for this study. In-stream review of study data items and processes should be considered during exceptional situations/circumstances, such as with pandemics like COVID-19, focusing on key data points, patient assessments and processes that are critical to ensure the rights, safety and well-being of study participants and the integrity of the study and data. 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. Monitoring Plan and Study-Specific Risk Register will be updated to include rSDV activities and Clinical Research Associates (CRAs) will be guided for the conduct of rSDV.

Option 1: Transfer of redacted source documentation

Process for transfer and review of redacted source documentation provided by the site:

- ***The CRA instructs study site on the source data needed for the rSDV activities.***
- ***The CRA instructs site staff that they must pseudonymize the requested documentation, do a quality check that anonymized (redacted) areas cannot be read, and then delivers the documentation to the CRA in an encrypted form of communication (the site should have a documented process).***
- ***The minimum requirements regarding quality of the copies will be agreed with the site upfront:***
  - ***For the scanning of paper documents resolution will be a minimum of 300 dots per inch (dpi).***
  - ***For the scanning of photographs and images resolution will be 600 dpi minimum.***
  - ***Color scanners must be able to produce copies that match the original.***
  - ***A4 format as final size without loss of information.***
  - ***Documents will be saved as portable document format (PDF).***
  - ***In order to maintain quality standards, a captured image will not be subjected to non-uniform scaling (i.e., sizing) or re-sampling to a lower resolution.***

- ***Redacted source document scans will be sent to the CRA via email using one of the following secure options:***

  a. Transport Layer Security (TLS) connection:

  TLS connections are intended to support significant mail flow between GSK and external partners in a secure manner.

  b. GSK Secure

  In cases where only a handful of users are communicating or the volume of emails is low, the use of GSK secure, the GSK ad hoc message encryption solution is recommended.

  c. Password-protected PDF attachment

  A password protected scan (PDF) will be attached to an email. The password to open the attachment will be send in a separate email.

- ***The CRA may use the secure email website to assess whether the sites email address is secure (i.e., encrypted).***
- ***Prior to starting rSDV, the CRA ensures that the provided documents is complete and does not contain any Personal Information (PI).***
  - ***In case the CRA detects any PI that has not been redacted, the CRA informs the study site and deletes the files (including the Recycle bin).***
  - ***A Data Breach must be reported Data Breach Web Report Form.***
- ***Use of an external PC screen is recommended. The CRA will not generate any copies from the source data received.***
- ***Source data verification/review will be conducted according to the process outlined in the GSK Monitoring Standard Operating Procedure (SOP).***
- ***After completion of SDV activities, the CRA deletes all copies/images of participant data received from the site. This includes the deletion of the recycle bin and any temporary files.***
- ***A statement confirming that all documents were destroyed will be provided by the CRA via email to the site.***
- ***Details of what was monitored remotely will be documented in the appropriate section of the Monitoring Visit Report (MVR).***

<u>Option 2: Review of participant's source documentation remotely</u>

Process for use of Webcams, WebEx, MS Teams for viewing participant's source documentation remotely:

- ***The CRA ensures that the site personnel sharing information with GSK have authority to do so.***
- ***rSDV activities will be performed exclusively by the assigned site monitor.***

- ***Prior to conducting any rSDV activities, the CRA ensures that a written informed consent, covering the proposed SDV activities, has been signed by the participant.***
- ***For CRAs using GSK laptops, only use GSK-approved video conferencing tools (e.g., MS Teams or GSK WebEx). Live image transmission is fully encrypted and protected for authorized user. By using these systems, it will be assured that data will be viewed only but not transmitted/stored.***
- ***Functional Service Provider (FSP)/local Clinical Research Organization (CRO) CRAs not using GSK laptops, only MS Teams via Remote Access Application (RAA) may be used for meetings between the CRA and the site. WebEx is not permitted from non-GSK laptops. Other tools like FaceTime, WhatsApp or Zoom are not permitted since they do not have sufficient encryption features. GSK does not have enterprise contract/privacy agreement with these providers.***
- ***Prior to the remote monitoring visit, the CRA instructs study site on the specific data needed for the rSDV.***
- ***Source data verification will be conducted according to the process outlined in the Monitoring SOP.***
- ***The use of a headset is required; do not use computer audio.***
- ***The CRA does not capture screens or take pictures of screens to ensure we are not transferring content outside of clinical sites.***
- ***WebEx or Teams do not store or have access to any data, GSK staff is not allowed to make or store any screenshots or save any data which has been shared.***
- ***Details of what was monitored remotely will be documented in the appropriate section of the MVR.***
- ***In case of technical malfunctions or if the security of the transmission is no longer ensured, we will pause rSDV activities. GSK Issue Management Procedures will be initiated.***

10.5. Appendix 5: Abbreviations and glossary of terms

10.5.1. List of abbreviations (Amended: 01 April 2022)

AE:	Adverse Event
$AS01_E$:	Adjuvant System containing MPL, QS-21 and liposome (25 μg MPL and 25 μg QS-21)
CD:	Community Dwelling
CD40L:	Cluster of Differentiation 40 Ligand
CI:	Confidence Interval
CLS:	Clinical Laboratory Sciences
CMI:	Cell-Mediated Immunity
COVID-19:	Coronavirus Disease 2019
CRA:	***Clinical Research Associate***
eCRF:	electronic Case Report Form
ELISA:	Enzyme-Linked Immunosorbent Assay
EoS:	End of Study
ES:	Exposed Set
GCP:	Good Clinical Practice
GMC:	Geometric Mean Concentration
GMT:	Geometric Mean Titer
GSK:	GlaxoSmithKline
HLT:	***High Level Term***
HRP:	Horse-Radish Peroxidase
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Council on Harmonization
ICS:	Intracellular Cytokine Staining
IEC:	Independent Ethics Committee

IFN-γ:	Interferon-gamma
IgG:	Immunoglobulin G
IL-2/13/17:	Interleukin-2/13/17
IRB:	Institutional Review Board
LSLV:	Last Subject Last Visit
LTCF:	Long-Term Care Facility
MedDRA:	Medical Dictionary for Regulatory Activities
MGI:	Mean Geometric Increase
PBMC:	Peripheral Blood Mononuclear Cells
PI:	***Personal Information***
pIMD:	Potential Immune-Mediated Disease
PP:	Per-Protocol
PPS:	Per-Protocol Set
PT:	***Preferred Term***
QS-21:	*Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
rSDV:	***remote Source Data Verification***
RSV:	Respiratory Syncytial Virus
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SBIR:	Source data Base for Internet Randomization
SOP:	***Standard Operating Procedure***
SPM:	Study Procedures Manual
SRT:	Safety Review Team
TNF-α:	Tumor Necrosis Factor-alpha
US:	United States
YOA:	Years Of Age

10.5.2. Glossary of terms (Amended: 01 April 2022)

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which 1 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 open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.
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 diaries, receiving phone calls, planning study visits, etc.). However, at no time, the caregiver should evaluate the participant's health status while answering diaries or make decisions on behalf of the participant.
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 enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled participant:	'Enrolled' means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for 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.
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 (LTCF):	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 Harmonization (ICH) defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol". GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.***
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 1 or more investigational sites.
Site staff:	Site staff refers to qualified personnel who are trained on the study protocol and to whom the investigator has delegated significant study-related duties.
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 (non-serious and serious) reported in addition to those solicited during the clinical study. Also, any 'solicited' event with onset outside the specified period of follow-up for solicited events will be reported as an unsolicited AE.

TRADEMARKS

The following trademarked products are referenced in the present protocol.

Trademarks of the GSK group of companies	Generic description
Shingrix	Zoster vaccine (Recombinant, adjuvanted)
Trademarks not owned by the GSK group of companies	**Generic description**
TrueBlue peroxidase substrate (SeraCare)	Chromagenic substrate for visualization of horse-radish peroxidase-labeled reporter reagents

10.6. Appendix 8: 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**
Protocol	28 October 2020
Amendment 1	01 April 2022

Detailed description of Protocol Amendment:

Section 1.3 Schedule of Activities

Study visits should preferably be done on site. ***As of Protocol Amendment 1 implementation***, if deemed necessary, ***local regulations allow, and quality of study procedures is maintained,*** study visits during the follow-up phases can be done at home or at the long-term care facility (LTCF) […].

Table 1 Schedule of activities: RSV_annual

Type *(V = visit, C = contact)***	V	[…]	V/C[7]	V	V	V/C[7]	V/C	Notes
Timepoint	D1	[…]	M18[7]	M24	M25	M30[7]	M36	
Study participant informed consent[1]	●							See Section 10.1.3 for details
Check with participant if he/she will appoint a caregiver […]	O			O	O	O		See Section ~~10.1.3~~ ***5.2.5*** for details
[…]								
Clinical specimens for laboratory assays								
Blood sampling for antibody determination, **from HI subset**[3] (~10 mL)	●			●[6]	●			
Blood sampling for CMI, **from CMI subset**[3] (~25 mL)	●			●[6]	●			

[…]

Study visits should preferably be done on site. ***As of Protocol Amendment 1 implementation,* if deemed necessary, ***local regulations allow, and quality of study procedures is maintained,*** study visits during the follow-up phases can be done at home or at the LTCF, […]

[…]

[6] Blood sampling should be performed <u>prior</u> to vaccination (this has been clarified for the vaccination visit occurring after implementation of Protocol Amendment 1).

[7] Visits/contacts at Month 18 and Month 30 must not be performed before the 6-month post-vaccination timepoint to allow collection of safety data up to at least 6 months <u>after each</u> vaccination for each participant (this has been clarified for the vaccination visit occurring after implementation of Protocol Amendment 1).

Table 2 Schedule of activities: RSV_flexible revaccination

Type *(V = visit)***	V	[…]	V	***V***	**V(8)**	V	Notes
Timepoint	D1	[…]	M24	***M25***	**M30(8)**	M36	
Study participant informed consent[1]	●						See Section 10.1.3 for details
Check with participant if he/she will appoint a caregiver […]	O		O	***O***	O	O	See Section ~~10.1.3~~ ***5.2.5*** for details
[…]							
Check criteria for temporary delay for enrolment and vaccination	O		***O***				See Section 7.1.1 for more information
Check contraindications to vaccination			***O***				***See Section 7.1.2 for more information***
Recording pre-vaccination body temperature	●		●				See Section 8.2.1.6 for more information. The route […]
History-directed physical examination	O		***O***				See Section 8.2.1.5 for more information
Study group and intervention number allocation	O						See Sections 6.3.2 and 6.3.3 for more information
Intervention number allocation for subsequent dose			***O***				***See Section 6.3.3 for more information***
Recording of administered intervention number	●		●				The number of each administered study intervention must be […]
Vaccine administration (including 30-minute […])	●		●				See Section 6.1 for more information
Blood sampling for antibody determination, **from all […]**	●		●	●[7]	●	●	See Section 8.1.1 for more information
Blood sampling for CMI, **from CMI subset**[4] (~25 mL)	●		●	●[7]	●	●	See Section 8.1.1 for more information
Recording any concomitant medication/vaccination	●		●	●	●	●	See Section 6.5 for more information
Recording any intercurrent medical conditions	●		●	●	●	●	See Section 9.3.1.1 for more information
Distribution of paper diary cards for solicited events […]	O		***O***				See Section 8.2.1.7 for more information
Return of paper diary cards				***O***			
Recording of solicited events (Days 1–4 post-vaccination)	●		●	●			See Section 10.3.8 for more information
Recording of unsolicited AEs (Days 1–30 post-vaccination)	●		●	●			See Section 10.3.8 for more information
Recording of pIMDs and SAEs[5]	●		●	●	●		See Section 10.3.8 for more information
Recording of fatal SAEs, SAEs related to study vaccination […]	●		●	●	●	●	See Section 10.3.8 for more information
Recording AEs/SAEs leading to withdrawal from the study	●		●	●	●	●	See Section 10.3.8 for more information
Recording of SAEs related to study participation, or to […]	●		●	●	●	●	See Section 10.3.8 for more information
Study Conclusion						●	See Section 4.4 for more information

[…]

Study visits should preferably be done on site. ***As of Protocol Amendment 1 implementation,* if deemed necessary, ***local regulations allow, and quality of study procedures is maintained,*** study visits during the follow-up phases for the humoral subset can be done at home or at the LTCF, […]

[…]

[5] Recording of any SAE or any pIMD should only be done ***in the 6-month post-vaccination period, i.e.,*** from Day 1 to Month 6 ***and from Month 24 to Month 30***.

[…]

[7] Blood sampling should be performed prior to vaccination (this has been clarified for the revaccination visit occurring after implementation of Protocol Amendment 1).
[8] Visits at Month 30 must not be performed before the 6-month post-vaccination timepoint to allow collection of safety data up to at least 6 months after each vaccination for each participant (this has been clarified for the revaccination visit occurring after implementation of Protocol Amendment 1).

Table 3 Schedule of activities: RSV_1dose*

Type *(V = visit)***	V	[…]	Notes
Timepoint	D1	[…]	
Study participant informed consent[1]	●		See Section 10.1.3 for details
Check with participant if he/she will appoint a caregiver […]			See Section ~~10.1.3~~ ***5.2.5*** for details

[…]
Study visits should preferably be done on site. ***As of Protocol Amendment 1 implementation,* if deemed necessary, ***local regulations allow, and quality of study procedures is maintained,*** study visits during the follow-up phases for the humoral subset can be done at home or at the LTCF, [...]

Table 5 Intervals between study visits for groups RSV_flexible revaccination and RSV_1dose

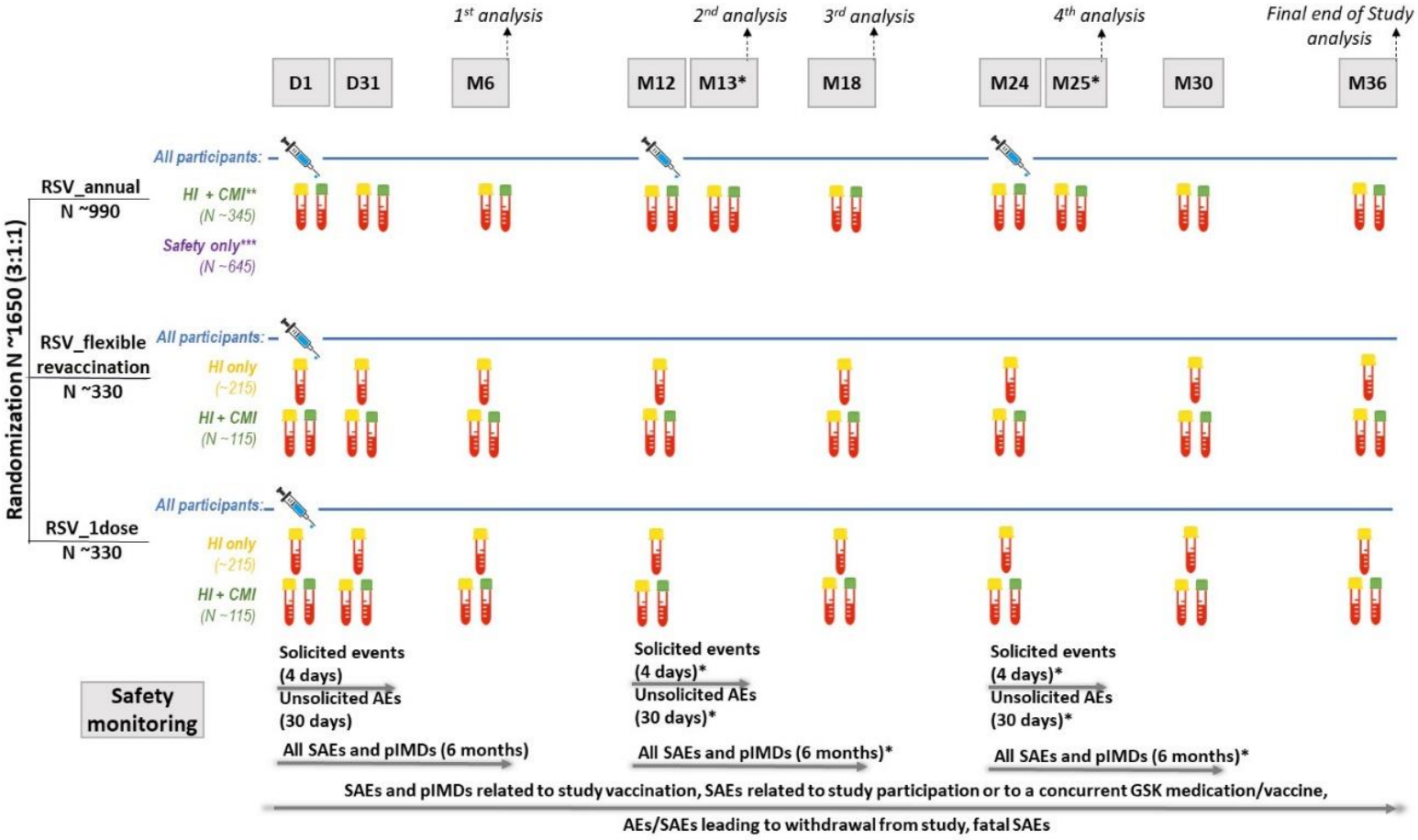
Interval	Length of interval	Allowed interval
Day 1 → Day 31	30 days	30-42 days
[…]	[…]	[…]
Month 24 → Month 25 [2]	***30 days***	***30-42 days***
Month 24 → Month 30	180 days	180-210 ***[1]*** days

[1] Visit must not be performed before the 6-month post-vaccination timepoint to allow collection of safety data up to at least 6 months post-vaccination for each participant. ***Note that the 6-month safety follow-up following revaccination at Month 24 is only applicable for the RSV_flexible revaccination group***.
[2] Only applicable for the RSV_flexible revaccination group.
[…]

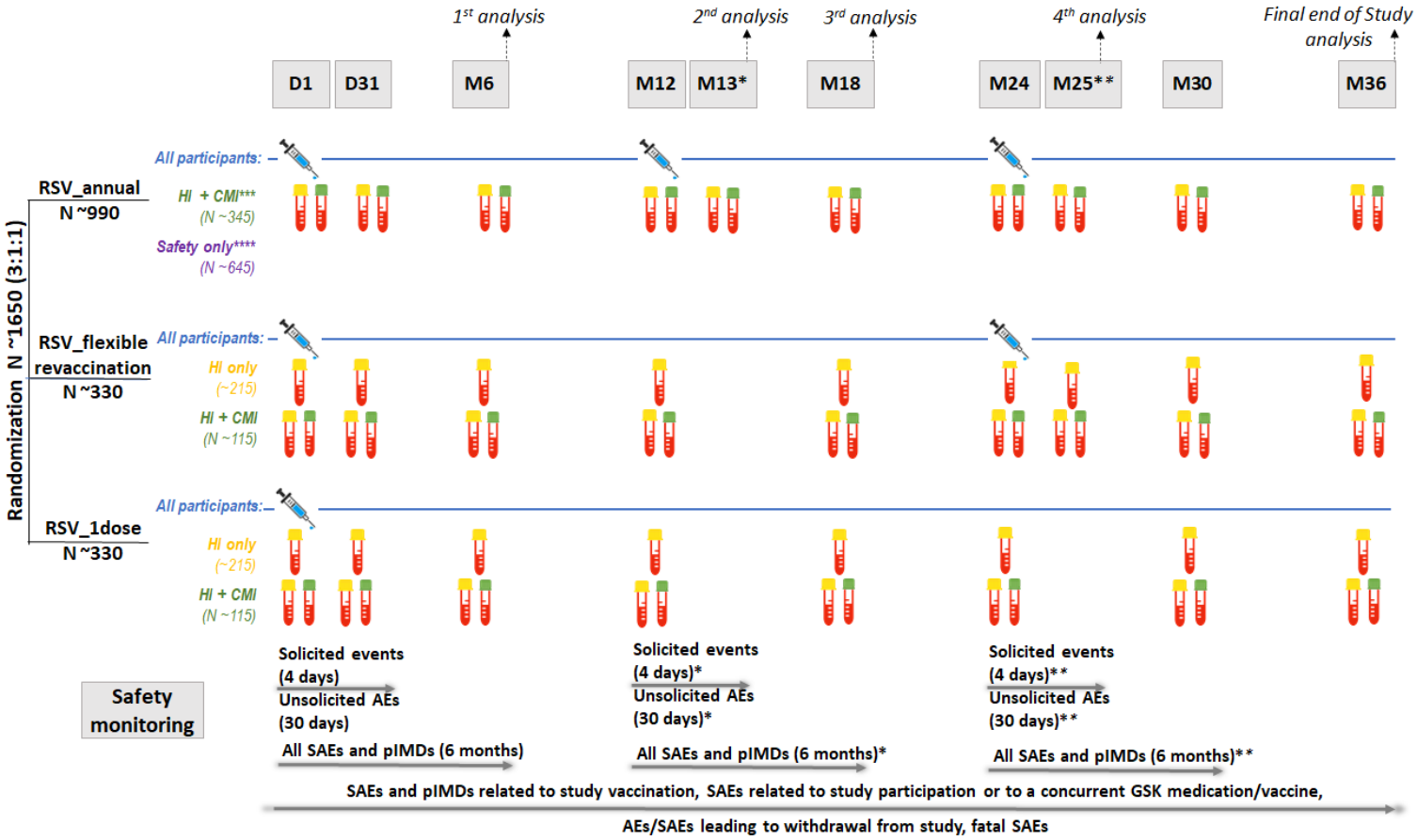
Section 4.1 Overall Design

Figure 1 Study design overview

Old figure:



New figure:



[…]

Note: For group RSV_annual: Revaccination Year 1 = Month 12; Revaccination Year 2 = Month 24***; for group RSV_flexible revaccination: Revaccination Year 2 = Month 24***.

[…]

****Visit and follow-up of solicited events, unsolicited AEs, SAEs and pIMDs are only applicable for RSV_annual and RSV_flexible revaccination groups.***

*****For the RSV_annual group, the same ~345 participants will be part of both the HI and CMI subsets. The remaining ~645 participants […].

******For those participants in the RSV_annual group without blood sample collections, visits at Months 6, 18, 30 and 36 may be held through a contact. However, […].

Table 7 Study groups, intervention and blinding foreseen in the study

Study groups	Number of participants	Age	Intervention			Blinding
			Primary vaccination	Revaccination Year 1 (Month 12)	Revaccination Year 2 (Month 24)	Open
RSV_annual	~990	≥ 60 years	RSVPreF3 OA investigational vaccine	RSVPreF3 OA investigational vaccine	RSVPreF3 OA investigational vaccine	X
RSV_flexible revaccination~~*~~	~330	≥ 60 years	RSVPreF3 OA investigational vaccine	***(none)***	***RSVPreF3 OA investigational vaccine***	X
[…]	[…]	[…]	[…]	[…]	[…]	[…]

~~*Based on immunogenicity data from this study and efficacy results from the Phase 3 study RSV OA=ADJ-006, a revaccination might be decided for this group.~~

Section 4.2 Scientific rationale for study design

[…]

For that reason, the study is designed not only to evaluate the safety, the reactogenicity, the immunogenicity profile and the long-term persistence of the immune response […]:

- RSV_flexible revaccination group will receive the first dose (Dose 1) at Day 1. A revaccination dose will be given ~~whenever a revaccination would be needed, based on immunogenicity data from this study and efficacy results from the Phase 3 study RSV OA=ADJ-006, which will assess the efficacy, immunogenicity and safety of a single dose of the RSVPreF3 OA investigational vaccine in adults aged 60 years and above~~ ***24 months post-Dose 1. Immunogenicity data from other studies using the same study intervention showed that following a two-dose vaccination schedule (0-2-month schedule), the immune response gradually declines over time but remains above baseline value up to 18 months post-Dose 2 and that a re-vaccination at 18 months post-Dose 2 (i.e., 20 months post-Dose 1) induced humoral and cellular immune responses***.

Section 6.1 Study interventions administered

Table 8 Study intervention administered

Study intervention name:	RSVPreF3 OA interventional vaccine
[…]	[…]
Number of doses to be administered:	RSV_annual: 3 doses RSV_flexible revaccination: ~~1~~ ***2*** dose***s*** RSV_1dose: 1 dose

Section 6.4 Study intervention compliance

~~When participants are dosed, they will receive~~ Study intervention ***will be administered to the participants*** directly from the investigator or designee, […]

Section 6.5 Concomitant therapy

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

- All concomitant medication including vaccines/products, except vitamins and dietary supplements, administered during the period of 30 days post each vaccine dose (Day 1 to Day 31 for all groups, Month 12 to Month 12 + 30 days ***for the RSV_annual group*** and Month 24 to Month 24 + 30 days for the RSV_annual ***and RSV_flexible revaccination*** group***s***).
- […]
- Any prophylactic medication (e.g., analgesics, antipyretics) administered on the day of study vaccination (Day 1 for all groups; Month 12 ***for the RSV_annual group*** and Month 24 for the RSV_annual ***and RSV_flexible revaccination*** group***s***) and in the absence of ANY symptom and in anticipation of a reaction to the vaccination.

Table 10 Timing of collection of concomitant medication

	Day 1		Month 24	Month 24 + 30 days	Study conclusion
All concomitant medication including vaccines/products, except vitamins and dietary supplements			*RSV_annual* ***and RSV_flexible revaccination*** *only*	*RSV_annual* ***and RSV_flexible revaccination*** *only*	
All concomitant medication […] SAE/pIMD					
Any prophylactic medication			*RSV_annual* ***and RSV_flexible revaccination*** *only*		
All concomitant medications including vaccines/products leading to discontinuation […]					

Section 7.1.2 Contraindications to subsequent vaccine administration

Participants in the RSV_annual ***and RSV_flexible revaccination*** group***s*** must be evaluated to confirm they are eligible for subsequent vaccination before administering each additional study vaccine dose.

Section 8 Study assessments and procedures

[…]

- 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 […].

*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 […] at a site other than the designated study site. Refer to European Medicines Agency (EMA) Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version ~~2~~ ***5***, ~~27 March, 2020~~ ***10 February 2022***) ***and to the Food and Drug Administration Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency (updated 30 August 2021)*** for more details.

Section 8.1.1 Biological samples

Table 11 Biological samples

Sample type	Quantity	Unit	Timepoint	Subset name*
Blood for humoral immune response	~10	mL	Day 1 […] Month 25***	HI subset
Blood for CMI	~25	mL	Day 1 […] Month 25***	CMI subset

[…]
******Only applicable for the RSV_annual and RSV_flexible revaccination groups***

The approximate overall volume that will be collected per participant during the entire 3-year study period is as follows:

Group	Participant subset	Number of participants	Total volume of blood	Notes
RSV_annual group	HI subset	~345	10x10 mL = ~100 mL	The same ~345 participants will be part of both […]
	CMI subset	~345	10x25 mL = ~250 mL	
RSV_flexible revaccination group	All participants	~330	~~8~~ ***9***x10 mL = ~~~80~~ ***90*** mL	
	CMI subset	~115	~~8~~ ***9***x25 mL = ~~~200~~ ***225*** mL	
RSV_1dose	[…]	[…]	[…]	

Section 8.1.3 Immunological read-outs

Table 13 Immunological read-outs

Blood sampling timepoint		Subset name	No. participants	Component	Components priority rank
Type of contact and timepoint	Sampling timepoint				
Humoral immunity (on serum samples)					
Day 1	Pre-Vacc	Humoral immunity subset	~1005	RSV-A neutralizing antibody	1
				RSV-B neutralizing antibody	2
				RSVPreF3-specific IgG antibody	3
[…]	[…]	[…]	[…]	[…]	[…]
Month 25[-1-][2]	Month 25[-1-][2]	Humoral immunity subset	~~345~~ ***675***	RSV-A neutralizing antibody	1
				RSV-B neutralizing antibody	2
				RSVPreF3-specific IgG antibody	3
Cell-mediated immunity (on PBMC samples)					
Day 1	Pre-Vacc	CMI subset	~575	IL-2, CD40L, TNF-α, IFN-γ, […]	-
[…]	[…]	[…]	[…]	[…]	[…]
Month 25[-1-][2]	Month 25[-1-][2]	CMI subset	~~345~~ ***460***	IL-2, CD40L, TNF-α, IFN-γ, IL-13, IL-17 or 4-1BB secreting CD4+ and CD8+ T cells	-

[…]
[2] ***Only applicable for the RSV_annual and RSV_flexible revaccination groups.***

Section 8.3.3.1 Contact information for reporting of SAEs and pIMDs

Table 16 Contact information for reporting of SAEs and pIMDs

Study contact for questions regarding SAEs and pIMDs
Refer to the local study contact information document
GSK Clinical Safety & Pharmacovigilance
[…]
Email address: ~~Rix.CT-safety-vac@gsk.com~~ ***ogm28723@gsk.com***

Section 9.2 Sample size determination

[…]

The proposed sample size is based on the following considerations:

- Ensure a sufficient number of participants to evaluate with adequate precision […] but also the immunogenicity after revaccination (based on RSV_annual ***and RSV_flexible revaccination*** group***s*** ~~only~~).
- […]

Approximately 345 participants will be enrolled in the humoral subset in the RSV_annual ***group*** and approximately 330 participants per group in the RSV_flexible revaccination and RSV_1dose ***groups***. […]. A total of 990 ***and 330*** participants will be enrolled in the RSV_annual ***and RSV_flexible revaccination*** group***s, respectively,*** for evaluation of reactogenicity and safety profile following revaccination.

Section 9.2.4 Evaluation of humoral and cellular immune response at Month 25 *in the RSV_annual and RSV_flexible revaccination groups* (secondary objective)

[…]

Approximately 211 participants in the RSV_flexible revaccination group receiving a revaccination dose of RSVPreF3 OA investigational vaccine will be evaluable for the humoral immune response at study Month 25. Table 21 shows the precision that can be obtained based on different values of standard deviations in terms of RSV-A/B neutralizing antibody titers, RSVPreF3-specific IgG antibody concentrations.

Approximately 74 participants in the RSV_flexible revaccination group receiving a revaccination dose of RSVPreF3 OA investigational vaccine will be evaluable for the cellular immune response at study Month 25. Table 22 shows the precision that can be obtained based on different values of standard deviations in terms of the frequency of RSVPreF3-specific CD4+ T cells.

[…]

Table 21 Precision and 95% confidence interval on the geometric mean antibody titers/concentrations at Month 25 based on different values of standard deviations for 211 evaluable participants in the RSV_flexible revaccination group

Number of enrolled participants in the humoral subset in the RSV_flexible revaccination	*Number of evaluable participants in the humoral subset at Month 13*	*Number of evaluable participants in the humoral subset at Month 25*	*Standard deviation in log10*	*Width ½ 95% CI in log10*	*Ratio upper limit 95% CI / GM*	*Ratio upper limit / lower limit 95% CI*
330	*264*	*211*	*0.30*	*0.041*	*1.10*	*1.21*
330	*264*	*211*	*0.35*	*0.047*	*1.11*	*1.24*
330	*264*	*211*	*0.40*	*0.054*	*1.13*	*1.28*
330	*264*	*211*	*0.45*	*0.061*	*1.15*	*1.32*
330	*264*	*211*	*0.50*	*0.068*	*1.17*	*1.37*

Precision estimated using PASS 2019: Confidence interval for one mean, alpha = 5%.
CI = Confidence Interval, LL = Lower Limit, UL = Upper Limit; GM = Geometric Mean

Table 22 Precision and 95% confidence interval of the frequency of RSVPreF3-specific CD4+ T cells at Month 25 based on different values of standard deviations for 74 evaluable participants in the RSV_flexible revaccination group

Number of enrolled participants in the CMI subset in the RSV_flexible revaccination group	*Number of evaluable participants in the CMI subset at Month 13*	*Number of evaluable participants in the CMI subset at Month 25*	*Standard deviation in log10*	*Width ½ 95% CI in log10*	*Ratio upper limit 95% CI / GM*	*Ratio upper limit / lower limit 95% CI*
115	*92*	*74*	*0.30*	*0.070*	*1.17*	*1.38*
115	*92*	*74*	*0.35*	*0.081*	*1.21*	*1.45*
115	*92*	*74*	*0.40*	*0.093*	*1.24*	*1.53*
115	*92*	*74*	*0.45*	*0.105*	*1.27*	*1.62*
115	*92*	*74*	*0.50*	*0.116*	*1.31*	*1.71*

Precision estimated using PASS 2019: Confidence interval of a mean, alpha = 5%.
CI = Confidence Interval, LL = Lower Limit, UL = Upper Limit; GM = Geometric Mean

Section 9.2.5 Evaluation of reactogenicity and safety profile following revaccination in the RSV_annual *and RSV_flexible revaccination* groups

As indicated in Table 23, the proposed sample size***s*** of 990 participants in the RSV_annual group receiving revaccination on an annual basis ***and 330 participants in the RSV_flexible revaccination group receiving revaccination at Year 2 (Month 24)***, give~~s~~ 99.3% ***and 80.9%*** probabili***ties, respectively,*** of observing at least one AE if a true incidence rate equals 0.5%. This probability increases to 100% for true incidence rates ≥0.8% ***for the RSV_annual group***. Although lower, the probability remains above 62% to detect at least one AE that would occur at a frequency of 0.1% (1/1000) ***and 0.3% (3/1000) in the RSV_annual and RSV_flexible revaccination groups, respectively***.

Table 23 Probability (%) to observe at least one AE depending on the AE true incidence rate with 990 ***and 330*** participants ***in the RSV_annual and RSV_flexible revaccination groups, respectively***

Incidence rate	Probability to observe at least one AE ***in the RSV_annual***	***Probability to observe at least one AE in the RSV_flexible revaccination***
0.01%	9.4%	***3.2%***
0.05%	39.1%	***15.2%***
0.10%	62.9%	***28.1%***
0.15%	77.4%	***39.1%***
0.20%	86.2%	***48.3%***
0.25%	91.6%	***56.2%***
0.30%	94.9%	***62.9%***
0.35%	96.9%	***68.6%***
0.40%	98.1%	***73.4%***
0.50%	99.3%	***80.9%***
0.60%	99.7%	***86.3%***
0.70%	99.9%	***90.2%***
0.80%	100.0%	***92.9%***
0.90%	100.0%	***94.9%***
1.00%	100.0%	***96.4%***

Section 9.3 Population for analyses

Table 24 Populations for analyses

Analysis set	Description
[…]	[…]
Per-Protocol set (PPS)	All participants who received at least 1 dose of the study intervention to which they are randomized and have post-vaccination ***immunogenicity*** data, minus […]

The primary analysis for immunogenicity will be performed on the PPS. If in any study group ***and for at least one visit***, the percentage of vaccinated participants with serological results excluded from the PPS for immunogenicity is at least ~~10~~ ***5***%, a second analysis will be performed […].

Section 9.4.1 General considerations

Analysis of data up to Month 12 will be performed by group (RSV_annual, RSV_flexible revaccination and RSV_1dose), and for the 3 groups pooled. ~~From~~ ***For*** Month 13 ***and Month 18***, the analysis will be tabulated for RSV_annual ***group*** versus the pooled RSV_flexible revaccination and RSV_1dose groups. ***From Month 25 up to study end, the analysis will be performed by group***~~, at applicable timepoints~~.

Section 9.4.1.2 Immunogenicity

- Any missing or non-evaluable immunogenicity […]. ***This is applicable to the standard way of computing geometric mean titers/concentrations (GMTs/GMCs).***
- ***During the computation of GMTs/GMCs from the mixed model, multiple imputation (MI) technique will not be applied for any missing immunogenicity measurement. This is because the mixed model inherently accounts for the missingness, under the assumption that the missing data are missing at random (MAR). Thus, considering that "missing data are MAR" is a reasonable assumption for this descriptive clinical trial, then it is not necessary to perform MI [Rubin, 1995]. More details about the mixed-effects model have been described in the SAP.***

Section 9.4.2 Demographics and participants' disposition

[…]

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

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

Withdrawal status will be summarized by group using descriptive statistics:

- […]
- The numbers of ~~withdrawn~~ participants withdrawn ***from the study*** will be tabulated according to the reason for withdrawal.

Participant disposition in the ES and PPS will be reported as a whole and per group~~, and for each age category~~.

Section 9.4.3.1 Humoral immune response – up to Month 12

[…]

Within groups evaluation:

- […]
- GMTs/GMCs and their 95% CI will be tabulated and represented graphically. Furthermore, to account for all the timepoints at which the blood samples are collected, a mixed ***effects*** model will be fitted, from which the GMTs/GMCs will be computed. ***More details about the mixed model have been defined in the SAP.***
- […]
- ~~Individual post-vaccination results (at Days 31 and at Months 6 and 12) versus pre-vaccination results (Day 1) will be plotted using scatter plots.~~
- ~~Distribution of the fold increase of the antibody titers/concentrations (post- over pre-primary vaccination titers) will be tabulated.~~

Section 9.4.4.1 Humoral immune response

The same analyses as described above for the primary endpoint […] (ELISA and RSV-A/-B neutralization). ~~The analysis of the post-primary vaccination timepoints from study Month 13 up to study end will be performed for each group and for the pooled RSV_flexible revaccination and RSV_1dose groups~~. ***For Month 13 and Month 18, the analysis will be tabulated for RSV_annual group versus the pooled RSV_flexible revaccination and RSV_1dose groups. From Month 25 up to study end, the analysis will be performed by group.***

Within groups evaluation:

- The MGI, i.e. geometric mean of ratios of antibody titer/concentrations, […]:
  - […],
  - ***For each post-revaccination timepoint over corresponding pre-revaccination (Month 24) in the RSV_flexible revaccination group,***
  - ***For 1 month post-revaccination at Month 24 (Month 25) over 1 month post Dose 1 vaccination (Day 31) in RSV_flexible revaccination group.***
- ~~Individual post-primary vaccination results (at Months 18, 24, 30 and 36 when applicable) versus pre-vaccination results (Day 1) by group and individual post-revaccination results versus the corresponding pre-revaccination results (Months 12/24) in the RSV_annual group will be provided using scatter plots.~~
- ~~Distribution of the fold increase of the antibody titers/concentrations (post- over pre-primary vaccination dose, post- over the corresponding pre-revaccination and 1 month post-revaccination over 1 month post-previous dose) will be tabulated when applicable.~~
- ~~The ratio of fold increase (pre to post-vaccination) of anti-RSVPreF3-specific antibody concentrations over the fold increase (pre to post-vaccination) of anti-RSV-A/-B neutralizing antibody titers will be tabulated using descriptive statistics and displayed graphically using scatter plots.~~

Section 9.4.4.2 Cell-mediated immune response

Within groups evaluation:

The following parameters will be summarized by […] up to study Month 12~~,~~. ***For Month 13 and Month 18, the analysis will be tabulated for RSV_annual group versus the pooled RSV_flexible revaccination and RSV_1dose groups. From Month 25 up to study end, the analysis will be performed by group*** ~~for the pooled RSV_flexible revaccination and RSV_1dose from study Month 13 up to study end~~ using descriptive statistics (N, geometric mean, min, Q1, median, Q3, max) in the CMI subset:

- Frequency of RSVPreF3-specific CD4+ […], IL-17***, measured by intracellular cytokine staining (ICS) using peripheral blood mononuclear cells (PBMCs)***.
- The kinetics of RSVPreF3-specific CD4+ ~~and/or CD8+~~ T cells frequencies will be plotted as a function of time for participants with results available at all ~~primary vaccination~~ timepoints.

- Fold increase of the frequency of RSVPreF3-specific CD4+ ~~and/or CD8+~~ T cells expressing at least 2 activation markers […] IL-17***, measured by ICS***, at each post-primary vaccination timepoint over pre-vaccination (Day 1) ~~by group~~, at each post-revaccination over the corresponding pre-revaccination ***(Month 12/Month 24) in the RSV_annual group and Month 24 in the RSV_flexible revaccination group)*** and at one month post-revaccination over 1 month post-previous dose in the RSV_annual group ***[one month post-revaccination at Month 12 (Month 13) over one month post-Dose 1 vaccination (Day 31) and one month post-revaccination at Month 24 (Month 25) over one month post-revaccination at Month 12 (Month 13)] and in the RSV_flexible revaccination group [one month post-revaccination at Month 24 (Month 25) over one month post-Dose 1 vaccination (Day 31)]***.

Section 9.4.4.3 Safety analysis

Primary vaccination and revaccination dose:

The safety analysis will be performed on the ES. A descriptive analysis by group, […] versus RSV_annual group ***for Month 13 and Month 18, and by group from Month 25 up to study end,*** ~~from study Month 13 up to study end~~ will present a summary of:

- […]
- ~~In addition, the prevalence of each solicited administration site event and solicited systemic event (any grade and Grade 3) will be represented graphically over time for each group after each dose.~~
- […]
- The number and percentage of participants with any unsolicited AEs […] (MedDRA) ***Primary System Organ Class (SOC), High Level Term (HLT) and*** Preferred Term ***(PT)***. Similar tabulation […].
- The number and percentage of participants with at least one report of SAE classified by the MedDRA ***Primary SOC, HLT and*** PTs and reported from Dose 1 […].
- The number and percentage of participants with at least one report of causally related SAE classified by the MedDRA ***Primary SOC, HLT and*** PTs and reported […].
- All SAEs will also be described in detail ***in a tabular listing.***
- ***All AEs/SAEs leading to study/intervention discontinuation from Dose 1 up to study end will be tabulated.***
- The number and percentage of participants with at least one report of pIMD classified by the MedDRA ***Primary SOC, HLT and*** PTs and reported […].
- The number and percentage of participants with at least one causally related pIMD classified by the MedDRA ***Primary SOC, HLT and*** PTs and reported […].
- All pIMDs will also be described in detail ***in a tabular listing***.
- ***The analyses of unsolicited AEs will include SAEs (unless otherwise specified).***

The analysis of safety will also be performed by age category (***age at Dose 1: ≥ 65 YOA, ≥ 70 YOA,*** ≥ 80 YOA, 60-69 YOA and 70-79 YOA) ***and region (North America, Europe, Asia)***.

9.4.5 Tertiary/exploratory endpoints

Please refer to the SAP for statistical analyses concerning tertiary endpoints and modeling of long-term persistence of post-primary vaccination antibodies (using mixed ***effects*** models for repeated measurements).

Section 9.5.1.1 Analyses for objectives and endpoints

Analyses to evaluate objectives and endpoints will be performed stepwise:

- **Month 6:** A first analysis~~*~~ will be performed on all reactogenicity, […].

  ~~*Note: the analysis at Month 6 may be merged with the analysis at the subsequent timepoint.~~

- **Month 25**: A fourth analysis will be performed on all safety, […], as well as data up to 1 month after the second revaccination (Month 25) in the RSV_annual ***group and up to 1 month after the first revaccination (Month 25) in the RSV_flexible revaccination*** group. This analysis will be considered as final for those endpoints.

Section 10.2.1 Laboratory assays

RSV-A and RSV-B neutralization assays

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

Virus neutralization is performed by incubating a fixed amount of RSV-A strain (Long, ATCC No. VR-26) or RSV-B strain (18537, ATCC No. VR-1580) with serial dilutions of […]. For the testing of phase 3 studies, secondary standards calibrated against the international reference (NIBSC 16/284) ***[McDonald, 2018; McDonald, 2020]*** will be included in every run to allow conversion into international units.

Section 10.3.5.1 Potential immune-mediated diseases

Table 27 List of potential immune-mediated diseases (pIMDs)

~~Neuroinflammatory disorders~~	~~Musculoskeletal disorders~~	~~Skin disorders~~
• ~~Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy).~~ • ~~Optic neuritis.~~ • ~~Multiple sclerosis.~~ • ~~Transverse myelitis.~~ • ~~Guillain-Barré syndrome, including Miller Fisher syndrome and other variants.~~ • ~~Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis.~~ • ~~Myasthenia gravis, including Lambert-Eaton myasthenic syndrome.~~ • ~~Demyelinating peripheral neuropathies including:~~ • ~~Chronic inflammatory demyelinating polyneuropathy,~~ • ~~Multifocal motor neuropathy~~ • ~~Polyneuropathies associated with monoclonal gammopathy.~~ • ~~Narcolepsy.~~	• ~~Systemic lupus erythematosus and associated conditions~~ • ~~Systemic scleroderma (Systemic sclerosis), including:~~ • ~~Diffuse Scleroderma~~ • ~~CREST syndrome~~ • ~~Idiopathic inflammatory myopathies, including:~~ • ~~Dermatomyositis~~ • ~~Polymyositis~~ • ~~Anti-synthetase syndrome.~~ • ~~Rheumatoid Arthritis and associated conditions including:~~ • ~~Juvenile Idiopathic Arthritis~~ • ~~Still's disease.~~ • ~~Polymyalgia rheumatica.~~ • ~~Spondyloarthropathies, including:~~ • ~~Ankylosing Spondylitis,~~ • ~~Reactive Arthritis (Reiter's Syndrome),~~ • ~~Undifferentiated Spondyloarthritis,~~ • ~~Psoriatic Arthritis,~~ • ~~Enteropathic arthritis.~~ • ~~Relapsing Polychondritis.~~ • ~~Mixed Connective Tissue disorder.~~ • ~~Gout.~~	• ~~Psoriasis.~~ • ~~Vitiligo.~~ • ~~Erythema nodosum.~~ • ~~Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis).~~ • ~~Lichen planus.~~ • ~~Sweet's syndrome.~~ • ~~Localized Scleroderma (Morphea).~~

Vasculitis	**Blood disorders**	**Others**
• Large vessels vasculitis including: • Giant Cell Arteritis (Temporal Arteritis), • Takayasu's Arteritis. • Medium sized and/or small vessels vasculitis including: • Polyarteritis nodosa, • Kawasaki's disease, • Microscopic Polyangiitis, • Wegener's Granulomatosis (granulomatosis with polyangiitis), • Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis), • Buerger's disease (thromboangiitis obliterans), • Necrotizing vasculitis (cutaneous or systemic), • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), • Henoch-Schonlein purpura (IgA vasculitis), • Behcet's syndrome, • Leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia. • Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia. • Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	• Autoimmune glomerulonephritis including: • IgA nephropathy, • Glomerulonephritis rapidly progressive, • Membranous glomerulonephritis, • Membranoproliferative glomerulonephritis, • Mesangioproliferative glomerulonephritis. • Tubulointerstitial nephritis and uveitis syndrome. • Ocular autoimmune diseases including: • Autoimmune uveitis • Autoimmune retinitis. • Autoimmune myocarditis. • Sarcoidosis. • Stevens-Johnson syndrome. • Sjögren's syndrome. • Alopecia areata. • Idiopathic pulmonary fibrosis. • Goodpasture syndrome. • Raynaud's phenomenon.
Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**
• Autoimmune hepatitis. • Primary biliary cirrhosis. • Primary sclerosing cholangitis. • Autoimmune cholangitis.	• Inflammatory Bowel disease, including: • Crohn's disease, • Ulcerative colitis, • Microscopic colitis, • Ulcerative proctitis. • Celiac disease. • Autoimmune pancreatitis.	• Autoimmune thyroiditis (Hashimoto thyroiditis). • Grave's or Basedow's disease. • Diabetes mellitus type I. • Addison's disease. • Polyglandular autoimmune syndrome. • Autoimmune hypophysitis.

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

Medical Concept	*Additional Notes*
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***

Medical Concept	*Additional Notes*
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	
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	

Medical Concept	*Additional Notes*
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)*

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

Medical Concept	*Additional Notes*
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	

Medical Concept	*Additional Notes*
Stevens-Johnson Syndrome (SJS)	*Including but not limited to:* • *Toxic Epidermal Necrolysis (TEN)* • *SJS-TEN overlap*
Sweet's syndrome	• *Includes Acute febrile neutrophilic dermatosis*
Vitiligo	
Vasculitis	
Large vessels vasculitis	*Including but not limited to:* • *Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION)* • *Giant cell arteritis (also called temporal arteritis)* • *Takayasu's arteritis*
Medium sized and/or small vessels vasculitis	*Including but not limited to:* • *Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified)* • *Behcet's syndrome* • *Buerger's disease (thromboangiitis obliterans)* • *Churg–Strauss syndrome (allergic granulomatous angiitis)* • *Erythema induratum (also known as nodular vasculitis)* • *Henoch-Schonlein purpura (also known as IgA vasculitis)* • *Microscopic polyangiitis* • *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)"*

Medical Concept	*Additional Notes*
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	

Section 10.3.8 Recording and follow-up of AEs, SAEs and pIMDs

[…]

- Collect and verify completed diary cards during discussion with the participant at Day 31 for all groups, and at Month 13 ***for the RSV_annual group only*** and Month 25 for the RSV_annual ***and RSV_flexible revaccination*** group***s***.

Section 10.4.2 Requirements for Germany

[…]

Remote Source Data Verification (rSDV) during exceptional situations in Germany

Frequent in-stream monitoring of safety data by the central study team at GSK is required for this study. In-stream review of study data items and processes should be considered during exceptional situations/circumstances, such as with pandemics like COVID-19, focusing on key data points, patient assessments and processes that are critical to ensure the rights, safety and well-being of study participants and the integrity of the study and data. 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. Monitoring Plan and Study-Specific Risk Register will be updated to include rSDV activities and Clinical Research Associates (CRAs) will be guided for the conduct of rSDV.

Option 1: Transfer of redacted source documentation

Process for transfer and review of redacted source documentation provided by the site:

- ***The CRA instructs study site on the source data needed for the rSDV activities.***
- ***The CRA instructs site staff that they must pseudonymize the requested documentation, do a quality check that anonymized (redacted) areas cannot be read, and then delivers the documentation to the CRA in an encrypted form of communication (the site should have a documented process).***
- ***The minimum requirements regarding quality of the copies will be agreed with the site upfront:***
  - ***For the scanning of paper documents resolution will be a minimum of 300 dots per inch (dpi).***
  - ***For the scanning of photographs and images resolution will be 600 dpi minimum.***
  - ***Color scanners must be able to produce copies that match the original.***
  - ***A4 format as final size without loss of information.***
  - ***Documents will be saved as portable document format (PDF).***
  - ***In order to maintain quality standards, a captured image will not be subjected to non-uniform scaling (i.e., sizing) or re-sampling to a lower resolution.***

- ***Redacted source document scans will be sent to the CRA via email using one of the following secure options:***

  a. Transport Layer Security (TLS) connection:

  TLS connections are intended to support significant mail flow between GSK and external partners in a secure manner.

  b. GSK Secure

  In cases where only a handful of users are communicating or the volume of emails is low, the use of GSK secure, the GSK ad hoc message encryption solution is recommended.

  c. Password-protected PDF attachment

  A password protected scan (PDF) will be attached to an email. The password to open the attachment will be send in a separate email.

- ***The CRA may use the secure email website to assess whether the sites email address is secure (i.e., encrypted).***
- ***Prior to starting rSDV, the CRA ensures that the provided documents is complete and does not contain any Personal Information (PI).***
  - ***In case the CRA detects any PI that has not been redacted, the CRA informs the study site and deletes the files (including the Recycle bin).***
  - ***A Data Breach must be reported Data Breach Web Report Form.***
- ***Use of an external PC screen is recommended. The CRA will not generate any copies from the source data received.***
- ***Source data verification/review will be conducted according to the process outlined in the GSK Monitoring Standard Operating Procedure (SOP).***
- ***After completion of SDV activities, the CRA deletes all copies/images of participant data received from the site. This includes the deletion of the recycle bin and any temporary files.***
- ***A statement confirming that all documents were destroyed will be provided by the CRA via email to the site.***
- ***Details of what was monitored remotely will be documented in the appropriate section of the Monitoring Visit Report (MVR).***

<u>Option 2: Review of participant's source documentation remotely</u>

Process for use of Webcams, WebEx, MS Teams for viewing participant's source documentation remotely:

- ***The CRA ensures that the site personnel sharing information with GSK have authority to do so.***
- ***rSDV activities will be performed exclusively by the assigned site monitor.***
- ***Prior to conducting any rSDV activities, the CRA ensures that a written informed consent, covering the proposed SDV activities, has been signed by the participant.***

- ***For CRAs using GSK laptops, only use GSK-approved video conferencing tools (e.g., MS Teams or GSK WebEx). Live image transmission is fully encrypted and protected for authorized user. By using these systems, it will be assured that data will be viewed only but not transmitted/stored.***
- ***Functional Service Provider (FSP)/local Clinical Research Organization (CRO) CRAs not using GSK laptops, only MS Teams via Remote Access Application (RAA) may be used for meetings between the CRA and the site. WebEx is not permitted from non-GSK laptops. Other tools like FaceTime, WhatsApp or Zoom are not permitted since they do not have sufficient encryption features. GSK does not have enterprise contract/privacy agreement with these providers.***
- ***Prior to the remote monitoring visit, the CRA instructs study site on the specific data needed for the rSDV.***
- ***Source data verification will be conducted according to the process outlined in the Monitoring SOP.***
- ***The use of a headset is required; do not use computer audio.***
- ***The CRA does not capture screens or take pictures of screens to ensure we are not transferring content outside of clinical sites.***
- ***WebEx or Teams do not store or have access to any data, GSK staff is not allowed to make or store any screenshots or save any data which has been shared.***
- ***Details of what was monitored remotely will be documented in the appropriate section of the MVR.***
- ***In case of technical malfunctions or if the security of the transmission is no longer ensured, we will pause rSDV activities. GSK Issue Management Procedures will be initiated.***

Section 10.5.1 List of abbreviations

CRA:	***Clinical Research Associate***
HLT:	***High Level Term***
PI:	***Personal Information***
PT:	***Preferred Term***
rSDV:	***remote Source Data Verification***
SOP:	***Standard Operating Procedure***

Section 10.5.2 Glossary of terms

Protocol amendment:	***The International Council on Harmonization (ICH) defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol". GSK further details this to include a change to an approved protocol that affects the safety of participants, scope of the investigation, study design, or scientific integrity of the study.***

Section 11 References

[…]

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